European Manual of Medicine

Neurosurgery

C. B. Lumenta, C. Di Rocco, J. Haase, J. J. A. Mooij
Editors
Foreword of the Series Editors

The European Manual of Medicine series was founded on the premise of offering residents as well as specialised clinicians the latest and most up-to-date information on diagnosis and treatment in Europe. In contrast to existing textbooks, the European Manual of Medicine series aims to find a consensus on the demands of modern European medicine based on the “logbooks” recommended by the Union of European Medical Societies (UEMS). Therefore, identical for each discipline, diagnostic and therapeutic principles are recommended as “recommended European standards”.

To fulfil these demands, we – together with Springer – recruit editors who are well established and recognised in their specialities. For each volume, at least three editors from different European countries are invited to bring the high clinical and scientific standards of their respective disciplines to the book.

Wherever possible, the book editors were asked to follow a standardised structure for each chapter so as to guarantee the reader easy and quick access to the material. High-quality illustrations and figures should provide additional useful information. For the interested reader, detailed references allow him or her to further investigate areas of individual interest.

The series editors are deeply grateful to Springer, especially to Mrs. Gabriele Schroeder, Mrs. Waltraud Leuchtenberger and Mrs. Stephanie Benko for their support and assistance in the realisation of this project from the early stages.

The third volume of the European Manual of Medicine series is Neurosurgery. The aim is to provide neurosurgery trainees with a comprehensive, yet condensed, guide to the core knowledge required in this speciality, and to give them the ability to work in their speciality in the entire European Union.

The volume editors Prof. Christiano B. Lumenta, Munich/Germany; Prof. Concezio Di Rocco, Rome/Italy; Prof. Jens Haase, Aalborg/Denmark; and Prof. Jan Jakob A. Mooij, Groningen/The Netherlands, leading European experts in Neurosurgery, recruited contributors from different European countries to compile a textbook that fulfils our original concept of the European Manual of Medicine series.

Wolfgang Arnold
Uwe Ganzer
Munich/Düsseldorf
Fall 2009
In a highly specialized field of medicine such as neurosurgery, specific knowledge is needed, and residents in training for neurosurgery also need to have such knowledge.

As we know, there are differences in the training programmes in the various EU countries, making it difficult to standardize medical training in the specialized field of neurosurgery. The basis for an international European consensus in neurosurgery is set out in this manual.

The book is written for residents as well as for students and other physicians with special interest in neurosurgery. Attempts were made to incorporate details of diagnostic and therapeutic procedures in different neurosurgical cases depending on the localization (cranial, spinal, peripheral nerves), with consideration of congenital defects and paediatric neurosurgical disorders, of functional and stereotactic neurosurgery as well as of critical neurosurgical care. The chapters on each organ contain the basics in anatomy and physiology. The book is structured with a clear description of the entities and their neurosurgical treatment options.

With better understanding of specific neurosurgical problems, the reader will be able to provide patients with better medical care. In preparing for the board examination, the resident will have a European standard for stepwise management of neurosurgical problems.

Munich, Germany  C. B. Lumenta
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Groningen, The Netherlands J .J. A. Mooij
Summer 2009
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*Edited by Concezio Di Rocco*

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Neurosurgery is defined as a special field of operative treatment of space-occupying lesions, such as tumors, infection, or hematomas, malformations, degenerative changes, injuries, and other surgically reachable entities of the central, peripheral, and vegetative nervous system and the associated necessary diagnostic procedures.

Modern neurosurgery is count as one of the newer fields of medicine, comparable to the fields of urology, orthopedic surgery, or vascular surgery which are now separated from the field of "general surgery" [1]. Nevertheless, the beginnings of neurosurgery go back to Stone Age times. Old Egyptian medicine had experience of and treatment guidelines for skull diseases 3,000 years bc. Since the middle of the nineteenth century archeologists have found, in different parts of the world, the remains of human skulls that have undergone trepanation and show evidence that the individuals have survived the procedure. Probably the procedures were for ritual purposes or for the treatment of some head injuries. Surgery on the nervous system, however, was reserved for more recent times. In the second half of the nineteenth century topographic anatomy was introduced after the development of asepsis and anesthesia. The first successful brain surgery was performed by R. Godlee in 1884, while, one year before, McEwen had removed a spinal tumor.

Modern neurosurgery could be realized after the development of examination methods such as myelography by W. Dandy in 1919, cerebral angiography by E. Moniz in 1927, electroencephalography by Berger in 1927, and echoencephalography by Leksell in 1953. With the beginning of the computer era in the 1970s, computed tomography was developed by Ambrose and Hounsfield, followed by magnetic resonance imaging (MRI) with the possibility for functional MRI, MRI spectroscopy, depiction of the pyramidal tract, and so on.

The results of brain surgery were improved after the introduction of clips and diathermy by Cushing at the beginning of the twentieth century. Modern neurosurgery, however, began with the introduction of the microscope, modern anesthesiology, and neurointensive management. Progress continued with the development of the ultrasonic aspirator, laser technology, neuroendoscopy, neuronavigation, and image-guided surgery. Functional neurosurgery for the treatment of pain and movement disorders changed from ablative procedures to electrode stimulation techniques.

Despite these rapid advances, in the last two decades the special field of neurosurgery has had to compete with other disciplines in the treatment of some conditions, such as stereotactic radiosurgery for the treatment of arteriovenous malformations (AVM) or small and well-defined brain tumors (metastasis, vestibular schwannoma, etc.), and endovascular neuroradiology for the treatment of intracranial aneurysms and AVM. Nanotechnology and molecular biology will bring in alternative treatments for many neurooncologic diseases. The most difficult cases, however, will be reserved for the neurosurgeon.

As a consequence of all these developments, it is very important to have standards in the training of neurosurgical residents and in basic training for the technical skills.

References

2.1 Training in Neurosurgery

HANS-JÜRGEN REULEN

2.1.1 Introduction

National authorities and professional bodies have the responsibility for monitoring and recognising training institutions and to provide certification or recognition of medical specialists. The European Union of Medical Specialists (UEMS) is the responsible authority in the EU for harmonisation and improvement of the quality of training of medical specialists. Harmonisation is a necessary prerequisite to enable free movement of medical specialists in the countries of the EU.

The European Neurosurgical Training Charter of the UEMS [1] summarises the requirements and standards for training in neurosurgery. National organisations are strongly recommended to adopt these requirements in their national guidelines. In the following, all referrals are made to the European Neurosurgical Training Charter.

Departments in the process of developing or improving their training programme may find comprehensive information in Training in neurosurgery in the countries of the EU, a guide to organize a training program [2].

2.1.2 Goals of a Neurosurgical Training Programme

The main goal is to provide a trainee with a broad knowledge base, the necessary operative and procedural skills and experiences, as well as professional judgement as preparation for independent neurosurgical practice. Further goals are to teach self-criticism, critical assessment of his/her results, and the ability to undertake self-directed learning, which will eventually lead to continued expert practice and professionalism.

2.1.3 Length of Training

Neurosurgical training requires a minimum duration of six years which includes a minimum of four years training in clinical neurosurgery in an accredited programme. Of these four years at least three years should be spent in a UEMS member state and not less than three years in the same recognised programme. Training must include adequate exposure to intensive care and to paediatric neurosurgery. Because of the future reduction in the hours of work there may be a need to extend the training time in clinical neurosurgery from four to five years.

Up to a total of two years may be spent in related disciplines (in a surgical discipline, neurology, neuropediatrics, neuroradiology, neuropathology, neurophysiology) and/or activities including research in neurosciences.

2.1.4 Contents of Training

The contents of training are described in the classical textbooks, encompassing knowledge in:

- General basics of surgery
- Complete neurological investigation tests and procedures
- Neurosurgical diseases, their diagnosis, prognosis, treatment indications, and their operative and non-operative treatment (including intensive care and possible complications)
- Conservative and operative treatment of head injuries and the spine/spinal cord
- Microsurgical operative techniques and neuronavigation
- Indications for and the interpretation of modern neuroradiological examination techniques (CT, MRI, myelography, angiography), as well as Doppler sonography and ultrasound
- Quality control (morbidity and mortality conference, infection control, risk management)

2.1.5 The Training Programme

- There should be a written Training Curriculum describing the contents and aims in each year of training. A structured Surgical Training Plan can be helpful to provide a systematic escalation of surgical competence
and responsibilities. Emphasis should be placed on adequate time allocated for study and tuition independent of clinical duties.

- There should be established Rotation Periods covering all main areas of neurosurgery. Each rotation should have clearly defined goals with regard to responsibilities in patient care, knowledge and operative experience.
- During each rotation a trainee should be assigned to a specific trainer.
- There should be a documented Education Programme with lectures, clinical presentations, neuropathological and neuroradiological conferences, a journal club, a morbidity and mortality conference, teaching meetings including subspecialties, and teaching in ethics, administration, management and economics.
- It is recommended that trainees participate at least once a year in a national/European training course, in a hands-on course or a national neurosurgical meeting, respectively.
- Each trainee must keep an authorised logbook (meeting the standards of the UEMS/European Association of Neurosurgical Societies [EANS] logbook) for documentation of his/her operative experience. The trainee will have to demonstrate that he/she has assisted in a wide range of cases, which should include a balance of trainer-assisted and personal cases under supervision. The logbook must be supervised and signed regularly by the respective trainer, and it must be available at Board examination.
- Trainees should be encouraged to participate in research and to develop an understanding of research methodology. In academic programmes, clinical and/or basic research opportunities must be available to trainees with appropriate faculty supervision.

2.1.6 The Training Institution

A training institution must have national recognition in accordance with the standards of the UEMS Training Charter. Participation of training institutions in the European accreditation process at present is voluntary and, if compliant, indicates that the department and the training programme fulfill the European Standards of Excellence for Education in Neurosurgery.

Units that cannot comply with the minimum standards of the UEMS Training Charter (case volume and mixture, number of trainers and beds, etc. as listed below) and cannot offer the full spectrum of neurosurgery cannot be training centres on their own. It is recommended that they develop a common training programme in cooperation with a larger department. Highly specialised centres can be included in the rotation of a recognised training centre.

2.1.6.1 Requirements for Training Institutions with Regard to Equipment and Educational Facilities

- There must be a referral base sufficient to provide an adequate case volume and mixture to support the training programme.
- There must be a minimum of four trainers (including the chairman/programme director).
- There must be at least 30 neurosurgical beds and in addition critical care beds (7–10/million population).
- There must be at least two designated, fully staffed operating theatres (neurosurgically trained staff), appropriately equipped and with 24-h availability.
- There must be an operating microscope with CCTV for each theatre. The following are deemed essential equipment: ultrasonic aspirator, image guidance and/or ultrasound, a stereotactic system, radiological imaging, and endoscopy equipment.
- Neurosurgical theatres should be covered by anaesthetists with a special interest in neuroanaesthesia. Anaesthesia coverage should be available at all times for neurosurgery.
- There must be designated and fully staffed neurosurgical intensive care beds. Neurosurgical intensive care may be managed by neurosurgery or there may be joint responsibility between neurosurgery and anaesthesia.
- There must be an emergency unit with 24-h admission.
- There must be outpatient clinics where non-emergency patients are seen before and after surgery.
- There must be exposure to paediatric neurosurgery as a mandatory component of a training programme. Where this does not form part of the routine work of a neurosurgical department, a 6-month secondment to an appropriate programme should be arranged (it must be recognised that in some European countries paediatrics requires special training and a protected environment).
- There should be opportunity to obtain experience in functional neurosurgery either within the department or in another neurosurgical department specialising in this field.
- All main specialities (neurology, surgery/traumatology, anaesthesiology, radiology, neuroradiology, neuropathology, radiotherapy, internal medicine, paediatrics) must be present to provide the trainee with the opportunity of developing his/her skills in a team approach to patient care.
- There should be an easily accessible library, with an adequate selection of books and journals on neurosurgery, as well as facilities for computer literature searches.
2.1.6.2 Institutional Quality Management Provisions

A training institution must have an internal system of quality assurance. There should be written guidelines concerning patient care and patient information (patient's consent), referrals, medical records, documentation, on-call and back-up schedules, days off, residents' working schedules, attendance at conferences and educational activities. An example may be found in [2]. There must be a structured procedure for the reporting of adverse events in the form of a mortality and morbidity conference; and the hospital should have an infection control committee and a drugs and therapeutics committee.

2.1.6.3 Responsibilities of a Training Programme Director

The training programme director does not need to be the head of the training institution. He/she must be a certified specialist of a minimum of five years, and demonstrate evidence of continuing professional development.

The Programme Director must establish a transparent and fair appointment process for trainees. A training agreement (contract) should be completed and signed by the director and the trainee at the beginning of training. The programme director should provide the trainee with a written Training Curriculum of his/her training (see Sect. 2.1.5). The promotion of an ethos of a high level of professional conduct and ethics within the training programme is essential.

The programme director has to:
- Organise and coordinate a balanced training programme with established rotations ensuring that the trainee will have exposure to all aspects of neurosurgery. The programme must be written and available to trainees and trainers.
- Ensure that there is dedicated time allocated to the trainers for training and that the trainers fulfil their training responsibilities.
- Ensure that there is dedicated time for trainees to attend educational meetings and approved courses, and that trainees can fulfil all training obligations.
- Ensure that the individual trainee's documentation (training portfolio) is up to date.
- Organise a transparent and fair semi-annual progress evaluation of trainees.
- Provide valid documentation as to satisfactory completion of training.

2.1.6.4 Responsibilities of Trainers

Trainers should be certified specialists and possess the necessary administrative, teaching and clinical skills, and commitment to instruct and support their trainees. They have to:
- Set realistic aims and objectives for a rotation period
- Supervise the day-to-day work of the trainee on the ward, in the outpatient clinic and in the operating theatre
- Support the trainee's operative and clinical progress and provide feedback
- Assess and report on the trainee's progress at the end of each rotation (progress evaluation)
- Inform the programme director of problems at an early stage

2.1.6.5 Requirements for Trainees

Trainees during their training must be exposed to at least four different trainers and the full spectrum of neurosurgical procedures.

The attached Operative List (Appendix 1) summarises the minimal and optimal numbers of so-called key procedures that trainees should have performed on completion of training. In addition to this mandatory list of operative procedures, the trainee should have assisted in or partly performed operations for pituitary adenomas, complex basal meningiomas, aneurysms, arteriovenous malformations, acoustic neurinomas, paediatric procedures, intramedullary tumours, etc. (see assistant figures in Appendix 1) [3].

Trainees should be directly involved in the pre- and postoperative management of these patients and should have a detailed understanding of the preoperative investigations.

Many of the above procedures demand the use of the operating microscope that the trainee must be fully familiar with.

The trainee must learn to record and document patient history, examinations and investigative findings, obtain patients' consent for operative procedures, clearly detailing the reasons for performing the procedure and the risks involved, as well as learn to communicate with patients and relatives and pass on distressing information (e.g. malignancies or bereavement) in a sensitive and caring manner.

He/she must maintain an operative logbook detailing his/her involvement in all cases. He/she should ensure that the goals and objectives of each rotation are met, that all problems are discussed with the assigned trainer and that copies of the progress evaluation forms are stored. Also it is recommended to keep a record of courses attended, publications and/or presentations (training portfolio).
2.1 Training in Neurosurgery

- A neurosurgical training record (Appendix 2) lists the cumulative operative experiences done by a trainee and shows the 'competence level' of each procedure expected at the end of training [4]. On completion of training the trainee tabulates his/her cumulative operative totals and indicates his/her level of competence. The training director certifies an adequate competency level for each procedure by signing the training record.

2.1.7 Periodic Progress Evaluation

Periodic evaluation at 6-month intervals or at the end of a rotation period is an objective and fair instrument to ensure that trainees progress satisfactorily throughout the training. The logbook is used as supporting documentation. The trainer produces a written summary, using a structured format (Trainee Evaluation Form), and discusses with the trainee whether:

- Agreed goals have been met during the past rotation
- Specific knowledge, operative totals and all other aspects of training have been reached
- Any weak areas have been identified that require intensified supervision, advice and support. Failure to meet the agreed target must be brought to the attention of the training programme director.

In addition, the further development of training should be discussed and aims and objectives for the next rotation may be formulated. The Evaluation Sheet must be signed by the trainer/programme director and trainee and kept in the trainee's portfolio.

In future a separate (anonymous) evaluation of their training by the trainees may become helpful to receive the feedback of the trainees concerning clinical and operative training, teaching, supervision and support, feedback of progress and career advice.

2.1.8 Certification at Completion of Training

An application for certification as a specialist must be sent to the national authority responsible for recognition/certification as a medical specialist. The application must include:

- Details of previous training posts, including dates, duration and trainers
- Satisfactory cumulative operative totals performed by the trainee (logbook and operative list)
- Signed Progress Evaluation Forms for each rotation/training period
- List of training courses attended, hands-on courses, meetings, etc.
- Letter from the programme director providing valid documentary evidence of the satisfactory completion of training
- Specific additional requirements may exist in individual countries (list of publications, list of presentations at meetings, reviews, expert opinion, etc.)

Many countries in Europe now have a compulsory written (MCQ) and oral examination, with the majority having an oral board examination. At present the level of such examinations varies considerably, and a common standard is needed urgently. It should be underlined that the EANS/UEMS offers a written and oral European Board Examination of high standard twice a year. Countries that do not have a full board examination in place may use the European written and/or oral examination as an equivalent, or organise their national examination with the support and advice of the EANS/UEMS Examination Committee.

2.1.9 Subspecialisation

Competence in complex procedures exceeding the knowledge and operative totals required at the end of training can be developed after completion of training within the framework of a 12- to 18-month subspecialisation fellowship. The definition and organisation of subspecialisation is presently being discussed in a UEMS/EANS committee and will be published in *Acta Neurochirurgica*.

Appendix 1

The New Operative Figures for Trainees

Key Procedures

In order to make neurosurgical training comparable in the various European countries, key procedures have been defined. Every trainee at the end of training should be able to perform these procedures independently, i.e. with a trainer supervising but not making a significant decision/practical manoeuvre during the operation. The list is detailed and ensures that a trainee has acquired broad operative experience (Appendix 1). With these key procedures, a certain standard of training is guaranteed and in future will become more and more important as subspeciality areas are developed.

Societies may wish to include additional key procedures and certainly can do so.
Minimum and Optimum Figures

Minimum figures should be attained. It is of great importance that within the specific categories the trainee acquires sufficient experience. If the minimum of one key procedure is not fully met, this can be counterbalanced by a comparable key procedure of the same area. The minimum operative total for each area should be attained.

The optimum figures are provided as a goal for a good training programme and also to allow for competency-based training. It takes into account that trainees progress at varying rates. For some operations only ‘optimum’ figures are indicated. National societies may define such operations as key procedures.

If minimum figures are not achieved, smaller departments may need to arrange a rotation of their trainees for part of their training with larger departments.

Assistant Figures

For many years, opinions among trainers have differed considerably as to whether each trainee should have performed complex operations personally, such as aneurysms, AVMs, acoustic neuromas, spinal intramedullary tumours, basal meningiomas, brain tumours in children, etc. To solve this problem, a separate list of assistant figures is included (Appendix 1, assistant figures). This list contains procedures that trainees have to assist in or perform in part but with no obligation to perform them personally/independently. Most of these procedures will be learned either after finishing residency or in a subsequent subspecialty programme. The requirement of the assistant figures ensures that trainees are exposed to such complex diseases during their training and become familiar with the diagnostic procedures, the treatment options and the follow-up required. The specified minimum figures should be attained.

Appendix 1 Neurosurgical Training Requirements – Adults

<table>
<thead>
<tr>
<th>1. Head injuries</th>
<th>Operative totals</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Optimum</td>
<td></td>
</tr>
<tr>
<td>Burr holes: external ventricular drainage/ICP monitoring/reservoir</td>
<td>15</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Chronic subdural haematoma</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Craniotomy: extradural/subdural/intracerebral haematoma/contusions</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Depressed skull fracture</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Dural repair (CSF fistula)</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cranioplasty</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Supratentorial tumours and lesions (excluding stereotactic procedures)</th>
<th>Total</th>
<th>40</th>
<th>61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic tumours: primary/metastatic</td>
<td>30</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Meningioma</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Pituitary adenoma (transsphenoidal/transcranial)</td>
<td>0</td>
<td>5b</td>
<td></td>
</tr>
<tr>
<td>Other benign lesions (epidermoid, arachnoidal cyst, etc.)</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Posterior fossa lesions</th>
<th>Total</th>
<th>7</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary and metastatic tumours</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Chiari malformation/posterior fossa decompression</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other benign lesions (epidermoid, arachnoidal cyst, von Hippel-Lindau, etc.)</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*a* It is of great importance that within the specific areas there is sufficient experience. If the minimum of one key procedure is not fully met, it can be counterbalanced by a comparable key procedure of the same area. The minimum operative total of each area should be attained.

*b* For some operations only ‘optimum’ figures are given. Some national societies may define such operations as key procedures.

*c* In a few European countries peripheral nerve procedures have, in the past, not been a mandatory requirement.
Appendix 1  Neurosurgical Training Requirements – Adults

<table>
<thead>
<tr>
<th></th>
<th>Operative totals</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Optimum</td>
<td></td>
</tr>
<tr>
<td>4. Infection (cranial/spinal)</td>
<td>Total</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Abscess/subdural empyema</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>5. Vascular</td>
<td>Total</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Craniotomy: aneurysm</td>
<td>0</td>
<td>8*</td>
</tr>
<tr>
<td></td>
<td>Craniotomy: arteriovenous malformations (AVM)</td>
<td>0</td>
<td>2*</td>
</tr>
<tr>
<td></td>
<td>Cavernous angioma</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Haematoma (spontaneous intracerebral/intracerebellar)</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>6. Hydrocephalus (≥ 16 years)</td>
<td>Total</td>
<td>42</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Shunting procedure, initial</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Shunt revision</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Endoscopic fenestrations</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>External ventricular drainage</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>7. Spine</td>
<td>Total</td>
<td>92</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>Cervical disc disease/spondylosis: anterior decompression/foraminotomy</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Cervical instrumentation (anterior/posterior)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Lumbar disc disease/spondylosis: lumbar disc</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Laminotomy/laminectomy for spondylosis</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Lumbar instrumentation</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Spinal tumours: extradural</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Spinal tumours: intradural extramedullary</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Spinal tumours: instrumentation in vertebral tumours</td>
<td>0</td>
<td>5*</td>
</tr>
<tr>
<td></td>
<td>Spinal trauma: decompression/instrumentation</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>8. Trigeminal and other neuralgias</td>
<td>Total</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Injection techniques/radiofrequency lesion</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Microvascular decompression</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>9. Stereotactic and functional neurosurgery</td>
<td>Total</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Stereotactic tumour biopsy</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Surgery for epilepsy</td>
<td>0</td>
<td>3*</td>
</tr>
<tr>
<td></td>
<td>Therapeutic electrostimulation (peripheral nerve, spinal)</td>
<td>2</td>
<td>5*</td>
</tr>
<tr>
<td></td>
<td>Implantation of ports/pumps for intrathecal drug delivery</td>
<td>2</td>
<td>5*</td>
</tr>
<tr>
<td>10. Peripheral nerve</td>
<td>Total</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Entrapment decompression/transposition</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>11. Computer-aided interventions (not the procedures)</td>
<td>Total</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>12. Basic techniques</td>
<td>Total</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Craniotomy supratentorial</td>
<td>8</td>
<td>20</td>
</tr>
</tbody>
</table>

* It is of great importance that within the specific areas there is sufficient experience. If the minimum of one key procedure is not fully met, it can be counterbalanced by a comparable key procedure of the same area. The minimum operative total of each area should be attained

* For some operations only ‘optimum’ figures are given. Some national societies may define such operations as key procedures

* In a few European countries peripheral nerve procedures have, in the past, not been a mandatory requirement
Appendix 1 Neurosurgical Training Requirements – Paediatric through 15 Years of Age

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total</th>
<th>Minimum</th>
<th>Optimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hydrocephalus and congenital malformation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External ventricular drainage</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Shunting procedure</td>
<td>2</td>
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<tr>
<td>2. Head and spine injuries</td>
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<tr>
<td>Burr holes: ICP monitoring/drainage/reservoir</td>
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<td>Chronic subdural haematoma/hygrroma</td>
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<td>3. Brain tumours and lesions</td>
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<td>Supratentorial tumours</td>
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</table>

* For some operations only ‘optimum’ figures are given. Some national societies may define such operations as key procedures

Appendix 1 Neurosurgical Training Requirements – Assistant Figures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number</th>
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<tbody>
<tr>
<td>Craniopharyngioma</td>
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<tr>
<td>Pituitary adenomas (transsphenoidal + transcranial)</td>
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<tr>
<td>Acoustic neurinoma</td>
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<tr>
<td>Complex basal/posterior fossa meningioma</td>
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<tr>
<td>Craniotomy: aneurysm</td>
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<tr>
<td>Craniotomy: AVM</td>
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<tr>
<td>Occlusive: endarterectomy</td>
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</tr>
<tr>
<td>Thoracic disc disease</td>
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<tr>
<td>Spinal tumours: intramedullary</td>
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<tr>
<td>Thalamotomy, pallidotomy/stimulation technique</td>
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<tr>
<td>Implantation of ports/pumps for intrathecal drug delivery</td>
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<tr>
<td>Single suture craniosynostosis</td>
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<tr>
<td>Paediatric infratentorial tumours</td>
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<tr>
<td>Meningocele/meningomyelocele</td>
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<tr>
<td>Tethering syndromes</td>
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<tr>
<td>Spinal dysraphism</td>
<td>2</td>
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<tr>
<td>Peripheral nerve sutures (with graft)*</td>
<td>3</td>
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</tbody>
</table>

* In a few European countries peripheral nerve procedures have, in the past, not been a mandatory requirement
### Neurosurgical Training Record

<table>
<thead>
<tr>
<th>Nature of operation – Adults</th>
<th>T</th>
<th>Operative Totals</th>
<th>Minimum Competency level end of 6th Year</th>
<th>Training Director’s signature</th>
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<tr>
<td>Head Injuries</td>
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<tr>
<td>Burr holes ext. ventricular drainage /ICP-monitoring/reservoir</td>
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<td>Chronic subdural haematoma</td>
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<tr>
<td>Craniotomy - extradural/subdural/intracerebral haematoma/ contusions</td>
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<tr>
<td>Depressed skull fracture</td>
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<tr>
<td>Dural repair (CSF fistula)</td>
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<td>Cranioplasty</td>
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<tr>
<td>Supratent.Tumours + Lesions (excl. stereotactic procedures)</td>
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<tr>
<td>Intrinsic tumours – primary / metastatic</td>
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<tr>
<td>Meningioma – vault</td>
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<td>Meningioma – parasagittal</td>
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<td>Meningioma – complex basal</td>
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<td>Pituitary adenoma (transphen. – transcranial)</td>
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<td>Craniopharyngioma</td>
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<tr>
<td>Other benign lesions (epidermoid, arachnoidal cyst, etc.)</td>
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<td>Posterior Fossa Lesions</td>
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<tr>
<td>Primary and metastatic tumours (cerebellar hemisphere)</td>
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<tr>
<td>Arnold Chiari malformation/ Posterior fossa decompression</td>
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<td>Acoustic neurinoma</td>
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<tr>
<td>Other benign lesions (epidermoid, arachnoidal cyst, H. Lindau, etc.)</td>
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<tr>
<td>Infection (cranial – spinal)</td>
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<tr>
<td>Abscess / subdural empyema</td>
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<tr>
<td>Vascular</td>
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<td>Craniotomy AVM</td>
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<td>Haematoma (spontaneous intracerebral/intracerebellar)</td>
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<td>Carotid endarterectomy</td>
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<tr>
<td>Hydrocephalus (≥ 16 years)</td>
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<td>Shunting procedure, initial</td>
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<td>Shunt-revision</td>
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<td>Endoscopic fenestrations</td>
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<td>External ventricular drainage</td>
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## Appendix 2

### Nature of operation – Adults

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<th>Minimum Competency Level End of 6th Year</th>
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<td>– lumbar instrumentation</td>
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<tr>
<td>– Intradural intramedullary</td>
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<td>– Instrumentation in vertebral tumours</td>
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<td>Spinal Trauma: Decompression/Instrumentation</td>
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<th>8. Trigeminal and other Neuralgias</th>
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<td>Surgery for epilepsy</td>
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<tr>
<td>Therapeutic electrostimulation (peripheral nerve, spinal)</td>
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<td>Implantation of ports/pumps for intrathecal drug delivery</td>
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<td>Entrapment decompression/transposition</td>
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<tr>
<td>Peripheral nerve sutures (with graft)</td>
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<th>11. Computer-aided interventions (not the procedures)</th>
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<td>Craniotomy posterior fossa</td>
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<tr>
<td>Transsphenoidal approach</td>
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</table>

**Definitions:**

- **T** = The trainee has done the operation. The supervising consultant must not have made a decision/practical manoeuvre significantly affecting the execution of the operation.
- **TS** = The trainee has done the operation but the supervising consultant has made a significant decision/practical manoeuvre during the operation.
- **C** = The trainee has performed component parts during the operation under supervision of a senior surgeon: positioning, operative approach (i.e. craniotomy, opening) closure, drainage, draping, instructions for postoperative care.
- **A** = The trainee is the principal assistant during the operation.

**Competency levels:**

- **1** = should have assisted in, but is unable to perform the procedure
- **2** = competent to perform procedure under direct supervision
- **3** = competent to perform procedure without direct supervision
## Operative totals – Paediatric through 15 ys

<table>
<thead>
<tr>
<th>1. Hydrocephalus and Congenital Malformation</th>
<th>Operative Totals</th>
<th>Competency levels end of 6th year</th>
<th>Training director’s signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative Totals</td>
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<td>TS</td>
<td>A+C</td>
</tr>
<tr>
<td>External ventricular drainage</td>
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<tr>
<td>Shunting procedure:</td>
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<tr>
<td>Meningomyelocele</td>
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<td>Tethering syndromes</td>
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- 1 = should have assisted in, but is unable to perform the procedure
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## References

2.2 Basic Training in Technical Skills: Introduction to Learning ‘Surgical Skills’ in a Constructive Way

JENS HAASE

That one, when in truth shall succeed in bringing a man to a destination, first and foremost you have to be careful to find him where he is and start from there. This is the secret of all art of assistance, and anyone who cannot understand this is conceited when he thinks that he can help others.

(Fragment of a straightforward message: Danish philosopher, Soren Kierkegaard 1856)

2.2.1 Introduction to ‘Basic Training Skills’

What is a good surgeon? This question cannot be easily, sincerely or precisely answered despite the fact that we ‘all know’ [54]. I assume that we all agree that a surgeon needs manual dexterity. Dexterity usually refers to skills and ease in physical activity especially manual activity which in the context of surgical dexterity should be understood as motor skills [1, 16]. Dexterity is closely connected to performance in surgery although a strict definition is not obtainable [46, 54].

Conventional surgical teaching is a daily working relationship between experienced teachers and trainees [6]. A young MD’s training has been described as an opportunity to have access to patients, but experience as such, without training, increases only confidence and not competence [14]. Traditional teaching makes steep learning curves take place during interaction with real patients. This is not acceptable in modern societies as we know that the first surgical procedures performed by an inexperienced surgeon carry greater risks for the patient and often even unacceptable risks [11].

We have therefore tried to establish different methods of learning surgical skills such as manual dexterity.

2.2.2 Learning: Theories

Concerning learning and teaching, the so-called instructional approach has become synonymous with effective cognitive growth = learning [8].

Teaching neurosurgical skills today must be based on the concept: not to teach, but to facilitate learning and development of the abilities the trainee possesses.

Much surgical experience consists of procedural knowledge in the form of perceptual-motor or spatial skills that cannot be expressed verbally or in writing [49]. How we shall function in a microsurgical brain habitat teaches us that we must learn the true three-dimensional (3D) anatomy of the brain and not rely on simple pictures in our books. By spatial training in 3D models we learn where this anatomy is within the skull enhancing our chances of finding our designated targets more safely without complicated neuronavigation [20].

Learning in general is also tied to the motivation of the trainee, and effective learning of surgical skills depends on creating the right environment for learning. We have to accept that learning is connected with mental and emotional growth in which information access plays only a subordinate role [31].

Learners = trainees should therefore be viewed as active constructors rather than passive recipients of knowledge. In modern learning sciences, learning is a construct of the trainee’s ‘personality’ and of the surroundings in which the trainee functions.

It has been documented that surgeons need a certain psychological and personal profile in order to become true experts in their field, as is the case with world-class athletes. Unless surgeons are prepared to learn and hence develop professionally, all training is doomed. The teacher’s role is merely to support. In this ‘enzymatic’ way they facilitate the learner in the process of ‘learning’ [37]. It is therefore nowadays also accepted that even the teachers need to learn to perform as teachers [6].

We must ask ourselves these questions:
• How do we learn?
• What is the purpose of this for me?

These philosophical questions bring us far away from the concept of surgery. The Dreyfus brothers [14] argue that learning can be seen as a stepwise development through five stages. Briefly summarised these are as follows:
1. Novices act on the basis of context-independent elements and rules.
2. Advanced beginners begin to take account of situational factors, which they have learned to identify and interpret on the basis of their own experience from similar situations.
3. **Competent performers** are characterised by the involved choice of goals and plans as a basis for their actions. Goals and plans are used to structure and store masses of both context-dependent and context-independent information.

4. **Proficient performers** identify problems, set goals and plan intuitively from their own experientially based perspective, and these choices are checked by analytical evaluation prior to action.

5. **Experts** whose behaviour is building on intuitive, holistic and synchronic judgements in a way that, in a given situation, releases an adequate picture of the problem together with goal, plan, decision, and action in one instant and with no division into phases. This is the level of true human expertise. Experts are therefore characterised by a flowing, effortless performance, unhindered by analytical deliberation.

To these you may add a sixth level:

6. **Innovator experts**: Here we find persons who also understand the necessity of a debriefing session after a performance in order to consider the adequacy of old skills in order to develop new ones. In this way these experts become true innovators of new techniques.

Classical ‘information feeding’ of declarative knowledge will never take us above the first level of proficiency, i.e. novices. Information is NOT knowledge!! It is an error to assume that possessing a vast quantity of information is the same as having knowledge and understanding. Every 6–8 years our scientific knowledge has doubled! In a setting where more trainees must learn more and more in less and less time, this places an unrealistically high burden on the teachers and is a rather cost-intensive way of teaching.

From the second level on, the learning development depends on practical training, and in this process, declarative knowledge only supports the learning development up to the third, or perhaps fourth, level. It is therefore a prerequisite for the trainee to have a personal goal for the learning per se. Based on that, he/she has to develop a subset of tasks to be rehearsed. This learning is a group-monitored and group-oriented process and not a simple ‘result-oriented’ task [12, 20, 21]. The ‘lonely wolf’ training, which has been the standard set up in medicine for many years, is outdated. A prerequisite for making declarative choices is that the trainee learns to make the decision that seems ‘right’, that the trainee does not seek power over other trainees and that a disappointing result of a training session is considered a sign of a ‘failure of the training process’ and not a personal failure of the trainee [4, 9, 22, 44, 49].

Neurosurgeons have learned to be independent, and therefore tend to be very individualistic – which makes it difficult for most physicians to work together in a cooperative situation or in practice. (James I. Ausmann 1997)

By organising the surgical performance teaching in a structured systematic base system based on problem-based learning and by introducing virtual reality (VR) learning methods, we can enhance speed and effect of learning basic dexterity and visualisation skills needed to perform surgery at the expert level [3, 23, 54].

It is well known that pilots are tested for both abilities and for psychological behaviour before they are introduced into a training programme. The same should perhaps also be a natural part of any surgical training programme [3, 40].

### 2.2.3 Length of Training Periods

Learning automatic dexterity = procedural memory, also means that we must learn these skills in a continuous manner. Although much surgical interference during an operation depends on declarative knowledge in terms of solid background knowledge of anatomy, physiology, pathology and surgical techniques and procedures, the ‘true’ surgical performance is significantly a procedural knowledge of ‘knowing how’ [15, 20, 37]. Procedural memory is stored in the cerebellum and basal ganglia. All training aimed at obtaining this procedural knowledge must be tailored to this fact.

The performance of a motor function is through reaction in the premotor and motor centres of the brain. In addition we have the supplementary motor area (SMA) on the mesial part of the frontal lobes where we visualise our movements. We can literally think of a specific movement, visualise it (without performing it) and see this SMA area light up on functional imaging [18]. In surgery our movements should be as automatic as they are when we are writing with a pen or riding a bicycle. It is further shown that training the non-dominant hand leads to a higher performance increase. Non-dominant left-hand stimulation also increases 3D space observation. Therefore rehearsal of movements via SMA and with the left hand may be of benefit for surgeons [41]. As Merleau-Ponty points out: ‘A movement is learned when the body has understood it, that is, when it has incorporated it into its “world”, and to move one’s body is to aim at things through it; it is to allow oneself to respond to their call, which is made upon it independently of any representation.’ [14]. Learning to play a piano from simple notes (procedural knowledge) and in a standard fashion can be achieved in 5–7 weeks by continuous training. This procedural skill of playing the piano stays with you for life and the novice can proceed in the learning from there.
This also means that we can learn movements or tasks by visualising them without being in a real operating theatre. Studies suggest that humans may form internal models of these primitive movements, which they can combine into more complex tasks. So when a task is broken down and learned in simple steps, rather than ‘all at once’, learning a complex task can be faster, and even performance improves [35, 36, 40]. One dexterity skill, which is often used, is moving a curved needle precisely along its own form. You may rehearse this in the air or through a piece of rubber or cloth, not necessarily through a human vessel or a rat vessel [39].

From our own microsurgical learning system at the Microsurgical Laboratory at Aalborg University Hospital, we have realised that it takes around 400 h of microsurgical training, from scratch, to be able to carry out, for example, a free flap transfer on a rabbit. When spending 8 h daily rehearsing in the laboratory, this means that it takes at least 50 days of training to become fully educated! Not 24 h as is the standard of a hands-on course.

### 2.2.4 Magnification of Surgical Dexterity

Competence in surgery depends on a plethora of factors and skills, and one among these is to perform surgery with the aid of the microscope, i.e. with magnification [44, 46]. When introduced to endoscope techniques, these are so different from daily life dexterities that all trainees understand the necessity for learning to use the endoscope before carrying out endoscope operative procedures on patients [17, 19, 29, 49]. For neurosurgeons the use of the microscope is nowadays essential; however it is often thought of being a simple tool for surgery, a tool that needs no ‘training’ to be used [5, 35]. This is a grave mistake.

Microsurgical techniques are specific tasks carried out in a specific microenvironment, a microhabitat created by the operative microscope [24]. Therefore our goal settings include performance using specific microsurgical instruments in this habitat, a task that demands a better understanding of the microscope. The microsurgical habitat lacks definition of sizes, which gives rise to perceptual problems in training [13]. The operative microscope has an enormous effect on surgical performance as it offers excellent light at the surgical stage under all circumstances with preservation of true 3D imaging, in contrast to endoscope surgery. The lenses of modern microscopes are of outstanding quality so that the images we receive at our retinas are perfect.

For microsurgery the surgeon needs to be able to control hand/finger tremor at the micro level and to master changed hand–eye coordination with angles rotated and distances magnified by the microscope. The learning of microsurgical techniques or skills requires the surgeon to learn to work in a microsurgical environment using and understanding microsurgical instruments serving as interfaces between hand/brain and the target.

When the surgeon becomes familiar with a new tool (instrument), this tool will become ‘internalised’, forming a ‘functional organ’ together with the surgeon’s hand [28]. While the two terms ‘tool’ and ‘interface’ are far from having identical meanings, the tool can thus now be thought of as an interface between the holistic surgeon and the object (e.g. the patient that is to be operated on). However, in this process of internalisation of the microsurgical instruments, the surgeon has to develop specific skills in order to use the tool. The surgeon must also learn to control the behaviour of tissues and threads involved.

Despite the fact that microscopes have been on the market for more than 35 years, surgeons still forget the simple adjustments of these instruments, most pronounced in the continuous balancing of the microscope. In modern microscopes, this balancing is constant despite the position of any part of the microscope. Movements are augmented server driven in some, which decreases the muscle power needed to adjust the position and thereby reduces fatigue and tremor [26]. The surgeon that grabs the microscope and some microsurgical instruments and trusts that he/she can carry out the microsurgical procedure has not fully understood this paradigm, and disasters will follow.

Experiments have shown major differences in touch sensing among inexperienced and experienced surgeons/students [10] documenting this problem. For accurate control the trainee must develop new motor strategies involving only the fine motion of the fingers [18]. Arm movements used in macrosurgery induce too much tremor. The overwhelming use of the operative microscope’s ‘zoom function’ delays the learning of micro sizes and thereby our functionality in the micro space. If we position a structure of known size in the operative training field this could facilitate the understanding of sizes. What is the length of the tip of an instrument? Measure it, watch it using the microscope with variable magnification and it will help to develop these skills of determining sizes. For the beginner, fixed magnification settings should therefore be used from a didactic point of view. The operative microscope is however only a part of the normal macro habitat – the operation room. Although the microscopes may be similar and therefore easy to learn to use, all operative rooms are different, which makes surgical rehearsal difficult compared with what aeroplane pilots experience – all their cockpits = macrohabitats are equal!

The solution to the problem of timing is to accept that the pace of learning, of whatever skill, is a personal one. This means that all our dexterity learning should be self-administered, self-monitored and continuous [7, 17, 39, 50].
2.2.5 Virtual Reality as Part of the Learning Process

Surgeons need to learn how to use all the modern technological facilities that exist today including information technology (IT) and virtual reality (VR). VR is defined as an artificial world resembling ‘real life’ (RL) [52, 53]. Most research is that which changes the way we think about an issue or a technical problem. The data explosion we all must deal with needs to be more manageable, more coherent and more meaningful to give us a superior performance [24, 30, 40]. We will filter more and more of the surgical ‘chaff’, allowing truly imaginative and creative research results, whether clinical or basic, to have their appropriate input [2, 47]. One of the goals of surgical media management should be to decrease the volume of data distributed and thereby increase the significance of new information presented. We must reduce the ‘information fatigue syndrome’ that is so common today [2].

Virtual reality gives a substantial contribution to interactive learning environments. Virtuality in this context should be used according to its meaning ‘potential/possible’, making it a medium for communication of surgical skills. This is in accordance with our own findings with the Dextroscope training [5, 24, 30]. It combines the realism (as in a video recording) with the manipulative reality as in simulation programs.

Virtual reality is a desired technology for those applications in which reality does not exist (yet), cannot be accessed, or is too dangerous or expensive to disclose [24, 30]. VR gives us the possibility to rehearse complications before they occur and without injuring patients [25, 32, 50]. VR has also been described as a tool that allows a ‘broadening of our channels of sensation and communication’ [52]. The power of VR as a learning tool comes from the possibilities to explore cause-and-effect relationships in a safe environment, and to understand and prepare for various difficult scenarios [16]. Learning in a VR world is interactive and not merely receptive. Learning in the VR space also lacks the stressed atmosphere of the operating theatre and is therefore an optimal educational environment for the novice surgeon [3, 17, 34].

Within high-risk organisations such as the military and the aircraft, nuclear and chemical industries, the opportunities to learn are not only through normal learning means but also always with simulation included [27]. The VR environment can also allow the trainee to practice a skill several times as a refresher course. Surgeons and pilots that continuously make a certain type of mistake generally make more of other types of mistakes too.

Findings have also proved skill acquisition by VR training in that subjects with lower spatial abilities demonstrated a significant positive transfer from a simulator-based training task to a similar real world robotic operations task [50].

As already stated, the trainee must develop a plan for his/her dexterity training. A key point in surgical training today is to set personal dexterity goals, develop personal methods/protocols for reaching these goals, secure validation of how the goals are reached and learn to perform these dexterity tasks in settings that simulate the operating theatre environment with all its distraction [4, 6, 35, 42]. VR can be employed to test the essential abilities of a surgical candidate, and to test and train his/her surgical skills in order to orchestrate his/her actions in a new surgical habitat. Subjects with higher spatial skills did not response as positively from training in a simulated environment.

Virtual reality systems introduce the alluring possibility of a completely objective measurement and assessment of the trainee’s ability [44, 46, 48, 51]. VR also makes it possible to track training developments, being an electronic and digital environment. This enhances the opportunities of the trainee to receive feedback from ‘a supervisor’ that is always available and thus gives the possibility of tracking development in training and rehearsal. In Lufthansa they showed that 75% of all failures were caused by non-human errors, only 13% by technical mistakes and 12% were due to environmental causes. The personality of a neurosurgeon influences the operative outcome significantly – but is never tested today [38].

To me the purpose of our new technology is to broaden our channels of sensation and communication, allowing us to experience reality more fully and making us more creative in the face of life’s challenges. I think it is plausible to suggest that progress toward this goal may depend more on technology expanded sensual experience than on computer-supported reason. (John Waterworth)

Surgery is today a ‘high-risk’ task. In high-risk surgery, surgeons are facing special demands in terms of both physical stress and emotional stress. VR introduces the possibilities for learning surgical performance in a setting where failures will not lead to human disasters. Another important feature of surgery is preparedness and control of stress, e.g. mental status of the surgeon. If we make surgical mistakes, such as occluding a vessel by suturing, rupture of an aneurysm during dissection or not being able to localise our target, this will not injure our virtual models as it would a real patient. We know from athletes that one of the most important issues for them to be ready for an Olympic gold medal is to have dealt with all possible mistakes and thus know that they can manage the situation. We know that 70% of surgeons tend to feel that they can cope with a surgical procedure even when tired,
whereas only 26% of aeroplane pilots think the same [45]. By making the mistakes, experience grows and perfection is developed. For surgeons this is only morally allowed in a VR scenario [24, 37].

In every surgical procedure there are a few key steps that the trainee is more likely to perform incorrectly leading to complications. VR is therefore considered a new medium for communication of surgical skills. The value of a surgical simulator and of continuous training is analogous to the proven value of a flight simulator [27]. A surgical simulator should train surgeons for principal pitfalls. However, the transfer of learning from such contexts to that of the operating theatre may not be as easy as is assumed by many medical training programmes [19, 36, 39, 41, 43, 44, 49, 50].

The fast propagation of www-based tele-learning can benefit from the VR prospects in the coming years, as VR programs can now be accessed by the most common web browsers such as Explorer, Safari, Mozilla, etc. [33, 43, 47].

Virtual reality will replace the customary physical congregation for lectures, workshops, scientific communications and personal interactions. Features of virtual conferences will quite easily include lectures, workshops and poster presentations [2].

If the goal of the educational experience is to foster excitement about a subject or to encourage learning through exploration, VR may be worth the expense.

### 2.2.6 Conclusion

In surgery one trains at random, based on a time-based system; some trainees will devote a significant amount of time to their education while others will rely on relatively passive knowledge receiving. There is often no plan for developing surgical skills and absolutely no information in the training on the role different working spaces gives us. We know today that 70% of all mistakes and unintended failures are linked to human errors. Therefore a close evaluation of the surgical skills/task performances must be included in future education. A considerable amount of evidence proves that training by computerised models facilitates the learning process [5, 16, 24, 29, 30, 33–35, 40, 53]. We cannot depend on the techniques and information learned during a short training period being adequate for an entire career: learning surgical skills is a lifelong task.

If we do not learn from our mistakes we are doomed to continue with these.

### References

2.2 Basic Training in Technical Skills: Introduction to Learning 'Surgical Skills' in a Constructive Way


3.1 Basics

3.1.1 Anatomy

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3.1.1.1 The Skull and Its Solid Contents

The central nervous system has a hard and a soft cover: the skull and the meninges (Figs. 3.1.1–3.1.4).

The skull is divided into the neurocranium and the viscerocranium. The neurocranium encloses the brain, and is formed by the frontal, parietal, temporal, occipital, sphenoid and ethmoid bones. The frontal, both parietal, a small part of the temporal and a large part of the occipital bone make up the skullcap, while the orbital roof, the sphenoid, the petrosal, and the suboccipital bones constitute the skull base, which is divided into anterior, middle and posterior fossa. The cranial bones are connected by cranial sutures: the sutura coronalis, the sagittalis and the lambdoidea. In childhood the sutures have not been ossified; therefore, on X-ray films the sutures seem to be gaping. We call the gap the fontanel, which is closed by the end of the second year of life.

The cranial bone is covered by a layer of skin called the pericranium.

The brain is covered by the soft meninges, which consists of three layers: the dura mater, the arachnoidea and the pia mater.

The whole nervous system is divided into the central nervous system, which includes the brain and the spinal cord, the peripheral nerves and the vegetative nervous system.

The brain consists of three parts: the cerebrum, the cerebellum and the brain-stem. All body functions are controlled by the cerebrum, while the brain-stem plays the role of an instinctive control system. The cerebellum coordinates all movement impulses coming from the cerebrum, before they reach the muscle via the spinal cord and peripheral nerves.

The cerebrum is in humans the largest part of the brain. It has four lobes: the frontal, parietal, temporal and occipital lobes. The cerebral cortex is structured out of the sulci and gyri. The sulcus centralis differentiates the frontal lobe from the parietal one, and the Sylvian fissure (sulcus lateralis) is the border between the frontal and parietal lobes and the temporal one. The sulcus parieto-occipitalis marks off the parietal lobe from the occipital one. There is, however, no border between the temporal and occipital lobes. If we perform a section through the brain, we recognise the grey and the white matter, in which grey-coloured areas are also localised (brain nuclei). The most important area for the motoric function is the gyrus precentralis. The nerve cells localised to this gyrus nerve cells are the origins of the pyramidal tract, the most important tract of the arbitrary motoric system. Eighty-five percent of the pyramidal tract crosses to the contralateral side at a small mound at the medulla oblongata. In fact, the pyramidal tract goes straight to the anterior horn cells of the spinal cord, but all motoric functions are controlled by connections between the precentral gyrus and other centres of the brain, especially the cerebellum.

The connection tracts between each brain zone are called association and commissural tracts. The most important commissural tracts, which connect the two hemispheres to each other, are localised to the corpus callosum, which can be recognised as white structure in the median section of the brain. While the precentral gyrus represents the motoric control of the body, the postcentral gyrus is responsible for sensoric control, with defined functional areas for different body parts. The two hemispheres are functionally dissimilar; in the normal case of a right-handed person the left hemisphere is the dominant one. The motoric speech centre of Broca – its disturbance causes so-called motoric aphasia – is localised to the lateral part of the frontal lobe, while the sensoric speech centre of Wernicke is situated in the temporal lobe below the Sylvian fissure. A disturbance of the Wernicke speech centre leads to so-called sensoric aphasia, i.e. to be unable to understand.

The cerebellum is localised to the posterior fossa, it has two hemispheres and a middle part (vermis; Fig. 3.1.5). The connection tracts between the cerebrum and the cerebellum pass the cerebellar peduncles. The main functions of the cerebellum are to coordinate and to control all movements of the body.

The following brain areas belong to the brain-stem:

- The diencephalon: consisting of the thalamus, hypothalamus and corpus pineale
The mesencephalon, including the lamina quadrigemina
- The tegmentum and crura cerebri
- The pons and medulla oblongata

The unarbitrary control of all life functions is performed in the reflex centres of the brain-stem, which consists of the main parts of the tracts to and from the cerebrum.

The pituitary gland is localised in the middle fossa and divided into:
- The adenohypophysis, which produces:
  - Growth hormone (somatotropin, STH, GH)
  - Adrenocorticotropic hormone (ACTH)
  - Follicle-stimulating hormone (FSH)
  - Luteinising hormone (LH)
  - Interstitial cells-stimulating hormone (ICSH)
  - Thyrotropin hormone (TSH)
  - Prolactin
- The neurohypophysis, which transfers the hormones that are produced in the hypothalamus into the blood circulation:
  - Anti-diuretic hormone (ADH)
  - Oxytocin

The centre of cardiac and blood circulation and the breath function is localised in the medulla oblongata.

### 3.1.1.2 The Cerebral Blood Vessels

The arterial intracranial blood vessel system (Fig. 3.1.6) consists of:
- The two internal carotid arteries (ICA) with their branches: the ophthalmic artery (OA), the posterior communicating artery (PCommA), the anterior choroidal artery (ACHoA), the anterior cerebral artery (ACA) and the middle cerebral artery (MCA)
- The two vertebral arteries (VA) linked to the basilar artery (BA) with its branches: the posterior cerebral artery (PCA), the superior cerebellar artery (SCA), the anterior inferior cerebellar artery (AICA) and the posterior inferior cerebellar artery (PICA)

The two internal carotid arteries are connected by the anterior communicating artery (ACommA), and the basilar artery is connected to the carotid arteries by the posterior communicating arteries. We call this structure at the skull-base the circulus arteriosus or the circle of Willis. The ACA, MCA and PCA come from this circle.

The large venous system of the brain is called the venous sinus, which is a duplication of the dura: the superior sagittal sinus (SSS) and the rectus sinus (RS) → the confluens sinuum (CS) → the transverse sinus (TS) → the sigmoid sinus (SS) → the jugular vein (JV).
3.1.1.3 The Cerebrospinal Fluid and Ventricle System

Cerebrospinal fluid (CSF) is produced in the ventricles by the plexus choroides, and washes around the central nervous system within the subarachnoid space.

The CSF circulates in the ventricle system of the brain:
- From both lateral ventricles via the foramen of Monro to
- The third ventricle via the aqueduct to
Fig. 3.1.4 Localisation of motor and sensory cortex as well as of motor speech and sensory area

Fig. 3.1.5 The cerebellum: view from the top and from below
3.1.2 Pathophysiology

Although the weight of the brain is around just 2% of that of the whole body, it needs around 20% of the cardiac minute volume for its blood flow. The cerebral blood flow (CBF) remains constant, as long as the systolic blood pressure is not lower than 60 mmHg and not higher than 150 mmHg, the so-called autoregulation of the brain. It controls the width of the blood vessels in the brain depending on the pH, \( P_{O_2} \) and \( P_{CO_2} \) values of the blood, and thus the CBF. A shock occurs if the systolic blood pressure falls below 60 mmHg. This situation leads to a disturbance of the brain's autoregulation. The CBF and the brain blood volume decrease. The result is unconsciousness or irreversible brain function damage, if it persists.
A long period of increase in the blood pressure of more than 150 mmHg also leads to general changes of the brain vessels, e.g. arteriosclerosis.

The brain, which consists of three components: brain tissue, CSF and intracranial blood, is surrounded by the rigid skull, which is not able to compensate for any elastic pressure changes. Because of this, an increase in volume within the skull leads to an increase in the intracranial pressure. In the case of intracranial haemorrhage, the blood volume increases and consequently the intracranial pressure too. A similar situation is present in the case of increased CSF volume due to hydrocephalus or in the case of increased brain tissue volume due to a mass lesion such as a tumour.

The normal intracranial pressure is around 5–15 mmHg or 50–200 mm H₂O.

A cerebral oedema occurs as a reaction to brain damage. In a cytotoxic brain oedema, the tissue water increases in the glial cells (intracellular), in the case of a vasogenic oedema, the water content between the white matter tissue increases (interstitial).

A raised ICP with decreased cerebral blood flow causes an accumulation of acid metabolite products → acidosis → cytotoxic brain oedema → raised ICP; therefore, a pathophysiologic vicious circle occurs.

Vasogenic brain oedema is based on brain vessel damage caused by severe head injury, ischemic brain infarction, brain tumour etc.

### 3.1.3 Clinical Symptomatology

#### 3.1.3.1 Sensorimotor Deficit

The supplementary motor area (SMA) is the cortical centre of the pyramidal system. There is a regulation circle around the primary and the supplemental motor area as well as the cerebellum. Due to this fact, a tumour in the SMA can cause the symptom of gait disturbance. A lesion
of the SMA leads to spastic hemiparesis on the contralateral side. All voluntary movements start at the pre-central gyrus, the primary motor cortex. A lesion in this area causes a flabby contralateral hemiparesis.

The primary somatosensory cortex is localised to the post-central gyrus. A lesion of this area leads to a decreased perception for pain, temperature, pressure and touch as well as loss of discriminative perception and of position sensitive.

### 3.1.3.2 Speech Disturbances

A lesion of the basal pre-central gyrus next to the Sylvian fissure (Brodmann field 44, Broca's area) in the left hemisphere of a right-handed person leads to motor aphasia, the patient can understand, but cannot speak, although the speech muscles are not weak.

In sensory aphasia the patient loses their understanding of words, names and sentences due to a lesion in the temporo-parietal region on the left of a right-handed person (Wernicke's area).

In the case of apraxia the voluntary movements are not disturbed by a paresis. The symptom occurs due to a lesion in the SMA. The patient neglects the extremities, normally those on the left.

### 3.1.3.3 Optic Function Disturbance

The primary visual cortex is localised to the sulcus calcarinus at the occipital lobe. A homonymous hemianopia occurs in the case of a lesion in this area.

A lesion of the optic nerve leads to vision disturbance, and one of the chiasm to bitemporal hemianopia.

Functional disturbance of the CN 3, 4 and 6 leads to diplopia.

### 3.1.3.4 Cerebellar Symptomatology

Ataxia, dys- or adiadochokinesis, intention tremor, and hypotonic muscle of the ipsilateral side are the typical cerebellar symptoms.

In addition to the focal symptoms described, one has to differentiate between general and distant symptoms. Very early, a mass lesion leads to raised ICP due to a blockade of the CSF circulation somewhere in the skull, or distant symptoms occur due to transtentorial herniation or due to incarceration of the vessels. Other symptoms are caused by pressure to the hypothalamus or to the brainstem. Because of this, it is very important to analyse the first symptoms and the following ones as they develop.

Raised ICP is characterised by headache, vomiting, bradycardia and papillary oedema. The patient is increasingly somnolent and in the final stage, unconscious.

### 3.1.4 General Clinical Examination

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There is currently an increasing tendency among young residents to rely upon the modern diagnostic tools such CT, MRI, PET scans etc., whilst neglecting neurologic evaluation. Only through careful neurological history and examination can the use of special diagnostic procedures be applied to their best advantage. These procedures are often costly to the patient and in time consumption for diagnostic personnel. Complications and discomfort may accompany their use. Only the careful clinician will be able to evaluate the various tests in light of the patient's complaints and findings.

#### 3.1.4.1 The Present and the Past Histories of the Patient and the Family

The examiner should first ascertain whether the patient's complaints develop spontaneously or after trauma, whether the onset was recent or remote, and whether there was a progression or regression of the findings. Because of possible defects in judgement and memory, the patient's version may not always be reliable. He or she may also omit details of the history for psychiatric reasons or even economic gain, and he or she may exaggerate.

Since many neurological conditions are recurrent and have a genetic background, the past and family histories make up an important part of the evaluation.

#### 3.1.4.2 The Neurological Examination

The assessment of blood pressure, pulse rate and respiration (vital signs) should be a part of any neurological examination.

The objective of the examination of the sensorium is to determine the level of consciousness and the general mental, emotional and intellectual make-up of the patient. The European standard for assessing the level of consciousness is the Glasgow Coma Scale, which was introduced in 1976 by Teasdale and Jennett [1].

The cranial nerves, the sensorimotor system, the reflexes, the cerebellum, speech and coordination must be examined.

The examiner must come to the conclusion that due to the tests the findings are normal or there are signs of intracranial mass lesion with deficit, such as functional impairment of the cranial nerve(s), hemiparesis with flaccid or spastic weakness, hemihypoaesthesia or gait disturbance, dysdiadochokinesis etc.
With these results, neurological examination can be followed by further appropriate radiological and other cerebral diagnostic measures.

**Selected Reading**


### 3.1.5 Cerebral Diagnostics

#### 3.1.5.1 Radiology: Fundamentals of Cranial Neuroimaging

**Joaquín Zamarro Parra, Mariano Espinosa de Rueda Ruíz, Guillermo Parrilla Reverter and Antonio Moreno Diéguez**

The following section is intended to familiarise the neurosurgeon with different imaging techniques in an easy manner, and to be a guide to the key imaging findings in the main pathologies. In order to stick to the essentials a neurosurgeon will need in his first steps in neuroradiology, we have reduced the physics, technical details and many atypical presentations of different pathologies to a minimum. We will focus only on the requisites for understanding the techniques, and on the most important general features of the different pathologies, as they will be thoroughly explained in detail in their specific chapters. This should make this chapter easy and fun to read for the first approach in the first year, and maybe serve as a fast review of the requisites for neuroimaging in later years. The aim is to make it easy for you to diagnose these main pathologies and to make basic differential diagnoses.

#### 3.1.5.1.1 Fundamentals of Neuroimaging Techniques

**3.1.5.1.1.1 Plain X-Rays**

Many would say (I would) that plain skull X-rays have no place in an emergency and a limited place in any other situation. Due to the accessibility and amount of information given by CT and MRI, skull plain X-ray images are almost never used in neurosurgery if a CT can be performed instead. Nevertheless, it can be helpful in evaluating shunts, cranial sutures in children, looking for metallic foreign bodies prior to performing MRI and as part of an imaging protocol for specific clinical problems after discussion of these protocols with radiologists (e.g. a skeletal survey for a myeloma). Some authors still consider it helpful in evaluating the sella turcica in preoperative planning. Skull films are not indicated routinely for headache, pituitary problems, nasal trauma or sinus disease.

#### 3.1.5.1.2 Computed Tomography

Introduced in the mid 1970s, computed tomography (CT) changed the diagnostic approach of neurosurgeons, neurologists and any doctor in emergency and non-emergency medicine. CT is based on X-ray attenuation of tissues acquired in a tomographic way. The information displayed on CT images in grey scale for every pixel is related to the different X-ray attenuation properties of each tissue, dependent on the “radiodensity” of the atoms of the tissue. This is represented on an arbitrary scale (the Hounsfield scale, in Hounsfield units – H) in which bone is +1,000 H, air –1,000 H and water 0 H. Other useful attenuation coefficients are: blood, approximately +100 H, brain, +30 H and fat, –100 H. The higher number of Hounsfield units, the whiter the pixel will be displayed, and the more “hyperdense” it will be called. The lower numbers of Hounsfield units will be darker, and will be called “hypodense”. After the addition of intravenous contrast, tissues that enhance will appear whiter.

To start with, CT was always axial CT. Acquisition was made while the table was still, then the table would move to the next position, and data were acquired again, and so on. Nowadays, most acquisitions will be made in a helical way. That is, the highly collimated X-ray will be spinning and acquiring while the table moves continuously. These data are later transformed by a computer using mathematical algorithms that allow further reconstructions. Axial CT used to have much better image quality, and studies such as those of brain parenchyma, ear, paranasal sinuses and others would be performed axially. The quality of the new machines is almost identical using the helical and axial methods, even though brain parenchyma is still studied using axial acquisition. This is important to know, as you can improve the image quality of a non-collaborating patient if you make the acquisition helically instead of axially, as it is faster and less sensitive to movement.

Computed tomography is a very good imaging modality for evaluating bones and blood. It is very fast, needs little preparation, acquisition can be performed in about 12 s, and it is very useful for non-collaborating patients. Multidetector CT also allows reformattting in slices as small as 0.5–0.6 cm and reformattting in different planes (multi-planar-reconstruction [MPR]) even after the normal axial data acquisition. That way, you can make thinner slices without acquiring new data and without radiating the patient again. This is called “volumetric CT acquisition”, which can be useful in non-cooperative patients, or in the study of subtle changes or small lesions.
such as hyperacute stroke, infectious small cysts (cysticerci), paranasal study, fractures etc.

Brain perfusion CT (BPCT) techniques for stroke and tumours and angio-CT techniques for intracranial and neck vessels are used on an everyday basis in most hospitals. BPCT is performed by acquiring data on the same table position, without moving it, and injecting a bolus of intravenous iodinated contrast. We radiate and get information about a slice, whether it is thinner or thicker (64-row CT covers slices as thick as 4 cm, or up to 8 cm with special table movement techniques, and future CT multidetectors will cover the whole brain). This way we “lose” information in the “z-axis” (cranio-caudally), but we gain the temporal aspect, which will allow us to study the hae-modynamics of this slice of parenchyma, and indicate in which location biopsy of a neoplastic lesion is most likely to give higher diagnostic rentability, or to assess the func-tional status and viability of brain parenchyma in stroke patients (see Sect. 3.1.5.1.2.3 later in this chapter).

Computed tomography plays a key role in emergency imaging of the head. There is controversy with regard to studies about what clinical factors to use in order to reduce the amount of cranial CTs being performed in emergencies. Some say there are, others say there are no symptoms or signs that can reduce the amount of cranial CTs carried out in emergencies without missing patients with significant intracranial lesions. CT is indicated to diagnose intracranial haemorrhage, skull fractures, oedema, mass lesions, hydrocephalus, and arterial and ve-nous infarction. It is the imaging modality to choose in head injury, as it will give information about brain, bones (including cranium, face, orbit etc.) and soft tissues.

If neoplastic illness is suspected, intravenous contrast administration is advised. Normal intact blood–brain barrier is impermeable to any contrast agents injected. Areas with impaired (e.g. tumour, infection, vascular anomaly) blood–brain barrier are permeable to contrast agents and show greater enhancement than normal areas.

### 3.1.5.1.3 Magnetic Resonance

Discussion of MRI physics is beyond the scope of this fo-rum. MR is not based on X-rays, but on radiofrequency and magnetic stimulation. Medical MRI relies on the relaxation properties of excited hydrogen nuclei in water and lipids. The MR image depends on the amount of protons (H) of each tissue that will produce a signal that will be received by antennas/arrays. H₂O (water) will therefore be very important for image formation, and for contrast between structures. Bone will show little signal and brain and CSF will show a greater amount of signal. In order to selectively obtain image voxels (volume picture elements) of the subject, orthogonal magnetic gradients are applied. Although it is relatively common to apply gradients in the principal axes of a patient, MR allows flexible orientations for images. Magnetic gradients are generated by three orthogonal coils, oriented in the x, y and z directions. The scanners used in medicine have a typical magnetic field strength of 0.2 to 3 Teslas. On the image, the white pixels are called hyperintense, and the dark ones hypointense.

Different types of acquisition of MR imaging give different information. Here are some tips regarding some of these sequences:

- T1-weighted images give a lot of anatomical information as well as information about venous sinus permeability or pathologic blood. CSF is dark and fat is white in T1-weighted sequences. Lesions bright in T1-weighted sequences are: fat (lipoma, dermoid), subacute haemorrhage (metHb), metastatic melanoma (melanotic), protein-containing fluid (colloid cyst) and paramagnetic agents (gadolinium).
- T2-weighted images give information about oedema, arteries and sinus permeability. Water is white in T2-weighted sequences, fat appears intermediate to dark, and haematomas have a variable signal intensity. Some dark lesions on T2-weighted images are acute haemorrhage (deoxyHb), haemosiderin, iron and mucinous lesions. A proton density-weighted image is an image dependent primarily on the density of protons in the imaging volume. The higher the number of protons in a given unit of tissue, the brighter the signal is.
- Proton density-weighted images have excellent grey matter–white matter contrast, as their brain–CSF con-trast is much lower. It is good to study basal nuclei anatomy and differentiate lacunar infarctions from Virchow-Robin spaces, and to evaluate gliosis.
- FLAIR (fluid attenuation inversion recovery) is also called the “dark fluid technique”. It is used to remove the effects of fluid from the resulting images. Lesions that are normally covered by bright fluid signals on T2-weighted images are made visible by FLAIR. Its use is very common in many specific illnesses, and is very important in some of them, such as multiple sclerosis.
- Diffusion is the process by which molecules or other particles intermingle and migrate due to their random thermal motion. Diffusion-weighted imaging (DWI) is sensitive to diffusion, because the diffusion of water molecules along a field gradient reduces the MR signal. In areas of lower diffusion the signal loss is less intense and the display from these areas is brighter. This will show images in which areas of rapid proton diffusion can be distinguished from areas with slow diffusion. Multislice diffusion-weighted imaging is today a stan-dard for imaging brain infarction. The whole brain can be scanned within seconds. Certain illnesses show restrictions of diffusion, for example demyelinisation and cytotoxic oedema. Areas of cerebral infarction have decreased apparent diffusion, which results in...
increased signal intensity on diffusion-weighted MRI scans. Diffusion-weighted imaging has been demonstrated to be more sensitive for the early detection of stroke than standard pulse sequences.

If neoplastic illness is suspected, intravenous contrast administration is advised. Gadolinium is a non-iodinated contrast material that is hyperintense on T1-weighted images and hypointense on T2-weighted images. Normal intact blood–brain barrier is impermeable to injected contrast agents. Areas with impaired (e.g. tumour, infection, vascular anomaly) blood–brain barrier are permeable to contrast agents and show greater enhancement than normal areas.

It is also possible to evaluate blood flow and CSF flow, perform MR angiography and MR perfusion. Brain perfusion MR (BPMR) techniques for stroke and tumours and angio-MR techniques for intracranial and neck vessels are used on an everyday basis in most hospitals, although they are not as easily accessible as CT techniques in some smaller hospitals. It allows us to study the hemodynamics of the parenchyma, and indicate in which location biopsy of a neoplastic lesion is most likely to give higher diagnostic reliability, or to assess the functional status and viability of brain parenchyma in stroke patients (see Sect. 3.1.5.1.2.3 later in this chapter). Perfusion MRI techniques are sensitive to microscopic levels of blood flow. Contrast-enhanced relative cerebral blood volume (rCBV) is the most used type of perfusion imaging. Gadolinium is a suitable agent for perfusion imaging. The rapid passage of contrast agent through the capillary bed will induce a T2*-weighted MRI signal drop within a brain region caused by spin dephasing. The signal decrease is used to compute the relative perfusion to that region. Since the transit time of the bolus through the tissue is only a few seconds, high temporal resolution imaging is required to obtain sequential images during the wash-in and wash-out of the contrast material and, therefore, resolve the first pass of the tracer.

The basis of spectroscopy was discovered by Edward Purcell and Felix Bloch in 1946. Magnetic resonance spectroscopy (MRS) is an analytical tool, based on nuclei that have a spin (nuclei with an odd number of neutrons and/or protons) like 1H, 13C, 17O, 19F, 31P etc. Through nuclear magnetic principles such as precession, chemical shift etc., the analysis of the content, purity, and molecular structure of a sample is possible. The spectrum produced by this process contains a number of peaks; the highs and the positions of these peaks allow exact analysis. Unknown compounds can be matched against spectral libraries. Even very complex organic compounds such as enzymes and proteins can be determined. This information will allow differential diagnosis of different lesions, such as glioma, metastasis, meningioma, abscesses etc., depending on the metabolites found on the lesion.

3.1.5.1.4 Cerebral Angiography
Cerebral angiography was first performed by Egas Moniz in 1927. This is an alias of Antonio Caetano de Abreu Freire (1874, Avanca, Portugal). He was awarded the Nobel Prize in medicine in 1949 for his work in describing the effects of prefrontal leukotomy in psychotic patients. Out of a total of nine patients, he successfully obtained angiographic images of two, one of whom demonstrated a fatal complication of the procedure. It was first used to evaluate intracranial mass effect from intracranial neoplasm or oedema, or to diagnose ventricular enlargement or shift. Nowadays, it is used specifically to study brain vessels. This includes the study of sub-arachnoid haemorrhage and many vascular diseases, such as aneurysms, non-aneurysmal sub-arachnoid haemorrhage, dissections, arteriovenous malformations (AVMs) of the brain and spine, arteriovenous fistulas, vasculitis and other vascular diseases.

New possibilities arise from advances in materials as microcatheters, coils, stents, embolic agents, new balloons etc. Not only diagnosis, but also treatment can be achieved by endovascular means. Interventional neuroradiologists can now treat many illnesses, such as aneurysms, with a deposition of coils, close arteries or veins in order to treat aneurysms or dural fistulas with coils or balloons, treat epistaxis with embolic solid agents (particles), treat vasospasm after subarachnoid haemorrhage, close the feeders of brain AVMs with embolic liquid agents, or use direct intra-arterial fibrinolytic agents to treat thromboembolic events.

All this work is achieved more efficiently and the patient gains greater benefit when there is close team work between neuroradiologists, neurosurgeons, radiosurgeons and neurologists, as a combined treatment is often the best approach to some of these lesions. A very good example of this need for a combined approach is brain AVMs, as they can be (and often are) treated sequentially by neuroradiologists, neurosurgeons and radiosurgeons.

3.1.5.1.2 Key Imaging Findings in Main Cranial Pathologies

3.1.5.1.2.1 Cranial Trauma
Trauma is one of the most important causes of mortality and morbidity in the modern world. It is the leading cause of death in children and young adults in the United States, over 50% of them from head injury.

Computed tomography is very important in the evaluation of head trauma, and is the first technique to use. It is very fast (with an acquisition time of less than 1 min), very sensitive to blood and good for studying bones, air (pneumocephalus) and radiologically dense foreign bodies. To maximise the diagnostic capabilities of CT in cranial trauma the images should be reviewed in different windows.
to better visualise from narrower to wider windows early signs of stroke, parenchyma, blood and bone/air/fat.

### 3.1.5.1.2.1.1 Skull Fractures
Computed tomography is capable of diagnosing the three types of skull fractures, linear, depressed and diastatic. Specific reconstruction algorithms and filters will help to visualise linear and small fractures. Skull fractures may be associated with haematomas, contusions, pneumocephalus or foreign bodies, all of which can also be studied using CT. When there is an overlying scalp laceration leading to potential communication between the intracranial space and the environment, the fractures are called “open”. Otherwise they are called “closed”.

**Key imaging findings:**
- Conspicuous fractures need no explanation on how to diagnose them.
- For others, on normal CT slices look for air inside the skull (pneumocephalus), or lack of air where it should normally be, such as paranasal sinuses, mastoid cells, middle ear, or the external auditory canal.
- Providing there was no pathology prior to trauma, the liquid filling these spaces may be CSF or blood, which will be hyperdense to CSF.
- Look also for subdural/epidural haematomas or brain contusions.
- Then look for the fracture in the vicinity of these findings on thin-slice CT with a specific bone filter/reconstruction algorithm.
- You will see them as lines on bones without cortical bone.
- Differentiate them from normal sutures or nerve paths (they have cortical bone; if there is any doubt, check for the same line on the contralateral side).
- After that, check for associated lesions on parenchyma windows or nerve course disruption.
- Remember to check on the mandible, temporo-mandibular joint (TMJ) and the orbit.
- For the latter two it is better to use multi-planar reconstructions to study them on coronal, sagittal and oblique views.

### 3.1.5.1.2.1.2 Epidural Haematoma
Epidural haematoma (EDH) is a collection of blood between the skull and the dura, usually from arterial shear- ing, and rarely from veins/dural sinus.

**Key imaging findings:**
- A biconvex (lentiform) hyperdense mass between bone and brain.
- It displaces the brain tissue.
- It is bound by suture lines, and will only rarely cross them.
- It may cross the midline.
- These last two facilitate differential diagnosis with subdural haematoma.
- Usually unilateral (95%) and supratentorial (95%), and associated with fracture in 90%.

### 3.1.5.1.2.1.3 Subdural Haematoma
Subdural haematoma (SDH) is a collection of blood between the dura and the arachnoid. It is caused by the tearing of the bridging veins (often after acute changes in head velocity associated with parenchymal lesions). Chronic SDHs may occur without trauma or as a result of minor trauma, especially in an elderly patient.

**Key imaging findings:**
- A subdural haematoma is a crescent-shaped mass between the bone and brain and is often associated with other lesions (70%).
- The density will decrease approximately 1.5 h/day.
- It can cross sutures, but not the midline (it does not cross dural insertions).
- Always remember to check on the falx and the tentorium for small subdural haematomas.
- CT findings are different depending on the age of the bleeding:
  - Hyperacute SDH: heterogeneous (40%) or hyperdense (60%). If heterogeneous, the hypodense part represents CSF or unclotted blood (acute bleeding).
  - Acute SDH (several days): hyperdense.
  - Subacute SDH (2 days to 2 weeks): isodense to brain. Be careful with subacute SDHs; because they are isodense to brain, they can be missed. The way to differentiate them from brain and to diagnose them is to check that the grey matter and sulci are in touch with bone or CSF, and the grey–white matter union is not medially displaced. Otherwise, there may be interposed subacute SDHs. If in doubt, intravenous iodinated contrast can show displaced veins and the dural capsule.
  - Chronic SDH (weeks to months): it can be homogeneously hypodense; sometimes you can see a horizontal line separating hyperdense (inferior) and hypodense (superior) liquid in chronic SDHs in patients with anticoagulation treatment or coagulation illnesses, and heterogeneously hypo-/isodense, with trabeculae, and may be calcified. It can also be a heterogeneous mixture of hyper- and hypodensities if there is a chronic SDH with recurrent haemorrhage representing CSF or unclotted blood (acute bleeding).
  - Changes with age of the haematoma can also be observed as changes in the intensity of signal on MR, but this is not commonly used in an emergency setting, and its use for child abuse dating has been questioned by some authors.
3.1.5.1.2.1.4 Traumatic Subarachnoid Haemorrhage

Subarachnoid haemorrhage (SAH) is blood between the arachnoid membrane and the pia mater of the brain. It is present in most cases of moderate to severe head trauma, which is the most common cause of SAH.

Key imaging findings:
- Hyperdensity that follows the sulci over the cerebral convexities or (less commonly) in the CSF cisterns at the base of the brain.
- Always look in the interpeduncular cistern and occipital horns.
- Check in the vicinity of the SAH for fractures and for associated primary parenchymal brain injury such as contusions, which, together with the history of the trauma and the location of the SAH, will help in the differential diagnosis with SAH caused by aneurysm.

3.1.5.1.2.1.5 Primary Parenchymal Brain Injury

Primary injury is defined as the injury produced at the moment of trauma as a direct consequence of the traumatic force. Secondary lesions are usually a consequence of primary ones. Primary lesions are those of the scalp, fractures, extra-axial haemorrhages, direct vascular lesions and primary parenchymal brain injury. Primary parenchymal brain injury can be divided into diffuse axonal injury, cortical contusions, parenchymal haematomas and subcortical grey matter lesions.

3.1.5.1.2.1.5.1 Diffuse Axonal Injury

This pathological mechanism is a shearing injury to axons as a result of acceleration/deceleration or rotatory forces applied to the head. Typical locations of diffuse axonal injury (DAI) are at the grey–white junction, the corpus callosum, or the dorsolateral brainstem, fornix, basal nuclei, and the internal capsule.

Key imaging findings:
- Computed tomography is often normal, mostly in mild DAI.
- It can show mild brain oedema or micro-haemorrhage (20–50%) in the prior locations, or mass lesions (10%).
- If CT is normal, and the patient is neurologically impaired, MR should be performed.
- MR is more sensitive than CT in detecting DAI, which is better visualised on T2- and FLAIR-weighted images as multiple, poorly defined, hyperintense areas located in the white matter.
- On T2*-weighted images they will be hypointense.

3.1.5.1.2.1.5.2 Cortical Contusions

Cortical contusions are haemorrhages resulting from the brain hitting the skull. Therefore, they are frequently found at the frontal and temporal poles. They are often associated with depressed skull fractures and are the most common parenchymal lesions.

Key imaging findings:
- Early CT can be normal.
- On non-contrast CT they appear as heterogeneously hyperdense areas within the brain tissue, with blood and oedema.
- The oedema will become more conspicuous in further CTs.
- MR is more sensitive in diagnosing them.

3.1.5.1.2.1.5.3 Parenchymal Haematomas

Parenchymal haematomas are caused by the rupture of the small parenchymal vessels, and are not related to cortical contusions. They can occur some days after the trauma.

Key imaging findings:
- Hyperdense blood on the white matter of the frontal and temporal lobes or basal nuclei.

3.1.5.1.2.1.5.4 Grey Subcortical Matter Lesions

Grey subcortical matter lesions are odd primary brain injuries, caused by the rupture of the penetrating vessels. They are only seen in severe trauma.

Key imaging findings:
- Multiple petechial haemorrhages on basal nuclei (hyperdense on non-contrast CT).

3.1.5.1.2.2 Intracranial Haemorrhage

Intracranial haemorrhage (ICH) can occur as a result of many situations such as hypertension, haemorrhagic infarction (arterial or venous), ruptured cerebral aneurysm, AVM, arteriovenous dural fistulas, amyloid angiopathy, haemorrhagic tumours or cysts, encephalitis, trauma or vasculitis. CT is the image strategy to use, as it is easily accessible, fast, and sensitive to the presence or absence of blood.

3.1.5.1.2.2.1 Parenchymal Haematomas

Hypertensive, haemorrhagic infarction and tumours.

3.1.5.1.2.2.1.1 Hypertensive Haematomas

Hypertension is the most common cause of intracerebral haemorrhage in the adult population.

Key imaging findings:
- Hyperdensity is located in the basal ganglia, especially in the putamen, followed by the thalamus, pons, cerebellum, and subcortical white matter.
- You should ask the patient and family about hypertension history and check on CT for radiologic signs of hypertension such as lacunar infarctions and small vessel leukoencephalopathy.
3.1.5.1.2.1.2 Haemorrhagic Infarction

Haemorrhagic infarction can result from either arterial (5–15% within 48 h, caused by reperfusion) or venous infarcts.

**Key imaging findings:**
- On non-contrast CT, arterial infarction will show hypodensity with a vascular distribution caused by ischaemia, and hyperdensity if it is haemorrhagic.
- Venous infarcts demonstrate patchy areas of oedema (hypodense, hyperintense on T2-weighted and FLAIR images) that do not show vascular distribution; they are often bilateral and often associated with haemorrhages (hyperdense, hyperintense on T1-weighted images, hypointense T2-, T2*-weighted images).

3.1.5.1.2.1.3 Intracranial Haemorrhage

Intracranial tumours may present as ICH. Contributing factors include neovascularity, necrosis, direct vascular invasion, and a coagulopathic state. Primary tumours prone to haemorrhage include glioblastoma multiforme, oligodendroglioma, pituitary adenoma and haemangioblastoma. Metastases particularly prone to haemorrhage include melanoma, renal cell carcinoma and choriocarcinoma, as well as lung carcinoma.

**Key imaging findings:**
- Extensive oedema surrounding a haematoma should raise the suspicion that there may be an underlying lesion.
- Contrast CT or MRI should be performed in this situation and any known primary extracranial tumour should be checked for.

3.1.5.1.2.2 Subarachnoid Haemorrhage and Vascular Malformations, Aneurysms, Benign SAH, AVM, Cavernomas, Venous Angiomas, Capillary Telangiectasias

Intracranial vascular malformations are normally divided into four or five types, depending on whether or not you include aneurysms: aneurysms, AVMs, cavernous angiomas, capillary telangiectasias, and venous angiomas.

3.1.5.1.2.2.1 Aneurysms

A ruptured intracranial aneurysm is the most common cause of non-traumatic SAH. CT is the first imaging strategy for diagnosis of SAH. MRI is also useful for detecting acute subarachnoid haemorrhage, but it has a heterogeneous appearance on MRI sequences, depending on the age of the SAH; T2*-weighted sequences are very sensitive to blood. Once SAH is diagnosed, angiography should be performed. In some institutions, angiography is performed as soon as the SAH is diagnosed, as it is also a good diagnostic tool and will diagnose most aneurysms. MR angiography is also useful, mostly in evaluating the three-dimensional anatomy of giant aneurysms in relation to the brain or cranial nerves. If angio-CT and angio-MR are not available in your hospital, angiography should be performed as soon as possible. Angiography remains the gold standard for the diagnosis of cerebral aneurysm.

**Key imaging findings:**
- On non-contrast CT, acute SAH is hyperdense compared with brain.
- After 1 week, blood has cleared from the CSF and is therefore not visible on CT.
- Depending on the location of the SAH, the location of the aneurysm can be suspected: basal cisterns – aneurysms in the Circle of Willis, posterior communicating artery; Sylvian fissure – middle cerebral artery, terminal internal carotid, posterior communicating artery aneurysms; interhemispheric fissure – anterior cerebral and anterior communicating artery aneurysms; fourth ventricle – posterior inferior cerebellar artery aneurysms.
- The study of aneurysmatic SAH is better performed by angiography.
- Angiography should include both carotid and both vertebral arteries (called “four vessels angiography”), as well as the three communicating arteries (some authors call this “seven vessels angiography”).
- Information given should always include location, size and shape of the aneurysm, neck size, perforating arteries, possibility of collateral circulation, vasospasm, the possibility of more than one aneurysm and accessibility for treatment, endovascular or surgical based on proximal vessel status (internal carotid artery, common carotid artery), arteries arising from the sac of the aneurysm, the ratio dome–neck, etc. To determine which aneurysm has ruptured when multiple aneurysms are present, it is helpful to correlate aneurysm location with the clot location. Ruptured aneurysms tend to be larger, more irregular, or have outpouchings.

3.1.5.1.2.2.2 Benign, Perimesencephalic or Idiopathic SAH

Benign, perimesencephalic or idiopathic SAH – if no lesion is found on angiography, benign or idiopathic SAH is diagnosed.

**Key imaging findings:**
- Often located perimesencephalically, it is thought to be caused by venous rupture, probably due to thrombosis.
- They have a good prognosis.
- Always check for aneurysms, arteriovenous fistulas, AVMs, and dural fistulas of the cervical spine or spine tumours before diagnosing benign SAH.
3.1.5.1.2.2.2.3 Arteriovenous Malformations

Arteriovenous malformations (AVMs) are direct artery to vein fistulae. They are thought to cause haemorrhage at a rate of 4% per year. They usually have tortuous feeding arteries, a dense nidus, and large draining veins that may be seen on CT. AVMs may have associated feeding artery or venous drainage aneurysms secondary to the high flow. If the AVM is treated, these flow-related aneurysms will regress. AVMs most commonly present as an ICH or seizure and less commonly as a focal neurologic deficit from vascular steal or mass effect.

**Key imaging findings:**
- Arteriovenous malformations appear isodense on CT with occasional calcifications on non-contrast studies and enhancement of serpentine vessels after contrast administration.
- MRI will show flow voids, and is useful in defining the cerebral anatomy around the AVM as well as the oedema it is causing.
- The typical appearance of AVM on MRI is a tight "honeycomb" of flow-voids.
- If an AVM is suspected the patient should undergo cerebral angiography to define the number, location and size of the feeding arteries, the size and location of the nidus, the number and size of the draining veins-related aneurysms or stenosis and degree of fistulous component.
- All these items are important in deciding how to treat the AVM.

3.1.5.1.2.2.2.4 Cavernous Angiomas

Cavernous angiomas are composed of cystic vascular sinusoids lined with a vascular endothelium monolayer and no interposed neural tissue. They can present as haemorrhage (0.5% per year) or seizure.

**Key imaging findings:**
- The classic popcorn-like appearance on CT and MRI is caused by haemorrhage of multiple ages and calcification.
- There is often a classical haemosiderin ring (a hypointense ring on T2-weighted images).
- Cavernous angiomas have a very variable appearance.
- Always check on a T2* sequence to look for other cavernomas (seen as hypointense on T2*).
- They are angiographically not visible, slow-flow lesions, and show minimal or no enhancement.
- They are angiographically invisible.
- They are sometimes associated with venous angiomas.

3.1.5.1.2.2.2.2 Venous Angiomas

Venous angiomas are thought to be extreme variants of normality and do not bleed. Therefore, they should not be treated. They are collections of veins within the periventricular white matter that empty into a larger, transcortical draining vein.

**Key imaging findings:**
- They may not be visible on non-contrast CT, and subtle on MR, but appear as a tuft of vessels near the ventricle on contrast CT or MRI.
- Angiography shows normal arterial phase and venous structures with a "Medusa head" appearance.
- They are sometimes associated with cavernous angiomas, which are the ones supposed to be really responsible for the rare "bleeding venous angiomas" reported.
Often detected as subtle changes in cortical–subcortical (grey–white matter) differentiation or the very subtle effacement of the sulci. Occasionally, a hyperdense artery is visible or the basal nuclei become hypodense.

- Acute infarcts (12–24 h) will show loss of cortical–subcortical (grey–white matter) differentiation or sulcal effacement.
- At 24–72 h the infarct becomes a more defined, wedge-shaped hypodense area, and it becomes oedematous.
- At 4–7 days the infarct becomes more hypodense and will show gyral enhancement after contrast administration.
- Later scans (months to years) will show an area of encephalomalacia and volume loss.

Computed tomographic perfusion studies can delineate ischaemic zones, the infarct core (supposedly “dead”), “penumbra” and mismatch. In particular, significant ischaemic zones, the infarct core (supposedly “dead”), also called “tissue at risk”, as it is theoretically the salvageable parenchyma. Mismatch on BPCT is measured by comparing cerebral blood flow (ischaemic parenchyma) with cerebral blood volume (supposedly similar to diffusion, both supposedly dead parenchyma, although it has now been seen that it is not always dead).

Computed tomographic angiography can define the occlusion site, depict arterial dissection, grade collateral blood flow, and characterise atherosclerotic disease.

Computed tomography offers a number of practical advantages over other cerebral perfusion imaging methods, including its wide availability. Using perfusion CT and CT angiography to define new individualised strategies for acute reperfusion will allow more acute stroke patients to benefit from thrombolytic therapy.

Magnetic resonance imaging demonstrates hyperacute and acute infarction better than CT. Diffusion will be restricted almost from the beginning of ischaemia. MRI will show sulcal effacement and loss of grey–white differentiation at ≤12 h. From 12 to 24 h, the area of the infarct develops hyperintensity on T2-weighted images. Contrast enhancement of the affected parenchyma begins to appear at 24–72 h, and becomes more striking between days 4 and 7. MRI perfusion and diffusion studies can delineate ischaemic zones, penumbra and mismatch (between diffusion and perfusion). Diffusion is supposedly dead parenchyma, but recent experience shows that it is not always so.

Angiography plays an important role in ischemic cerebrovascular disease. It is the gold standard for diagnosing ischaemic disease of the main arteries. It may be used to treat patients with mechanical thrombus extraction techniques and intra-arterial thrombolytic agents in the hyperacute state. It can also be used to diagnose carotid extra- or intra-cranial stenosis and to decide the better treatment option (pharmacological, surgical or endovascular).

### 3.1.5.1.2.4 Intracranial Tumours

Describing the imaging characteristics of each type of brain tumour is beyond the scope of this discussion. Nevertheless, we will provide an overview of the characteristic imaging features of common primary brain tumours and metastatic tumours.

#### 3.1.5.1.2.4.1 Intra-Axial Tumours

Intra-axial tumours can be divided in primary and metastatic tumours. Primary tumours include gliomas (astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, oligodendroglioma, and ependymoma), tumours of neuronal origin, pineal region tumours and CNS lymphomas. Metastatic disease may affect not only the brain parenchyma, but also the leptomeninges and calvarium.

#### 3.1.5.1.2.4.1.1 Primary Tumours

##### 3.1.5.1.2.4.1.1.1 Gliomas

Gliomas represent approximately 40% of all intracranial tumours. Astrocytic tumours are the most common of the glial tumours. Typically, they are infiltrative or diffuse, but some specific subtypes are circumscribed. Infiltrative astrocytic tumours include astrocytomas, anaplastic astrocytomas, glioblastoma multiforme, oligodendroglioma and ependymoma. Circumscribed tumours of astrocytic origin include pilocytic astrocytomas and subependymal giant cell astrocytomas.

**Key imaging findings:**

- On non-contrast CT, gliomas may be evident only as white matter oedema or an ill-defined isodense white matter lesion.
- They are usually found supratentorially in adults, but more frequently infratentorially in children.
- With the addition of contrast, low-grade astrocytomas enhance poorly.
- Anaplastic astrocytomas and glioblastomas show stronger enhancement patterns and may have areas of heterogeneity.
- These high-grade gliomas often show spread of oedema or enhancement along white matter tracts such as the corpus callosum, which indicates infiltration of the tumour into normal brain.
- They may also show central areas of haemorrhage or necrosis. On MRI, low-grade astrocytomas are iso- or hypointense on T1-weighted images and homogeneously hyperintense on T2.
- They may show minimal to no enhancement with gadolinium.
- Anaplastic astrocytomas and glioblastoma multiforme are iso- to hypointense on T1 and heterogeneous on T2, with strong heterogeneous enhancement.
- The T2 signals are more sensitive to oedema, which often correlates with the degree of tumour infiltration.
3.1.5.1.2.4.1.1.2 Pilocytic Astrocytomas
Pilocytic astrocytomas are tumours of glial origin and are more common in children and young adults.

**Key imaging findings:**
- Well-circumscribed tumours located near the third or fourth ventricles that arise from the cerebellum and optic chiasm/hypothalamus.
- They frequently appear cystic with an enhancing, solid mural nodule, without surrounding oedema.
- The cyst is hypodense, hyperintense on T2-weighted and FLAIR images, and hyperintense to CSF on T1-weighted images.
- Check for leptomeningeal spread on contrast-enhanced MRI.

3.1.5.1.2.4.1.1.3 Oligodendrogliomas
Oligodendrogliomas are relatively slow-growing tumours arising from oligodendrocytes.

**Key imaging findings:**
- Heterogeneous, enhancing mass in the cerebral hemispheres (especially frontal lobes), often with calcification.

3.1.5.1.2.4.1.1.4 Ependymomas
Ependymomas are derived from ependymal cells, which line the ventricular system.

**Key imaging findings:**
- Most of these tumours are found infratentorially, arising in the fourth ventricle (<3 years old).
- The supratentorial ependymomas (>3 years old) are usually found outside the ventricular system and may resemble astrocytomas on imaging.
- Fourth ventricular ependymomas are isodense with some areas of hyperdensity representing calcification (50%) on non-contrast CT and mildly heterogeneous-ly enhancing on MRI.
- They appear to “fill” the ventricles, may extend up or down the fourth ventricle, and have a “plastic” appearance.
- They are iso/hypointense on T2-weighted MRI. Check for hydrocephalus, which occurs very often.

3.1.5.1.2.4.1.2 Metastases
Metastases represent one-quarter to one-third of all adult brain tumours. Common metastases to brain include lung, breast, melanoma, renal cell carcinoma, and gastrointestinal (GI), and genitourinary (GU) tumours. Between 60 and 85% of all metastases are multiple.

**Key imaging findings:**
- On non-contrast CT, metastases are iso- or hyperdense lesions usually found at the grey–white matter junction, but which can occur anywhere in the brain.
- With contrast administration, metastases will enhance either homogeneously or peripherally.
- On MRI, most metastases are hypointense on T1-weighted images, hyperintense on T2-weighted images and enhance with gadolinium in the same pattern as on CT.
- Cerebral metastasis should be considered first in the differential diagnosis of any patient with multiple lesions, since primary brain tumours are usually solitary.
- Extensive vasogenic oedema generally surrounds the tumour. If the metastases are haemorrhagic, you will have to consider them when you find parenchymal haematoma surrounded by extensive oedema.
- Metastases prone to being intra-axial are those from the lung, breast, melanoma and colon; extra-axial are usually those from the breast, lymphoma, prostate and neuroblastoma; and metastases that are haemorrhagic are melanoma and kidney, thyroid and choriocarcinoma.
- Although less common, a cerebral abscess may mimic metastases on imaging and should be ruled out either clinically or by biopsy, diffusion or spectroscopy.

3.1.5.1.2.4.2 Extra-Axial Tumours
The distinction between intra-axial and extra-axial tumours is important in surgical planning and prognosis. Extra-axial tumours are generally benign tumours, such as meningiomas, vestibular schwannomas, pituitary tumours, dermoids and epidermoids. Malignant extra-axial tumours include metastases, malignant meningioma, sarcoma and chordoma.

3.1.5.1.2.4.2.1 Meningiomas
Meningiomas are the most common primary intracranial tumour of non-glial origin. They are derived from arachnoidal cap cells and can be found on any surface carrying arachnoid tissue. The most common locations are the sagittal sinus (parasagittal), the cerebral convexity, the sphenoid ridge, the olfactory groove and the posterior fossa.

**Key imaging findings:**
- Plain skull films may show hyperostosis adjacent to a meningioma and dilated vascular channels leading to the tumour.
- CT will show a well-circumscribed, hyperdense mass that abuts the dura.
- Some meningiomas show calcification on CT and demonstrate peritumoral oedema.
- They enhance strongly with intravenous contrast.
- On MRI, meningiomas are isointense to brain, enhance strongly and often have a dural tail corresponding to the migration of tumour cells.
- Angiography can demonstrate an extracranial blood supply as well as parasitised pial vessels.
• There may be a persistent vascular blush.
• Angiography can help decide if presurgical embolisation for surgical comfort is safe and advisable.

3.1.5.1.2.4.2.2 Vestibular Schwannoma
Vestibular schwannoma, or acoustic neuroma, is a benign tumour arising from the nerve sheath of the vestibular portion of the eighth cranial nerve.

Key imaging findings:
• They are seen only in the cerebellopontine angle, often with extension into the internal acoustic canal (IAC).
• On CT they are iso- or hypodense and enhance strongly.
• The bone windows may show widening of the IAC. On MRI, vestibular schwannomas are well-circumscribed, enhancing masses that extend into the IAC.
• They are hyperintense on T2-weighted images.
• Meningiomas should be considered in the differential diagnosis: schwannomas are lesions centred on the IAC, with widening of the IAC, no dural tail, non-calcified, iso/hyperdense to brain and hyperintense on T2-weighted images; meningiomas have a dural tail, hyperostosis, they are isointense to cortex on T2-weighted images, calcified and are not centred on the IAC, with no widening of the IAC.

3.1.5.1.2.4.2.3 Pituitary Adenomas
Pituitary adenomas represent approximately 10% of all primary intracranial tumours. They are grouped into microadenomas (≤10 mm) and macroadenomas (>10 mm). Most adenomas are slow-growing and 50% are endocrinologically active, the most common type being the prolactinoma.

Key imaging findings:
• Microadenomas appear hypodense on contrast-enhanced CT and MRI because there is stronger enhancement of normal pituitary.
• Macroadenomas appear as isodense intra- and suprasellar masses that enhance strongly on CT and MRI.
• Cysts, haemorrhage, or necrosis may also be seen in the macroadenoma.

3.1.5.1.2.5 Hydrocephalus
Hydrocephalus is a condition in which the ventricles become enlarged and intracranial pressure becomes elevated. It is commonly divided into two types: communicating, which is due to the inability of the arachnoid granulations to adequately absorb CSF and non-communicating, which is caused by an obstruction of CSF flow within the ventricles. Communicating hydrocephalus may occur after subarachnoid haemorrhage if the subarachnoid blood and its by-products impair the function of the arachnoid villi. Nowadays, these concepts are changing, and hydrocephalus is supposedly caused by the abnormal pulsatility of CSF, which would explain why ventriculostomy may help in hydrocephalus treatment.

Key imaging findings:
• On non-contrast CT and MRI, these patients have symmetric enlargement of all ventricles, which is particularly noticeable in the third ventricle and temporal horns of the lateral ventricles.
• Non-communicating hydrocephalus may occur with intraventricular tumours or cysts.
• In these cases there is enlargement of the ventricles proximal to the occlusion and normal-sized ventricles distally.

3.1.5.1.2.6 Cerebral Abscess
Cerebral abscesses are foci of parenchymal bacterial infections that result from contiguous spread, direct inoculation, or haematogenous spread. Haematogenous spread from an extracranial site such as the lung often results in multiple lesions, whereas local spread from mastoid air cells or paranasal sinuses usually creates a solitary lesion.

Key imaging findings:
• The appearance on CT or MRI depends on the age of the abscess.
• In the early cerebritis stage of a cerebral absciss (3–5 days), CT or MRI may show a small, ill-defined area of mild enhancement at the grey–white interface.
• From 5 days to 2 weeks, the late cerebritis stage develops, and CT and MRI show a thin ring of enhancement around a necrotic centre. During the early and late capsule stages (weeks to months), a thicker, more defined ring of enhancement forms, with a surrounding area of oedema. On diffusion images it shows restriction (hyperintense).

Selected Reading

3.1.5.2 Electroencephalography
ANDE R S FUGLSANG-FREDERIKSEN,
PE T ER OR M HANSEN

Electroencephalography (EEG) is the recording of electrical activity generated in the cerebral cortex.

The signal is a summation of excitatory and inhibitory synaptic potentials on cortical neurones. These potentials
rely on the functionality of cortical neurones as well as afferent input to the cortex from subcortical structures, e.g. the thalamus. Abnormalities on the electroencephalogram may reflect either disturbance of cortical neurones or the subcortical input to cortical neurones.

Many abnormalities seen in the electroencephalogram are non-specific, as different diseases may produce similar EEG abnormalities. It is not possible from the scalp-recorded potentials to identify the mechanism disturbing the synaptic events responsible for abnormal EEG waves. Furthermore, electrical activity is not equally well recorded in every part of the brain: inter-hemispheric and mesial cerebral cortices, as well as the basal parts of the brain, are less responsive to the scalp electrodes than the cortex over the lateral convexities and potentials originating from the surface of the gyri are more readily recorded than those originating from the sulci. Consequently, a large cortical area must be involved in a disturbance in order to be shown on the electroencephalogram. In addition, electrical abnormalities may be of such low amplitude that scalp electrodes do not detect them.

Despite these limitations, some abnormalities seen on EEG are suggestive of specific diseases, e.g. epilepsy, metabolic encephalopathy and herpes encephalitis.

Approximately 20 electrodes placed symmetrically on the scalp in the midline and on both sides of the head in a standardised way (10–20 system) pick up the electrical signals. For standard purposes surface electrodes are often used, but needle or wire electrodes are used under certain circumstances. The recording electrodes are interconnected, and the potential difference between pairs (or groups) of electrodes is either printed on paper or digitised and stored for inspection.

The duration of standard EEG is 30–45 min. The patient is awake, but with eyes closed. Several provocations are applied to the patient in order to provoke EEG abnormalities not otherwise seen: stroboscopic flash stimulation (1–60 Hz), hyperventilation and sleep (or a doze). In patients with decreased consciousness, reactivity to applied stimuli (commands, eye opening, painful tactile stimuli) is tested.

The frequency of EEG activity is referred to as alpha activity if it is in the range 8–13 Hz. Activity with frequencies above 13 Hz is referred to as beta activity. Slow wave activity is known as theta activity when the frequency is within the range 4–7 Hz and as delta activity when it is below 4 Hz.

The electroencephalogram is traditionally displayed (or printed) as eight or 16 continuous graphs showing the spatial and temporal distribution of the electrical activity recorded. In the case of digital EEG, the arrangements of pairs (or groups) of electrodes can be changed during inspection in order to examine different parts of the cerebral cortex and elucidate various aspects of its electrical activity.

The normal EEG has an amplitude of 10–100 μV. Frequency varies according to different activities. In the adult who is awake, 8–13 Hz activity is seen. Eye opening, drowsiness and mental activity attenuate the activity. Activity above 13 Hz may normally be seen in the frontal regions and is more pronounced in patients receiving, for example, benzodiazepines. Small amounts of activity ranging from 4 to 7 Hz are normally seen in the temporal regions, especially in children, young people and after the age of 50–60 years. Activity below 4 Hz is not normally seen in adults except during the deeper stages of sleep. In newborn and young children low frequency activity dominates, but disappears with maturation.

The abnormal EEG is characterised by either low amplitude of background activity, excessive slow activity (<8 Hz) or spikes and sharp waves (high amplitude potentials of short duration). Abnormal EEG activity may appear focal, diffuse or generalised.

Low amplitude indicates cortical disturbance. When localised it may correlate to atrophy, porencephaly and subdural haematoma. General attenuation of amplitude is associated with more diffuse depression of cortical activity, as seen in degenerative brain disorders and following cerebral anoxia. In its most pronounced form no electrocerebral activity is recorded, which may support the diagnosis of brain death.

Focal slow waves correlate to a localised brain lesion, e.g. tumour, infarct and haemorrhage. When the slow activity is more diffusely distributed, disturbance of afferent input to cortical neurones, as seen following lesions in the posterior fossa or hydrocephalus, may be suspected. In encephalopathy, e.g. encephalitis, slow waves are often seen to be diffuse or generalised.

Spikes and sharp waves are seen in patients suffering epilepsy – either during seizure or inter-ictally. They may appear generalised, often followed by a high amplitude slow wave as in absence epilepsy or during generalised tonic-clonic seizures. Localised spikes and sharp waves may be suggestive of a focal cortical lesion, e.g. tumour, infarct or abscess, but can also be seen without any structural lesion. Spikes may be seen in complex discharges appearing repetitively in one hemisphere (periodic lateralised epileptiform discharges, PLEDs) which may be associated with a hemisphere lesion, e.g. tumour, infarct, metabolic encephalopathy and herpes encephalitis.

3.1.5.2.1 Clinical Application

Electroencephalography is a dynamic examination in which brain function is measured over time. It may detect abnormalities not necessarily related to structural lesions in the brain, as in encephalitis, encephalopathy and idiopathic epilepsy, where MRI and CT may not show abnormalities. Compared with other tests of brain physiology (e.g. functional MRI and positron emission
tomography), EEG has a much shorter temporal delay (a few milliseconds). EEG is readily available and has relatively few resource requirements. Technologists have to be trained to place electrodes correctly and to detect and eliminate artefacts. High quality recording, in addition to systematic and rational interpretation of the electroencephalogram, is also of critical importance to the usefulness of EEG.

Electroencephalography is intended to answer specific questions about the brain function and is not just a screening procedure, and so clinical information on the patient and a precisely formulated questionnaire need to be available in order to design the EEG examination and to interpret the encephalogram.

### 3.1.5.2.2 Epilepsy

Electroencephalography is used to classify different types of epilepsy in order to optimise medical treatment and to make a prognosis. Most electroencephalograms of patients with suspected epilepsy are not obtained during a seizure, but electrical abnormalities are often found inter-ictally. However, inter-ictal findings have to be interpreted with care, as there is only a vague correlation with the recurrence of the seizures. Some patients, with a doubtless clinical diagnosis of epilepsy, show normal electroencephalograms, even on repeated examination. The abnormalities seen in epilepsy are spikes and sharp waves in addition to increased slow wave activity. These latter findings are non-specific, and are also seen in encephalopathy, brain tumour, migraine and following head trauma, and therefore need to be interpreted together with clinical information. In order to precisely locate cortical epileptic foci prior to epilepsy surgery, EEG may be performed after craniotomy with specialised electrodes on the surface of the brain (electrocorticography).

### 3.1.5.2.3 Focal Brain Lesions

Electroencephalography is no longer central in the diagnosis of focal brain lesions, as imaging techniques have developed and spread widely. The role of EEG is to detect neuronal electrical dysfunction in the absence of (macroscopic) structural lesions, as well as to assess dysfunction created by known lesions (e.g. electrocorticography is done as intraoperative monitoring to search for epileptic foci in the vicinity of a cortical tumour, in order to include the electrically abnormal cortex in the removal). The abnormalities seen in focal brain lesions are slow focal activity, with or without spike activity. The changes are non-specific, but a focal lesion is particularly suspected when slow wave activity occurs continuously with variable amplitude and shape, and if it is present both in the waking and sleeping states. Brain tumours are electrically quiet, and associated EEG abnormalities are localised to the adjacent non-neoplastic, transformed brain tissue. Abnormalities are caused by destruction of the neurone by tumour growth or by metabolic changes induced by changes in blood flow. More diffuse EEG changes are seen in patients with increased intracerebral pressure and hydrocephalus. After head trauma, transitory generalised slowing of the background activity is frequently seen. If the changes persist, it suggests a cerebral contusion even if no structural abnormalities are seen on CT. During the first 3 months, it is not possible from the EEG to predict whether or not post-traumatic epilepsy will develop. In subdural haematoma low amplitude background activity may be seen unilaterally.

### 3.1.5.2.4 Decreased Consciousness

In comatose patients, EEG can provide useful prognostic information and detect potentially treatable causes. EEG is useful to determine whether or not apparent decreased consciousness may be caused by reasons other than altered brain electrophysiology, i.e. psychogenic mechanisms or locked-in syndrome. EEG can also be utilised to evaluate the extent of pathology causing impaired consciousness (focal, multifocal or diffuse). In addition, EEG is often applied to prove progress in cerebral function, despite minor or no change in the clinical evaluation, as electrophysiological improvements may precede clinical betterment. Moreover, EEG may recognise epileptic activity in patients with impaired consciousness, e.g. non-convulsive seizures or “status epilepticus” and periodic discharges (e.g. PLEDs). Non-convulsive status epilepticus is a condition that is often overlooked in neurosurgical intensive care units, and is associated with a worse outcome. About 20% of patients in neurosurgical intensive care units because of moderate to severe head trauma may develop convulsive and non-convulsive seizures during the first 2 weeks. The non-convulsive seizures are not detected if an electroencephalographic examination is not performed. This raises the question of continuous electroencephalographic recording in intensive care units to diagnose potentially treatable conditions, which, if left untreated, will worsen the neurological condition, e.g. non-convulsive seizure and cerebral ischaemia at a reversible stage. Continuous electroencephalographic recording in intensive care units also implies the possibility of directing the depth of anaesthesia in, for example, patients with head injury.

In comatose patients, the EEG may contain prognostic data, as poor outcome is associated with alpha coma, burst suppression and periodic discharges. Alpha coma is the appearance in a comatose patient of rhythmic activity of normal frequency (8–13 Hz), often with maximal amplitude frontally, but showing no reactivity to eye opening or other stimuli. Burst suppression indicates generalised bursts of slow wave activity of high amplitude, with or
3.1 Basics

3.1.5.2.7 Brain Death

Brain death is the clinical diagnosis of irreversible loss of brain function. On EEG brain death is characterised by electrocerebral inactivity. Electrocerebral inactivity is non-specific, and is also seen in, for example, severe hypothermia and overdose of CNS depressants. In the right clinical context, electrocerebral inactivity supports the brain death diagnosis. Therefore, similar to other EEG abnormalities, clinical information must be taken into consideration when an EEG is interpreted.

Suggested Reading


3.1.5.3 Evoked Potentials and Their Use in Neurosurgical Practice

JAN JAKOB A. MOOIJ, H.L. JOURNÉE

3.1.5.3.1 Introduction

- Evoked potentials form a variety of induced neurophysiological responses that can evaluate the function of certain specific components of the central and/or peripheral nervous system. Therefore, they can be used in the diagnostic work-up of various neurological symptoms and diseases.
- In neurosurgical practice, they are useful for the monitoring of certain functions that are at risk during surgical procedures.
- Intraoperative monitoring in general is based on the reversibility of “events”, abnormal values that are recognised during such monitoring; reversibility means that there is a time frame during which measures can ideally be taken to restore the system back to normal. A well-known example is the constant measurement of blood pressure during surgery, where on the detection of deviating values measures are taken to restore the pressure immediately by adapting fluid delivery, drug application etc.
- In a comparable way, evoked potentials measurement can be used as a specific monitoring tool during neu-
rosurgery, but also during other kinds of surgery, like scoliosis surgery or thoraco-abdominal vascular surgery.

- The various evoked potentials that are currently in use for this purpose will be dealt with in this chapter.

### 3.1.5.3.2 Somatosensory Evoked Potentials

Somatosensory evoked potentials (SSEPs) are elicited by electrically stimulating a peripheral nerve – mostly the median nerve at the wrist and/or the tibial nerve at the ankle – and recorded on the scalp in the sensory area. In the case of median nerve stimulation, responses can also be recorded for the neck area (see Fig. 3.1.9).

In order to obtain responses, an averaging technique is necessary, using 50–300 stimuli; this takes time, 30 s to 3 min, which means that changes are detected with a delay. With the SSEPs one measures the conduction along the peripheral nerves, dorsal columns and central sensory pathways of the nervous system. The conduction time of action potentials from the neck to the scalp is defined as the central conduction time (CCT).

Intraoperative SSEP measurements are used in brain surgery (aneurysms, tumours, cortical surface mapping, posterior fossa/brain stem procedures), in surgery involving the spinal cord (tumours, vascular malformations) and the vertebral column (scoliosis, reconstructions) [1, 2]. In thoraco-abdominal vascular surgery the spinal cord can be at risk as well, due to interference with the vascular supply to the cord, which is the reason why SSEPs are also used in these procedures in some centres [3–6].

![Fig. 3.1.9 Set-up of somatosensory evoked potentials (SSEP) monitoring. Stimulation electrodes are placed on the median nerve at the wrist, or on the posterior tibial nerve at the ankle. Stimulation is usually performed with 200-μs wide rectangular monophasic pulses of 20–30 mA at a rate of 2–4 Hz. Details of the parameters are given in Table 3.1.1. Recording electrodes are mounted on the scalp, C3 and C4 for median nerve stimulation, and C'z for tibial nerve stimulation, with the position Fz as a reference. A dorsally placed neck electrode detects a locally generated positive peak, P14. The central conduction time (cct) is defined as the time difference between the negative cortical peak, N20, measured at C3 or C4, and P14. The cct is usually 5.5 ms and depends markedly on the temperature. Between 50 and 300 signals have to be averaged in order to obtain a clear response wave. Continuous stimulation can be performed, especially during periods of risk, leading to a continuous update of the averaged signal, called running averaging.](image-url)
When “events” are detected (see above) the surgeon and the anaesthetist can react, for example by raising the blood pressure, by relaxing retractors, removing temporary clips or by changing the position and angle of the vertebral column.

The reliability of the method depends on the aim of the monitoring. Only the sensory system is tested; thus, inadvertent immanent or permanent damage to the motor system cannot be detected [7, 8].

Somatosensory evoked potentials signals are sensitive to anaesthetic drugs; therefore, no inhalation anaesthesia should be used, and it is important to have stable anaesthesia and baseline recordings with adequate setting of stimulus and recording parameters in each individual patient. The operating room is not very “monitoring friendly”; which means that interference with for example 50- or 60-Hz electromagnetic waves may disturb or lengthen the averaging process. This results in less reliable monitoring.

Some basic values for SSEP monitoring are given in Table 3.1.1. An example of intraoperative SSEP monitoring is shown in Fig. 3.1.10.

### 3.1.5.3.3 Motor Evoked Potentials

Motor evoked potentials (MEPs) are elicited by the transcranial stimulation of axons in the corticospinal tract, and are recorded by the transcutaneous or intramuscular measurement of muscle action potentials in relevant muscles. The stimulation can be performed magnetically or electrically. Magnetic stimulation is used in patients who are awake for diagnostic work-up in the clinical neurophysiology unit. In the intraoperative situation, magnetic stimulation is cumbersome. Instead, transcutaneous needle electrodes and electrical stimulation can easily be used with a patient under anaesthesia, while such stimulation hurts in the patient who is awake. This is called transcranial electrical stimulation (TES). Opinions differ with regard to what is stimulated when: proximal axons of the motor neurones of the pyramidal track, more distal parts of the axons, or association fibres in the cortex as well. This will depend on the strength of the stimulation, the montage and the polarity of the electrodes [9–12].

For the muscle recording a set of four to eight muscles is chosen, in the arm and leg. Depending on the situation, other muscles (facial, for example) can also be monitored. With MEPs there is a one-to-one relationship between stimulus and response. The stimulus needs to consist of a train of four to seven pulses, with a short inter-pulse interval (see Table 3.1.1). There is hardly any delay between the “event”, when it occurs, and the recording of it, as long as frequent stimulation is performed.

Besides recording from the muscles, it is also possible to record from the spinal cord, epidurally, depending on the surgery and the accessibility of that area. These responses are called D-waves (from “direct”). The setting and mounting of the electrodes is shown in Fig. 3.1.11.

Motor evoked potentials monitoring is used in cranial and spinal surgery as with SSEP monitoring. The technique provides direct information on the motor system and is therefore most appropriate when the motor system is at risk. Combined monitoring with SSEPs can easily be performed, thus providing information on both the sensory and motor tracts.

Motor evoked potentials are, like SSEPs, sensitive to anaesthetic agents, especially the volatile ones. Moreover, muscle relaxants have to be used very carefully; with no relaxant there might be unacceptable movement of the patient, and with normal relaxation there will be no

| Table 3.1.1 | Generalised settings and warning criteria for the intraoperative use of evoked potential modalities. The montage choice of transcranial electrical stimulation (TES) electrodes depends on the type of surgery. SSEP somatosensory evoked potentials, MEP motor evoked potentials, BAEP brainstem auditory evoked potentials |
|-------------|-------------------------------------------------|------------------|-----------------|-----------------|
| **Stimulation** | **Recording electrodes** | **Warning levels** |
| | | **Amplitude from baseline** | | **Latency increase** |
| | | * absolute criterium* | | |
| SSEP | Arm | Median nerve | Contralateral C3 or C4 | Fz | <50% [2] | >10% |
| | Leg | Tibial nerve | Cz | | |
| MEP | mMEP (by TES) | D-wave | Muscle belly | Epidural electrode contact | Proximal Distal |
| | | | <20% [16] | <50% [17] | |
| BAEP | Ear phones | Ipsilateral A1 or A2 | Cz | | 0.6 and 1.0 ms [14] |
muscle response at all. Therefore, the setting of a baseline response with stable anaesthesia is very important. In the case of unacceptable movement, partial but stable relaxation levels may be considered. Achieving this can be time-consuming, and the reliability of motor potentials monitoring may be affected. Good interaction among the physiologist, anaesthetist and surgeon is mandatory for successful MEP monitoring and for rendering it a useful and reliable tool.

Basic values for MEP monitoring are given in Table 3.1.1. An example of intraoperative MEP monitoring is given in Fig. 3.1.12.

### 3.1.5.3.4 Visual Evoked Potentials

Visual evoked potentials (VEPs) are elicited by stimuli to the eyes, and recorded through surface or needle electrodes on the occipital scalp.

The stimulus can be shown as a flash, or as an alternating chequerboard image. The latter can only be applied in a patient who is awake. Similar to the SSEP, the set-up needs an averaging technique, with 200–300 stimuli given at 1–2 Hz. VEP measurements are routinely used in the clinical neurophysiologic units for diagnostic purposes in several neurological or ophthalmologic entities, for example, when multiple sclerosis is suspected. Actually, the whole visual system, from the retina to the occipital cortex, is included and tested [2].

In a surgical situation with patients under anaesthesia, flash stimuli can be delivered through closed eyelids using goggles with built-in LED devices. Unfortunately, the VEPs (three typical peaks) can be so variable and unstable – primarily due to the anaesthetics – that they may show too many false-positive and -negative changes, making them unreliable. Therefore, most practitioners who have been using intraoperative VEPs (mainly for anterior base procedures) have stopped the application of VEP monitoring. Therefore, we will not show any details or examples here.
Brainstem Auditory Evoked Potentials

Brainstem auditory evoked potentials (BAEPs) are elicited by auditory input – clicks – to the external auditory canal, and recorded by electrodes on the earlobes (Fig. 3.1.13). The recordings are difficult and need an averaging of 1,000–3,000 signals. The click rates used (at a hearing level of 70–100 dB) are between 10 and 30 pulses per second; thus, responses are ideally obtained at between 30 and 300 s. BAEPs give information about the whole auditory system, which comprises conduction to the inner ear, the cochlea, the cochlear nerve and the central auditory pathways. With optimal filtering techniques, five waves can usually be discerned (see Fig. 3.1.13). Each stands for a specific part of the neuronal pathway that is being checked.

Brainstem auditory evoked potentials are used in patients who are awake for testing and differentiating among various types of hearing loss. Intraoperative monitoring by BAEPs is used in surgery for acoustic tumours, and procedures in the posterior fossa where the brainstem is involved or at risk [2, 13–15]. Some centres have experience with direct recordings on the cochlear nerve, which bypasses the need for averaging. In that situation, however, only the first part of the neuronal acoustic pathway is monitored.

Sensitivity to interference by anaesthetics is comparable to that in MEP and SSEP monitoring. With the use
of total intravenous anaesthesia (TIVA) it should not be a problem. However, in many patients with acoustic tumours and preoperative hearing loss, the potentials are difficult or impossible to obtain. Moreover, the cochlear nerve is more vulnerable to manipulation than any other nerve, which makes reversibility in the case of “events” more problematic, and less accessible for useful monitoring. Indirect trauma, by cerebellar retraction for example, is however easily detected and mostly reversible, making BAEP monitoring especially useful for surgery in the posterior fossa where the cochlear nerve itself is not involved directly. Settings for BAEP monitoring are shown in Table 3.1.1.

**Selected Reading**


3.1.5.4 Radionuclide Imaging Studies

JAN ABRAHAMSEN

Nuclear medicine is often used to study cerebral physiology, while radiological examinations (MRI and CT) are most often used for anatomical studies.

3.1.5.4.1 Gamma Camera Scintigraphy (SPECT) and PET Scanning

For the purpose of nuclear medicine examinations, radioactive isotopes (radionuclides) are used. Due to their nuclear instability, they decay in different ways (for instance with gamma-ray radiation or positron emission).

Most studies of the cerebral are made tomographically with a rotating camera (Fig. 3.1.14). This technique is either called single photon emission computed tomography (SPECT), referring to the most often used radionuclide, $^{99m}$Tc (a single photon emitter) or positron emission tomography (PET) referring to the isotopes decaying by positron emission.

3.1.5.4.2 Radionuclides for PET

The detection of gamma rays from the annihilation process originating from the collision of a positron with an electron is made by a PET scanner. The most commonly used positron emitters are oxygen ($^{15}$O), carbon ($^{11}$C), nitrogen ($^{13}$N) and fluorine ($^{18}$F). These radionuclides are produced by a cyclotron. The cyclotron and PET scanners are not currently available in all departments of nuclear medicine. The PET radionuclides provide the possibility to measure blood flow quantitatively in different regions of the brain. With the $^{15}$O, the oxygen metabolism can be measured, e.g. the metabolic rate for oxygen. Such studies have been used to predict the survival of patients with cerebral gliomas.

3.1.5.4.3 Radionuclides for SPECT

The radionuclides most commonly used for cerebral studies are technetium ($^{99m}$Tc), iodide ($^{131}$I), xenon ($^{133}$Xe) and thallium ($^{201}$TI), which all decay with the emission of...
gamma rays to be detected by the SPECT gamma camera (Fig. 3.1.14).

A molybdenum/technetium generator is delivered to departments of nuclear medicine each week. The ready availability of $^{99m}$Tc at a reasonable cost from such a generator combined with the physical characteristics both for imaging and dosimetry makes $^{99m}$Tc superior to any other radionuclide. The use of $^{99m}$Tc-labelled agent is therefore often requested.

The radionuclides are in one way or another combined with a target-seeking molecule. The target could be the cerebral cells, receptors, or membrane transporters. Thus, the radionuclides are used as tracers, which give the possibility to trace the target-seeking molecule. For instance, in order to evaluate cerebral perfusion, $^{99m}$Tc is incorporated into a molecule passing through the blood–brain barrier and accumulating in the cerebral cells.

### 3.1.5.4.4 Measurement of Cerebral Blood Flow

The two most widely used tracers for regional cerebral blood flow (rCBF) studies are $^{99m}$Tc-labelled hexamethylpropylene amine oxime ($^{99m}$Tc-HMPAO; Fig. 3.1.15) and $^{99m}$Tc-labelled ethylcysteinate dimer ($^{99m}$Tc-ECD). For both these lipophilic labelled agents the mechanism of retention in the brain is the conversion to more hydrophilic compounds, trapping them in the brain tissue.

The rCBF studies are especially valuable in examinations for stroke, transitory cerebral ischaemia (TCI), dementia, epilepsy and Alzheimer’s disease. This physiological test (rCBF) often demonstrates changes prior to anatomic changes. To study the cerebral haemodynamic, two perfusion studies (one with and one without Diamox®) are needed. Diamox dilates cerebral vessels and may give rise to a steal phenomenon. By comparison with an rCBF study without added Diamox, a cerebral perfusion reserve can be detected. The territory at risk of stroke can be estimated by using this Diamox test (Fig. 3.1.16).

Quantitative CBF studies are also valuable as preoperative mapping of, for instance, the language centre prior to removal of a nearby tumour. For quantitative assessment of cerebral blood flow, $^{133}$Xe (Fig. 3.1.16) or the PET tracer $H_2^{15}$O is used.

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**Fig. 3.1.14** Gamma camera with single photon emission computed tomography (SPECT) possibilities. Rotating two-headed gamma camera

**Fig. 3.1.15** Regional cerebral blood flow using the $^{99m}$Tc-labelled hexamethylpropylene amine oxime (HMPAO)
3.1.5.4.5 Radionuclide Demonstration of Brain Tumours

Cells that depend on glucose metabolism are easily visualised with \(^{18}\)F-1 labelled deoxyglucose (\(^{18}\)FDG) due to their high glucose turnover. The metabolism in tumours can thus be shown by giving \(^{18}\)FDG intravenously. Furthermore, the brain itself is dependent on glucose metabolism. It is, however, possible to visualise a cerebral tumour even when the background metabolism is high. In particular, postoperatively and after radiation therapy, it is difficult to evaluate MRI and CT scans due to tissue scarring. A residual tumour or a recurrence will depend on glucose metabolism, while scar tissue will show only a limited glucose uptake. \(^{18}\)FDG will thus show a still viable tumour amongst the scar tissue (Fig. 3.1.17).

Cerebral infection will also have a high glucose turnover. It may thus be difficult to differentiate between cerebral tumours and abscesses.

3.1.5.4.6 Neuroreceptor Imaging

Both ligands for SPECT and PET imaging are available. For several years it has been possible to obtain imaging receptors for dopamine, serotonin, histamine, benzodiazepine, morphine, acetylcholine (muscarnergic, nicotinergic), noradrenaline, amino acids (GABA), steroids, purines and somatostatins, as well as several other neuropeptides. A huge variety of radiolabelled agonists and antagonists have been developed for the purpose of studying the localisation and in some cases the functions of these receptors.

Given the high number of radiolabelled receptor ligands it has been possible to study clinical entities such as Alzheimer’s disease, epilepsy, Parkinson’s disease (Fig. 3.1.18), depression, alcoholism, Gilles de la Tourette syndrome, schizophrenia, tardive dyskinesia, neografting of foetal mesencephalic tissue, olivopontocerebellar atrophy, panic disorders etc.

Neurotransmitter transporters for dopamine (Fig. 3.1.18) and serotonin have also been labelled with radionuclides, as have some neurotransmitter enzymes.

3.1.5.4.7 SPECT/CT and PET/CT, in Contrast to MRI and PET

At present, most new scanners are combinations of either SPECT/CT or PET/CT. These new possibilities create a combination of physiology and anatomy. MRI is especially appropriate for anatomic brain investigations and even better than CT. A combination of PET and MRI would be a very strong new tool for diagnosing cerebral tumours. For the time being, however, PET and MRI data are acquired with two scanners and a combined image is obtained by image fusion (Fig. 3.1.18). However, a combination of PET/MRI has recently been introduced. No validated clinical examinations have yet been reported using this new combination of scanners. It seems evident that molecular imaging, i.e. visualising molecular structures, will attract much attention in years to come. With the combined techniques (SPECT/CT, PET/CT, PET/MRI) molecular processes can be referred to the correct anatomic localisation. This will bring hope for a better understanding of the underlying pathophysiology of cerebral diseases.
3.1.5 Cerebral Diagnostics

Acknowledgements

The author would like to thank the Rigshospitalet in Copenhagen, Denmark for providing the images.

Selected Reading


Fig. 3.1.17a–c  Magnetic resonance imaging (MRI), positron emission tomography (PET) and MRI-PET image fusion. a Tumour recidive: MRI. b Tumour recidive: PET. c Tumour recidive, image fusion MRI-PET

Fig. 3.1.18  Parkinson’s disease: the presynaptic dopamine transporters are labelled with $^{123}$I-ioflupane (DaTSCAN) showing the caudate and putamen. Increasing severity (a–d) of Parkinson’s disease is shown
3.1.5.5  Cerebrospinal Fluid Diagnostics

FLEMMING GJERRIS

3.1.5.5.1  Basics

Even if the use of computed tomography and high-resolution magnetic resonance imaging is expanding, analysis of the cerebrospinal fluid (CSF) by a lumbar or ventricular puncture is still an important investigation in many different neurosurgical and neurological conditions.

3.1.5.5.2  The Cerebrospinal Fluid

3.1.5.5.2.1  Anatomy of the CSF Pathways

The anatomy is well known. CSF flows caudally in the ventricular system [6, 7]. The ciliary movements of the ependyma, the respiratory and arterial pulsations, and the pressure gradients between the ventricular and subarachnoid system and the venous side of the sinuses result in a flow of CSF. The driving forces for these pressure gradients are probably created by the continuous CSF formation and maintained by the arterial pressure pulsations of the brain (the CSF pump). The CSF ends up in the arachnoid villi or around the brain capillaries.

3.1.5.5.2.2  CSF Formation

The main production site of CSF (70–80%) is the choroid plexus in the two lateral, the third and the fourth ventricles. The choroidal formation is either a filtration across the endothelial capillary wall or an active secretion (sodium and bicarbonate) by the choroidal epithelium. The CSF formation is influenced by aquaporine1, enzyme inhibitors, the autonomic nervous system and the choroidal blood flow. The extrachoroidal part of CSF begins as interstitial fluid seeping away from the brain either transependymal to the ventricles or transspinal to the intracranial and intraspinal subarachnoid spaces [7]. The CSF formation rate is about 0.35 ml/min, a total of 500 ml/day, and may be inhibited by steroids, acetazolamide, diuretics, low temperature and changes in CSF osmolality. Humans have the highest overall rate of formation of CSF of all species.

3.1.5.5.2.3  CSF Composition and Volume

Cerebrospinal fluid resembles an ultrafiltrate of plasma, and the concentration of the single solute (protein, transmitter etc.) differs very much in the different CSF compartments [6]. Cranio-caudal gradients (even gradients in the opposite direction) exist for different proteins, amines and neuro-transmitters, which makes it difficult to interpret data based on concentrations measured at the lumbar level [6]. Intracranial CSF volumes are linked intimately to the formation rate, circulation and resistance to CSF outflow (Rout) and with factors such as intracranial pressure (ICP) and the dimensions of the brain. Measurements of the CSF volume in vivo using the MR technique in normal persons produce a total CSF volume ranging from 57 to 286 ml. The total CSF volume increases with age in both sexes, mostly as an increase in the cortical sulcal volume. The ventricular CSF volume ranges between 6.8 and 30 ml and correlates with the total CSF volume. The intracranial pressure (ICP) is normally maintained by the resistance factor of CSF outflow [6, 7]. An increased amount of CSF (hydrocephalus) presupposes a reverse volume change in one of the other intracranial volumes, the so-called Monro–Kellie doctrine.

3.1.5.5.2.4  CSF Absorption

The CSF is either absorbed through the arachnoid villi to the brain sinuses [6, 7], along the spinal (15%) villi, through the brain capillaries [9], helped by the recently discovered aquaporins, probably aquaporin4 [7, 18], or via a lymphatic route in animals [13]. There is a linear relationship between CSF absorption and ICP, and CSF absorption depends on the transvillus or the transcapillary pressure gradients. It is possible, that the aquaporins, besides facilitating the water absorption, may also work against a pressure gradient, which may explain the resorption through the capillaries in patients with hydrocephalus or increased intracranial pressure.

3.1.5.5.2.5  Resistance to CSF Outflow

The resistance of CSF outflow (Rout) can be measured by isotope dilution methods or by bolus, infusion or perfusion techniques [6, 7, 18]. Humans have the lowest outflow resistance of all species. Rout measurements can be used for evaluation of shunting in patients with hydrocephalus and idiopathic intracranial hypertension [6, 18].

3.1.5.5.3  Lumbar Puncture

The techniques of lumbar and ventricular puncture are described, together with the macroscopic findings, which are important for neurosurgeons. Laboratory analyses of CSF can be found in various textbooks or review papers [1–4, 8, 10–12, 14, 16]. The indications and contraindications for lumbar puncture are clear. The technique of lumbar puncture is simple, but withdrawal of CSF can still be dangerous, even fatal, and in many cases the diagnostic information acquired is limited. A lumbar puncture should be carried out if specific information is expected from the CSF analysis for the present disease. It should no longer be used for diagnostic purposes in patients with brain tumours or subdural haematomas.

3.1.5.5.3.1  Contraindications

The contraindications, although very clear, are still disregarded with surprising regularity.
3.1.5.3.1.1 Local Infection
Infected small lesions near the puncture site can be transferred in to the meninges.

3.1.5.3.1.2 Elevated ICP (Fresh Bilateral Papilloedema)
Persistent ignorance of this rule sooner or later causes fatalities from brain herniation. Symptoms and signs suggesting a space-occupying process, e.g. a tumour in the posterior fossa, might give incipient brain stem compression, whether there is papilloedema or not. This should be suspected when there is intense headache, drowsiness, vomiting, slowing of the pulse rate, neck stiffness or episodes of faintness, and should be ruled out by CT or MRI before lumbar puncture. Patients with papilloedema, but with no space-occupying brain lesion, are not in danger, i.e. idiopathic intracranial hypertension, subarachnoid haemorrhage and meningeal carcinomatosis of a lumbar puncture [6, 7].

3.1.5.3.2 Technique (Recommended European Standard)
For a normal diagnostic procedure the patient should lie flat on his side with his back at the edge of the bed (Fig. 3.1.19 [15]). The iliac crests must be maintained vertically above each other. The body is slightly curled up (flexion of the hips and knees) to separate the spinous processes and a line is drawn, joining the tops of the iliac crests. It usually intersects at the L3–L4 or L4–L5 space. Mark the space, clean the skin aseptically and use local anaesthesia with a fine needle in the skin and the interspinous ligament. Wait at least 2 min and many painful lumbar punctures are avoided. Remember to tell the patient that piercing the dura may cause a stab of pain. Introduce a 20- to 22-gauge needle (an atraumatic cannula with a special tip) with the stiletto exactly in the midline and in between two spinal processes, and pointing slightly towards the head of the patient. Push the needle with the cutting edge in a cranio-caudal direction to minimise the cut in the dura (Fig. 3.1.19) slowly, but firmly, forwards. A characteristic jerk is felt as the needle enters the dura, usually at a depth of 5–6 cm. Push the needle a further 2–3 mm inwards, withdraw the stiletto and allow a few drops of CSF to escape. When the fluid is obtained the pressure monitor is attached. Remember to replace the stiletto before removing the needle to avoid unintentional crushing of a nerve root, and never use a syringe to withdraw CSF.

3.1.5.5.3.3 The Pressure
Variations in the pressure of pulsations and respiration are seen. The normal pressure is below 200 mm of water or 15 mmHg and CSF should flow out of the cannula freely on coughing and abdominal pressure. The pressure is low below a complete spinal block and a block at the foramen magnum. A high pressure is commonly due to tension or abdominal compression in an obese patient. Queckenstedt’s test is no longer of any use.

3.1.5.5.3.4 Complications
The most common complication is the so-called post lumbar puncture syndrome, which occurs in up to 30% of cases and includes back pain, headache, nausea and dizziness. It usually continues for 3–5 days, but can persist for months. Bed rest (24–48 h) with the legs elevated usually has an effect in some cases, but the most effective treatment is an epidural blood patch.

3.1.5.5.4 Cisternal and Ventricular Puncture

3.1.5.5.4.1 Cisternal Puncture
Cisternal puncture is an uncommon procedure today. It is mostly used when CSF examination is vital and lumbar puncture has failed. The contraindications are the same as for lumbar puncture, and the procedure should only be carried out by specially trained personnel.

3.1.5.5.4.2 Ventricular Puncture
This procedure is only in use in neurosurgical clinics or intensive care units, often as a standard procedure for ICP monitoring. The technique is mentioned in Chap. 3.2.8. [5], Fig. 3.2.80.

3.1.5.5.5 CSF Composition During Normal and Pathological Conditions

3.1.5.5.5.1 Appearance and Blood Pigment
Allow CSF to drip slowly into one or two tubes, usually between 5 and 10 ml and look at it, first held up to the light, and then against a white coat. Normal CSF is clear

Fig. 3.1.19 Lumbar puncture. Position of the patient and anatomical demonstration of the structures passed by the lumbar puncture needle; drawing by Bo Jespersen [15]
and colourless like tap water. During pathological conditions it can be cloudy, bloody or xanthochromic. A cloudy fluid is seen with an increase in the cell count above 200–400/μl. A smoky or “snowy” appearance may be due to large numbers of red cells. The blood-stained fluid of the first few drops is mostly due to lesions of the local veins during the puncture. If the fluid remains equally blood-stained, it probably indicates an acute subarachnoid haemorrhage. The CSF must be centrifuged immediately. If the supernatant fluid is colourless this is unlikely to be anything, but traumatic or very near to the peak of the SAH. CSF usually turns out to be xanthochromic in SAH 6–12 h after the time of the bleeding, caused by breakdown products from the haemoglobin. It can also be seen in CSF with a high content of protein (neurinoma, Guillain–Barré syndrome). If the collected CSF clots, it is often caused by pure blood from a traumatic puncture or a very high proteinous fluid content. Blood in CSF caused by a stabbing lumbar puncture, repeated lumbar punctures or myelography results in an increase in the white cell count, which may persist for up to 2–3 weeks.

Some common findings in neurological and neurosurgical diseases are shown in Table 3.1.2.

### Table 3.1.2 Cerebrospinal fluid findings in normalcy and common neurosurgical and neurological diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Appearance</th>
<th>Pressure</th>
<th>Cell contents</th>
<th>Protein</th>
<th>Sugar</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear, colourless</td>
<td>Normal</td>
<td>0–3 leucocytes, 0 erythrocytes</td>
<td>0.30–0.85 g/l</td>
<td>⅓–⅔ of fasting</td>
<td>Leucocytes may increase</td>
</tr>
<tr>
<td>SAH</td>
<td>Bloody, yellow</td>
<td>Increased</td>
<td>Many red and white cells</td>
<td>Slightly increased</td>
<td>Normal</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Purulent meningitis</td>
<td>Yellowish, cloudy</td>
<td>Increased</td>
<td>Polymorphonuclear cells. &gt; 3,000</td>
<td>Increased</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Mononuclear meningitis</td>
<td>Clear or slightly opalescent</td>
<td>Normal or increased</td>
<td>Many monocytes</td>
<td>Slightly increased</td>
<td>Normal</td>
<td>Possible virus</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>Clear or slightly opalescent</td>
<td>Increased</td>
<td>Normal or slightly increased</td>
<td>Normal or slightly increased</td>
<td>Normal or decreased</td>
<td>Meningeal symptoms when breakthrough to ventricular system</td>
</tr>
<tr>
<td>IIH</td>
<td>Clear, colourless</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Spinal tumour; below block of CSF space</td>
<td>Yellowish, spontaneous coagulating</td>
<td>Normal or low</td>
<td>Normal</td>
<td>Drastically increased</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Polyradiculitis</td>
<td>Clear, colourless</td>
<td>Normal</td>
<td>Normal, few leucocytes</td>
<td>Normal or slightly increased</td>
<td>Increased after days</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Clear, colourless</td>
<td>Normal</td>
<td>Normal, a few leucocytes</td>
<td>Normal or slightly increased</td>
<td>Normal</td>
<td>Oligoclonal IgG bands</td>
</tr>
</tbody>
</table>
Selected Reading

3.2 Brain Tumors

3.2.1 Classification and Biology of Brain Tumors

H.D. Mennel

3.2.1.1 Introduction

The classification of brain tumors has had a long history. Both general pathology and neurosurgery have influenced the description and classification of tumors of the nervous system. Whereas neurosurgery attempts to “classify” tumors for practical reasons, pathology offer general rules for doing so.

Early attempts were made on the histogenetic level due to the collaboration between Percival Bailey and Harvey Cushing, but the emphasis was soon changed to the outcome of the patients. Thus, the prognosis has been one of the leading viewpoints of classification since the beginning [1].

Therefore, as well as the histogenetic considerations, different grading systems were established, mainly in the years between 1949 and 1960 [2–4]. Thereafter, the work of the WHO unified the concepts and nomenclature, gathering together different groups of experts. The results of these initiatives were presented in three issues of the WHO Classification of Brain Tumors, the last edition being in 2007 [5–8]. Few tumors have been added to this 2007 edition.

The different entities of this WHO classification are shown in Table 3.2.1. In addition to the WHO classification based on descriptive morphology, a sort of grading system has been added that provides some indications regarding the mean postoperative course of individual tumors. The latest draft includes a rearrangement of entities, especially in the group of gliomas, which are now arranged according to increasing grades (of malignancy). More recent developments have changed our attitude toward brain tumor biology in many respects. The advent of immunohistochemistry brought new insight into his-

Table 3.2.1 List of tumor entities following the WHO classification, 2007 draft [8]

<table>
<thead>
<tr>
<th>TUMOURS OF NEUROEPITHELIAL TISSUE</th>
<th>Other neuroepithelial tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Astrocytic tumours</em></td>
<td></td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Astroblastoma</td>
</tr>
<tr>
<td>– Pilomyxoid astrocytoma</td>
<td>Chordoid glioma of the third ventricle</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>Angiocentric glioma</td>
</tr>
<tr>
<td>Pleomorphic xanthoastrocytoma</td>
<td></td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td></td>
</tr>
<tr>
<td>– Fibrillary astrocytoma</td>
<td></td>
</tr>
<tr>
<td>– Gemistocytic astrocytoma</td>
<td></td>
</tr>
<tr>
<td>– Protoplasmic astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td></td>
</tr>
<tr>
<td>– Giant cell glioblastoma</td>
<td></td>
</tr>
<tr>
<td>– Gliosarcoma</td>
<td></td>
</tr>
<tr>
<td>Gliomatosis cerebri</td>
<td></td>
</tr>
<tr>
<td><em>Other neuroepithelial tumours</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuronal and mixed neuronal-glial tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)</td>
<td></td>
</tr>
<tr>
<td>Desmoplastic infantile astrocytoma/ganglioglioma</td>
<td></td>
</tr>
<tr>
<td>Dysembryoplastic neuroepithelial tumour</td>
<td></td>
</tr>
<tr>
<td>Gangliocytoma</td>
<td></td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td></td>
</tr>
<tr>
<td>Anaplastic ganglioglioma</td>
<td></td>
</tr>
<tr>
<td>Central neurocytoma</td>
<td></td>
</tr>
<tr>
<td>Extraventricular neurocytoma</td>
<td></td>
</tr>
<tr>
<td>Cerebellar liponeurocytoma</td>
<td></td>
</tr>
</tbody>
</table>
### Tumours of Neuroepithelial Tissue

<table>
<thead>
<tr>
<th>Oligodendroglial Tumours</th>
<th>Papillary glioneuronal tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendroglioma</td>
<td>Rosette-forming glioneuronal tumour of the fourth ventricle</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td><strong>Oligoastrocytic Tumours</strong></td>
<td><strong>Tumours of the pineal region</strong></td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td>Pineocytoma</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>Pineal parenchymal tumour of intermediate differentiation</td>
</tr>
<tr>
<td><strong>Ependymal Tumours</strong></td>
<td><strong>Embryonal Tumours</strong></td>
</tr>
<tr>
<td>Subependymoma</td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>– Desmoplastic/nodular medulloblastoma</td>
</tr>
<tr>
<td>– Cellular</td>
<td>– Medulloblastoma with extensive nodularity</td>
</tr>
<tr>
<td>– Papillary</td>
<td>– Anaplastic medulloblastoma</td>
</tr>
<tr>
<td>– Clear cell</td>
<td>– Large cell medulloblastoma</td>
</tr>
<tr>
<td>– Tanycytic</td>
<td>CNS primitive neuroectodermal tumour</td>
</tr>
<tr>
<td>Anaplastic ependymoma</td>
<td>– CNS Neuroblastoma</td>
</tr>
<tr>
<td><strong>Choroid Plexus Tumours</strong></td>
<td>– CNS Ganglioneuroblastoma</td>
</tr>
<tr>
<td>Choroid plexus papilloma</td>
<td>– Medulloepithelioma</td>
</tr>
<tr>
<td>Atypical choroid plexus papilloma</td>
<td>– Ependymoblastoma</td>
</tr>
<tr>
<td>Choroid plexus carcinoma</td>
<td>Atypical teratoid/rhabdoid tumour</td>
</tr>
</tbody>
</table>

### Tumours of Cranial and Paraspinal Nerves

<table>
<thead>
<tr>
<th>Schwannoma (neurilemmoma, neurinoma)</th>
<th>Malignant peripheral nerve sheath tumours (MPNST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Cellular</td>
<td>– Epithelioid MPNST</td>
</tr>
<tr>
<td>– Plexiform</td>
<td>– MPNST with mesenchymal differentiation</td>
</tr>
<tr>
<td>– Melanotic</td>
<td>– Melanotic MPNST</td>
</tr>
<tr>
<td>Neurofibroma</td>
<td>– MPNST with glandular differentiation</td>
</tr>
<tr>
<td>– Plexiform</td>
<td></td>
</tr>
<tr>
<td>Perineurioma</td>
<td></td>
</tr>
<tr>
<td>– Perineurioma, NOS</td>
<td></td>
</tr>
<tr>
<td>– Malignant perineurioma</td>
<td></td>
</tr>
</tbody>
</table>

### Tumours of the Meninges

<table>
<thead>
<tr>
<th>Tumours of Meningothelial Cells</th>
<th>Mesenchymal Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningioma</td>
<td>Lipoma</td>
</tr>
<tr>
<td>– Meningothelial</td>
<td>Angiolioma</td>
</tr>
<tr>
<td>– Fibrous (fibroblastic)</td>
<td>Hibernoma</td>
</tr>
</tbody>
</table>
### Tumours of the Meninges

<table>
<thead>
<tr>
<th>Classification</th>
<th>Tumour Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitional (mixed)</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Psammomatous</td>
<td>Solitary fibrous tumour</td>
</tr>
<tr>
<td>Angiomatous</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Microcystic</td>
<td>Malignant fibrous histiocytoma</td>
</tr>
<tr>
<td>Secretory</td>
<td>Leiomyoma</td>
</tr>
<tr>
<td>Lymphoplasmacyte-rich</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Metaplastic</td>
<td>Rhabdomyoma</td>
</tr>
<tr>
<td>Chordoid</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Clear cell</td>
<td>Chondroma</td>
</tr>
<tr>
<td>Atypical</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Papillary</td>
<td>Osteoma</td>
</tr>
<tr>
<td>Rhabdoid</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Anaplastic (malignant)</td>
<td>Osteochondroma</td>
</tr>
<tr>
<td></td>
<td>Haemangioma</td>
</tr>
</tbody>
</table>

#### Primary melanocytic lesions

- Diffuse melanocytosis
- Melanocytoma
- Malignant melanoma
- Meningeal melanomatosis

#### Other neoplasms related to the meninges

- Haemangioblastoma

### Lymphomas and Haematopoietic Neoplasms

- Malignant lymphomas
- Plasmacytoma
- Granulocytic sarcoma

### Germ Cell Tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinoma</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td>Yolk sac tumour</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Teratoma</td>
</tr>
<tr>
<td>– Mature</td>
</tr>
<tr>
<td>– Immature</td>
</tr>
<tr>
<td>– Teratoma with malignant...</td>
</tr>
<tr>
<td>Mixed germ cell tumour</td>
</tr>
</tbody>
</table>

### Tumours of the Sellar Region

<table>
<thead>
<tr>
<th>Tumour Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniopharyngioma</td>
</tr>
<tr>
<td>– Adamantinomatous</td>
</tr>
<tr>
<td>– Papillary</td>
</tr>
<tr>
<td>Granular cell tumour</td>
</tr>
<tr>
<td>Pituicytoma</td>
</tr>
<tr>
<td>Spindle cell oncocytoma of the adenohypophysis</td>
</tr>
</tbody>
</table>

### Metastatic Tumours
3.2 Brain Tumors

3.2.1.2 Morphology, Prognosis, and Clinical Malignancy

Early descriptions led to a nomenclature that is still broadly used today, despite the ongoing changes in concepts and names. Thus, increasing anaplasia has been thought to push back the line of differentiation that is achieved stepwise during ontogenesis. Many expressions such as glioblastoma, neuroblastoma, medulloepithelioma, and medulloblastoma have been coined following this line of thinking. The underlying dogma maintains that higher anaplasia (dedifferentiation) means increased malignancy. This general rule of descriptive oncology is only partly true, has numerous exceptions, and is particularly difficult under special conditions such as tumor growth within the intracranial space [14].

Therefore, a more pragmatic approach proved to be necessary and successful. The "biologic" connotation of the nomenclature had to be abandoned in parts and empirical definitions of biological entities established instead. The situation is even more complicated, because in intracranial tumor growth, biological "intrinsic" behavior and so-called clinical malignancy interact much more than in other locations in the field of oncology. Thus, the prognostic considerations are based on both clinical and pathological information. In therapy studies over the last few years, the high impact of clinical data (in addition to grading by morphology) became obvious [15]. However, conventional morphology, nowadays enriched by immunohistochemical markers of tissue derivation and proliferation estimation, contributes greatly to the evaluation of the patients' general prognosis.

Particularly in supratentorial gliomas in adults, increasing anaplasia can be found both on the cellular and the tissular level. This anaplasia has been known as "cellular and tissular pleomorphism." It led to the introduction of the group of "pleomorphic gliomas" (today anaplastic astrocytoma, oligodendroglioma, and mixed glioma), which is intermediate between the glioma, with a better prognosis, and the malignant glioblastoma [16]. Cellular pleomorphism means varying sizes and forms of nuclei and cells. Anaplastic gliomas exhibit a wide range of pleomorphic cells up to the formation of giant cells. Tissular pleomorphism is defined as the increasing formation of neovascularization and the occurrence of necrotic areas typically seen in glioblastomas. Thus, in adult supratentorial gliomas, by increasing cellular and architectural pleomorphism (anaplasia) three grades can be easily distinguished and roughly correlated with mean postoperative survival [17]. A simplified survey of adult supratentorial gliomas, with grades and mean postoperative survival figures, is shown in Table 3.2.2.

The general idea behind this sort of approach to grading tumors is that other intracranial new growths, by their natural course, can be compared with the three grades of supratentorial gliomas of the adult and thus receive a corresponding – or in the case of benign behavior – an even lower grade, i.e., grade I. The latter holds true for childhood glioma, formerly known as (polar) spongioblastoma, today called pilocytic astrocytoma. Historically, this grading with mixed morphological and clinical

<table>
<thead>
<tr>
<th>GRADE</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYTOLOGY</td>
<td>Isomorphic</td>
<td>Pleomorphic</td>
<td>Pleomorphic</td>
</tr>
<tr>
<td>HISTOLOGY</td>
<td>Isomorphic</td>
<td>Vascular</td>
<td>Vascular</td>
</tr>
<tr>
<td>ENTITIES</td>
<td>Astrocytoma</td>
<td>Anaplastic</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Astrocytoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oligodendroglioma</td>
<td>Anaplastic</td>
<td>– Oligodendroglioma</td>
</tr>
<tr>
<td></td>
<td>Mixed Glioma</td>
<td>Anaplastic</td>
<td>– Mixed Glioma</td>
</tr>
<tr>
<td>SURVIVAL (YEARS)</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 3.2.3 Survival chart of the different intracranial tumors. Nomenclature and scheme according to Zülch [16]

<table>
<thead>
<tr>
<th>Degree of malignancy</th>
<th>Prognosis after “total” removal</th>
<th>Tumors</th>
<th>Extracerebral</th>
<th>Intracerebral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I benign</td>
<td>Cure or at least survival time of 5 or more years</td>
<td>Neurilemmoma, Meningioma, Craniopharyngioma, Pituitary adenoma, Others</td>
<td>Astrocytoma, pilocytic, Ependymoma of the ventricles, Choroid plexus papilloma, Gangliocytoma (temporalbasal), Hemangioblastoma</td>
<td></td>
</tr>
<tr>
<td>Grade II semibenign</td>
<td>Postoperative survival time: 3–5 years</td>
<td>Neurilemmoma, anaplastic Meningioma, anaplastic</td>
<td>Astrocytoma, Oligodendroglioma, Ependymoma (cerebral, extraventricular), Choroid plexus papilloma, Ganglioglioma</td>
<td></td>
</tr>
<tr>
<td>Grade III relatively malignant</td>
<td>Postoperative survival time: 2–3 years</td>
<td>Pituitary adenocarcinoma, Meningioma, anaplastic “Neurosarcoma”</td>
<td>Astrocytoma, anaplastic Oligodendroglioma, anaplastic Ependymoma, anaplastic Gangliocytoma, anaplastic Germinoma</td>
<td></td>
</tr>
<tr>
<td>Grade IV highly malignant</td>
<td>Postoperative survival time: 6–15 months</td>
<td>Sarcomas and other highly malignant local extensions</td>
<td>Glioblastoma, Medulloblastoma, Sarcoma, primary</td>
<td></td>
</tr>
</tbody>
</table>

viewpoints was introduced by K.J. Zülch. He established a chart of mean survival periods for different intracranial tumors and attributed four grades, but avoided forcing every entity into one of them. This chart is shown in Table 3.2.3 [4, 5, 18]. Similar systems had been developed previously [2]. In particular, the three-grade scheme by Ringertz [3] acknowledged the fact that gliomas (and ependymomas) develop stepwise into glioblastomas. The (re)discovery of the concept of secondary glioblastoma and the genetic cascade of events that accompany the different steps have confirmed the earlier notion of increasing pleomorphism in gliomas [18].

Since its first draft in 1979, the WHO classification has also introduced [5] a modified four-grade system for many intracranial tumors; however, this is optional at this time. The latest edition gives grades for almost all tumors and stresses the continuous evolution of secondary glioblastoma as well as that of oligodendrogliomas and meningiomas of increasing malignancy [7, 8].

3.2.1.3 Genetics

The true indicator of benign or malignant behavior must be found in genetic alterations that are obviously much closer to the proliferation apparatus than the derived phenotypic features. One of the intracranial tumor entities has been a first candidate for genetic changes; namely, the meningioma, which presented alterations in the rough number of chromosomes. The first investigation showed that chromosome 22 was involved, a chromosome that played a role in the hereditary tumor syndrome of von Recklinghausen’s disease [19]. Accordingly, spontaneous meningiomas may exhibit mutations of different sorts in the NF 2 gene on chromosome 22q, which is considered to act as a suppressor [20]. Several other genetic loci in meningiomas are affected as well, but there are some indications that few are associated with increased malignancy. Thus, it has become possible to conceive a tentative stepwise progression toward more aggressiveness on the
A very similar chart of events in tumor progression was established for the secondary glioblastoma. This term was coined for clinical and also morphological reasons in 1940 by H. J. Scherer [21]. Its real occurrence has only been corroborated with the advent of molecular genetics, despite the fact that some histological differences may be found, especially regarding the extent of ischemic necroses [22]. In addition, there are possible clinical differences concerning the age at onset and the clinical course, but the most striking distinction between the more frequent primary (de novo) glioblastoma and the glioblastoma that arises through malignant changes of more benign astrocytomas concerns the genetic level. Thus, EGF-R overexpression or amplification is the hallmark of de novo growing glioblastomas, whereas in secondary glioblastoma, a cascade of genetic events is reached step by step [18]. Table 3.2.5 illustrates this.

### Table 3.2.4

Tentative list of genetic events in meningioma of different grades [7]

<table>
<thead>
<tr>
<th>Arachnoidal cell</th>
<th>NF2 mutation/loss 22q</th>
</tr>
</thead>
</table>
| Meningioma, grade I | Losses of 1p, 6q, 10q, 14q, 18q  
Gains of 1q, 9q, 12q, 15q, 17q, 20q |
| Atypical meningioma, grade II | Losses of 6q, 9p, 10q, 14q  
Amplification 17q  
Rare mutations TP53, PTEN |
| Anaplastic (malignant) meningioma grade III |

### Table 3.2.5

Genetic evolution in primary and secondary glioblastoma [8]

<table>
<thead>
<tr>
<th>Differentiated astrocytes or precursor cells</th>
<th>Low-grade astrocytoma</th>
<th>TP53 mutation (59%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO grade II</td>
<td>5.1 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anaplastic astrocytoma</th>
<th>TP53 mutation (53%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO grade III</td>
<td>1.9 years</td>
</tr>
</tbody>
</table>

| Secondary glioblastoma | LOH 10q (63%)  
EGFR amplification (8%)  
P16\textsuperscript{INK4a} deletion (19%)  
TP53 mutation (65%)  
PTEN mutation (4%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO grade IV</td>
<td>5% of cases</td>
</tr>
</tbody>
</table>

| Primary glioblastoma (de novo) | LOH 10q (70%)  
EGFR amplification (36%)  
P16\textsuperscript{INK4a} deletion (31%)  
TP53 mutation (28%)  
PTEN mutation (25%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical history</td>
<td>95% of cases</td>
</tr>
</tbody>
</table>
| < 3 months 68%  
< 6 months 84% |
3.2.1 Classification and Biology of Brain Tumors

In particular, the evolutionary steps of astrocytomas undergoing anaplasia to become the highly malignant glioblastoma form the basis of the above-mentioned increasing pleomorphism of the supratentorial gliomas in the adult. Consequently, the benign childhood glioma, the pilocytic astrocytoma, has no genetic similarity to the molecular findings shown above. Obviously, p53 mutation, so common in adult diffuse astrocytoma, does not play a significant role in pilocytic astrocytoma [23].

It must be mentioned that familial tumor syndromes have long been known to involve the central and peripheral nervous system. It is beyond the scope of this presentation to go into details regarding genetic data of both sporadic and familial nervous system tumors. It should be pointed out, however, that the most widely known syndromes, neurofibromatosis types 1 and 2 (mutations in the gene NF1 on chromosome 17q11 and NF2 on 22q12), von Hippel–Lindau syndrome (mutation on the VHL gene on chromosome 3p25) and tuberous sclerosis (two altered genes TSC1 and 2 on 9p34 and 16p13), and others, have contributed greatly to our better understanding of the pathogenesis of tumor growth and initiation.

3.2.1.4 Single Entities

3.2.1.4.1 Pilocytic Astrocytoma

Pilocytic astrocytoma is an astrocytic tumor that constitutes about 5% of intracranial tumors; it occurs preferentially in young people in midline sites. Synonyms are (uni)polar spongioblastoma, juvenile astrocytoma, and Bergstrand tumor. In the cerebellum the tumor can usually be removed, whereas in other locations of the midline such as the chiasma opticum, thalamus, and brain stem there may be difficulties. Growth within the spinal cord is also possible (so-called glial rod).

Pilocytic astrocytoma is classified grade I in the WHO classification. Malignant change has been described, but seems to be extremely rare (Fig. 3.2.1). Pilocytic astrocytoma may, however, be a good example of diverging biological and clinical malignancy.

Pilocytic astrocytoma may be grossly firm or cystic depending on the site of growth. It is composed of bipolar astrocytes that taper into curly glial fibers (pilocytic = hairy cells). If looser growth is possible, multipolar cells may be formed. Usually, the tumor is rich in glial fibers. The cytological hallmark of the tumor is the so-called Rosenthal fiber, a degenerated glial fiber product. The corresponding formations are known as the "granulated bodies" and are also considered as sequelae of glial degeneration. Regressive changes such as small calcifications and the formation of larger cysts occur. Often, there is considerable variability in newly formed vasculature, which, together with some cellular pleomorphism, may give the impression of aggressiveness; this (moderate) anaplasia, however, is not a sign of greater malignancy. A variant with a marked mucoid matrix has been described and was recently named pilomyxoid astrocytoma. Its biological behavior is obviously more aggressive (grade II) than that of the common pilocytic astrocytoma (grade I).

3.2.1.4.2 Diffuse Astrocytomas

Diffuse astrocytomas are supratentorial gliomas that occur in earlier adulthood. They account for 5–10% of intracranial new growths. A slight male preponderance has been noted. Astrocytomas are firm tumors; some of them form abundant minute cysts.

These tumors receive grade II in the WHO classification. With this grading a recurrence-free interval of about 5 years is to be expected. There are slightly differing prognoses concerning the subgroups (see below), but all behave in such a way that their grouping as grade II seems most appropriate.

Fibrillary, protoplasmic, and gemistocytic diffuse astrocytomas can be distinguished according to their cytology. Fibrillary astrocytomas are of low cell density, with naked nuclei embedded within a loose glial fiber network. This variety often forms small cysts, when the meshes of the network rupture (Fig. 3.2.2). There are many small capillaries; mitoses are typically absent. In the protoplasmic variant the somata of the astrocytes, in addition to their extensions, are visible with aniline dyes, with impregnation, and with immunohistochemistry (Fig. 3.2.3). Gemistocytic astrocytomas contain a wealth of huge cells with abundant cytoplasm and coarse fibers (Fig. 3.2.4). In the latter tumors, some vascular proliferation may be seen. The pleomorphic xanthoastrocytoma may have very variegated features resembling the glioblastoma, but has a favorable prognosis (grade II).
Fig. 3.2.2a, b Diffuse adult fibrillary astrocytomas most often grow in a loose network and may form small, microscopically visible cysts that in this case are surrounded by tumor cells with very slender astrocytic processes.

Fig. 3.2.3 Protoplasmic astrocytomas exhibit well recognizable cellular shapes and coarse glial fibrils.

Fig. 3.2.4a, b Gemistocytic astrocytomas are full of large cells with eosinophilic cytoplasm (a). These tumors invariably express the astrocytic marker glial fibrillary acidic protein (GFAP) (b).
3.2.1.4.3 Oligodendrogliomas
One to five percent of intracranial tumors are thought to be oligodendrogliomas, with an age peak of about 40 years and, again, a slight prevalence of the male. These tumors are mostly found in the cerebral hemispheres, occasionally extending into the cerebral cortex. The cyto logical picture is very uniform. Cells have small round dark nuclei that are situated in the center of small holes; the whole arrangement is known as “honeycomb” formation (Fig. 3.2.5). This tumor tends to form calcifications that can even be visible on conventional X-rays.

Oligodendrogliomas are classed as grade II in the WHO classification. Recurrence free-intervals are generally 5 years or more, and a good response with regard to certain drug protocols has been reported [24].

Mixed gliomas contain both astrocytic and oligodendroglial cells to variable extents. Since a considerable proportion of the oligodendroglial component confers a better prognosis and chemotherapy sensitivity, the composition of mixed glioma has to be analyzed skillfully.

3.2.1.4.4 Anaplastic Gliomas
Anaplastic gliomas may be considered intermediate between diffuse (isomorphic) gliomas and the highly anaplastic glioblastoma (multiforme). Pleomorphic (pleomorphic) glioma is a synonym emphasizing the variegation in cellularity and histology. Anaplastic gliomas comprise anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic mixed gliomas. The clinical course and epidemiological data, as well as the gross localization, are thought to be intermediate between diffuse glioma and glioblastoma.

The hallmark of anaplastic gliomas are variegated cell shapes and increased newly formed vasculature. The cellular pleomorphism is marked by the variable size and shape of the tumor cells (Fig. 3.2.6); giant cells may be formed. Mitoses and their pathological forms occur. Otherwise, anaplastic gliomas show the histological criteria of their more benign counterparts. Vascular proliferation may be present in anaplastic gliomas; in anaplastic oligodendrogliomas in particular the occurrence of microvascular proliferation, and even small necroses, is compatible with the diagnosis. However, necroses belong rather to the glioblastoma feature.

Anaplastic gliomas are classed as grade III in the WHO classification. Their recurrence-free postoperative interval is considered to be about 2 years. They are treated similarly to glioblastomas, but since anaplastic oligodendrogliomas have a better prognosis, the composition of the anaplastic gliomas has to be analyzed thoroughly.

3.2.1.4.5 Glioblastoma (Multiforme)
Glioblastoma is a malignant adult intracranial tumor. It accounts for 10–15% of all intracranial tumors. There is a clear male preponderance of 6:4.

The location of the glioblastoma in the brain is mostly supratentorial, but brain stem and spinal cord tumors have been found incidentally. Within the brain, temporal and other “lobar” locations are typical. Another characteristic growth pattern is that in butterfly manner, where the tumor spreads through the corpus callosum and grows in both hemispheres.

Macroscopically, glioblastoma is variegated in color (glioblastoma multiforme); necroses may be whitish or yel-
low and fresh or old hemorrhage may be seen (Fig. 3.2.7). The cellular content is usually very pleomorphic. Often small round cells constitute the major cell population (globuliform) or bipolar cells prevail (fusiform). In addition, identifiable protoplasmic or gemistocytic astrocytes are observed. Giant cells are common; if they predominate, the tumor is often named “giant cell glioblastoma.” The separation of this entity proved reasonable because of few differences compared with ordinary glioblastoma in the genetic make-up [25].

The histology of the tumor is marked by two regularly occurring features: prominent newly formed vasculature and necroses. Neovascularization is found in different formations: microvessels may form glomeruli and huge sinusoidal vessels may occur. Necroses are either large areas or small band-like foci surrounded by tumor cells, forming pseudopalisades. Large “territorial” necroses occur preferentially in de novo formed glioblastomas, whereas small serpiginous ones are found in primary and secondary glioblastomas. The cells forming pseudopalisades are thought to produce hypoxia-driven growth factors for neovascularization [26]. The classical method of visualizing such newly formed vessels is the staining of reticulin fibers, which nicely depicts vessels of all sizes. If the reticulin-stained fibers transgressed the vasculature, the tumor was considered to contain a “sarcomatous component” or was even called “gliosarcoma.”

Gliosarcoma was considered in the former WHO classification as a separate entity, but is now a subgroup of the glioblastoma, with a frank mesodermal component, proven by reticulin stain. It has been shown repeatedly that the genetic alterations in gliosarcoma are almost identical to those of primary glioblastoma; in the gliomatous and sarcomatous parts of the same tumor the findings were the same [27]. Glioblastoma, and even more so, gliosarcoma, have to be separated from the benign pleomorphic xanthoastrocytoma (see Sect. 3.2.1.4.2), a tumor with features that can all be found in malignant gliomas, except for signs of rapid growth [28]. To distinguish between them, the immunohistochemical visualization of proliferation markers is very helpful.

**3.2.1.4.6 Ependymoma and Papilloma of the Choroid Plexus**

Ependymoma and papilloma of the choroid plexus are localized within or near the ventricles of the brain (Fig. 3.2.8). Both tumors preferentially occur in children or young adults, but some are also found in the elderly. Both tumors may have a papillary structure on gross inspection.

Histologically, ependymomas group around vessels. The most prominent feature is the perivascular arrangement of cells, leaving free the zone between the endothelium and the cellular cuffs (pseudorosettes). Several subgroups can be distinguished by histopathology: papillary, clear cell, tanycytic, cellular, and myxopapillary. Some ependymomas form short ependymal channels and true rosettes that both mimic the architecture of the ependymal lining (Fig. 3.2.9).

A tumor with similarities to ependymoma is the so-called subependymoma [29], presenting with small clusters of round cells within a glial matrix and facultative formation of microscopic cysts. Papillary choroid plexus tumors are by their make-up very similar to normal choroid plexus, but may be much larger; the stroma and the superficial cells may be enlarged and/or thickened.

Ependymomas are usually classified as grade II; i.e., recurrence is possible after a few years. The myxopapillary variant, as well as the subependymomas and most
of the plexus tumors, are classified as grade I. Malignant ependymomas (anaplastic ependymomas, WHO grade III) share features with anaplastic gliomas, especially high proliferation indices (Fig. 3.2.10). Malignant plexus tumors (plexus carcinomas, WHO grade III) are equally polymitotic. The ependymoblastoma, an embryonal childhood tumor with the hallmark of layered rosettes is considered to correspond to WHO grade IV.

### 3.2.1.4.7 Tumors of the Pineal Parenchyma

Tumors of the pineal parenchyma comprise the pineocytoma on the benign and the pineoblastoma on the malignant side. Tumors of pineal origin represent less than 0.5% of intracranial neoplasms, and half of them are pineocytomas, half pineoblastomas. Harmless pineal cysts may be considered to be inert tumors at this site.

Pineocytomas are composed of small cells resembling pineal parenchymal cells. They are layered in sheets, but occasionally also form characteristic “large” rosettes. Pineoblastomas, in contrast, are less differentiated, polymitotic small cell tumors that can be compared to medulloblastomas and are included in the primitive neuroectodermal tumor group. Accordingly, the tumor cells have the polygonal shape of medulloblastoma cells and some rosette formations, cellular columns, and islands may be seen (Fig. 3.2.11).

In pineocytoma and pineoblastoma differentiation along the neuronal and glial line has been described. Pineocytomas receive grade II classification, but the course is often favorable. Pineoblastomas are classed as grade IV, as are other members of the primitive neuroectodermal tumor group. An intermediate form – pineal parenchymal tumor of intermediate differentiation – is included in the WHO classification, but without any comment concerning its actual clinical course. The designation "pinealoma" – isomorphic and anisomorphic – is no longer used. Most of the tumors diagnosed as pinealoma were in fact germinomas.

### 3.2.1.4.8 Medulloblastomas

Medulloblastomas are tumors with a clear-cut peak of occurrence in children at the age of 7–9 years, a location – by definition – within the fossa cerebri posterior, and a malignant course. Medulloblastomas in the adult are less frequent and are clustered around 30 years of age. Sixty-six percent of affected children and adults are male.

Most medulloblastomas are localized in and probably arise from the vermis of the cerebellum, possibly extend-
ing into the fourth ventricle (Fig. 3.2.12). Specimens that occupy the cerebellar hemispheres are often associated with later onset and desmoplastic behavior.

The nuclei of the tumor cells of these neoplasms are described as round to oval, carrot- or bean-shaped, hyperchromatic, and often presenting with mitotic figures. A typical but not constant feature is the so-called neuroblastic rosette and possible differentiation along the neuronal line is assumed; ganglion cell perikarya have been observed. A special formation is the occurrence of abundant reticulin fibers leaving free pale islands. This variant is now called desmoplastic medulloblastoma (formerly also arachnoidal sarcoma). Another, more recently described variety is the medulloblastoma, with extensive nodularity and advanced neuronal differentiation. Further, a large cell variant, medullomyoblastomas with focal myoblastic differentiation and melanotic medulloblastoma with pigmentations were treated as separate entities. Tumors with less differentiated histological features, often known as “blue” tumors, that grow in the supratentorial compartment, today receive the label of PNET – primitive neuroepithelial tumor (Fig. 3.2.13).

In PNET, as in other primitive tumors – pineoblastoma, medulloblastoma – various lines of differentiation, neuronal in the first instance, can be recognized. PNET and the mesenchymal–osteogenic Ewing sarcoma are considered to be identical because they present with the same immunophenotype [30].

All tumors of this group are malignant and as classified as WHO grade IV. Medulloblastomas tend to produce metastases through the spinal fluid pathway. Progress in the management of childhood medulloblastomas has been achieved in the last few decades.

**3.2.1.4.9 Neuronal Tumors**

Neuronal tumors form a heterogeneous group. They include the olfactory neuroblastoma, the adrenal neuroblastoma, and other tumors of the sympathetic nervous system, as well as centrally occurring neuroblastosmas, ganglioneuroblastomas, gangliogliomas, and gangliocytomas. The central neurocytoma of the third ventricle (formerly foramen of Monroe ependymoma) has been shown to be neuronal [31]. As one can see from the nomenclature, these tumors cover a wide range of malignancy grades. In addition, some partly malformative, partly tumorous conditions are included, such as the dysplasogenic neuroepithelial tumor, a lesion often found in connection with epilepsy neurosurgery, but with an uncertain definition [32]. A similar, highly benign lesion is the desmoplastic infantile ganglioglioma (DIG), today used synonymously with infantile desmoplastic astrocytoma (DIA).

All these tumors have overt or partial neuronal differentiation that can be unraveled by either conventional staining (Nissl stain; Fig. 3.2.14) or the formation of axons in mature gangliocytomas or gangliogliomas, or immunohistochemistry, or even electron microscopy in other cases. According to the heterogeneity of the group, varying morphological pictures are encountered; the common denominator is the proof of neuronal derivation. Similarly, the share of actively proliferating cells varies considerably, as measured by mitotic figures or Ki 67 (MiB-1) immunohistochemistry. Highly malignant neuroblastomas and almost nonproliferating dysplastic neuroepithelial tumors (DNT) are included.

Of the intracranial tumors, olfactory and other neuroblastomas are classed as grade IV, ganglioneuroblastoma and anaplastic ganglioglioma grade III, ganglioglioma and central neurocytoma mostly fall within grade II,
3.2.1 Classification and Biology of Brain Tumors

whereas gangliocytoma, DNT and DIG, receive grade I of the WHO classification.

3.2.1.4.10 Schwannomas
The terms neurinoma and neurilemmoma are used synonymously. These tumors grow within the cranial and spinal cavities and peripherally, but are objects mostly of neurosurgical intervention. Nerve roots are the main site; the overwhelming majority within the intracranial space are so-called acoustic nerve root schwannomas that in fact take their origin from the vestibular part of the eighth brain nerve. Spinal roots may be affected within and outside the column; these tumors then grow in a dumb-bell manner. Solitary peripheral schwannomas are found in connection with any peripheral nerve. A special gross growth pattern, mostly on the periphery, is the nodular or plexiform neurinoma.

Schwannomas account for 5–10% of nervous system tumors. They occur preferentially in the elderly, and there is a small female preponderance. Grossly, the tumors tend to be firm.

Schwannomas have two histologic patterns; namely, a reticular growth pattern (Antoni B) and the more common fibrillar variant (Antoni A). This fibrillar pattern is formed by the dense layering of slender bipolar cell nuclei surrounded by a cytoplasmic sheath tapering on both ends into fibrillary-like extensions. The nuclei may even be arranged in parallel rows (Fig. 3.2.15), called palisades, which are not so common, but highly characteristic of schwannomas. Short roundish bodies with nuclei roughly arranged in palisades are known as Verocay bodies.

Neurofibromas are characterized by the participation of connective cells and tissue in the histological picture. The mostly peripherally occurring tumor of the nerves with onion bulb formation is called the perineurioma. Schwannomas and the tumors mentioned here are all classed as grade I in the WHO classification. The malignant variant of these Schwann cell neoplasms is designated the malignant peripheral nerve sheath tumor (MPNST). It is graded III or IV in the WHO classification. MPNST corresponds to the earlier malignant neurinomas, neurosarcomas, neurogenic sarcomas or malignant neurofibromas.

3.2.1.4.11 Meningiomas
These tumors of the meninges are frequent. They constitute about 15–25% of primary intracranial tumors. They are tumors that occur in older people, and some special locations and even some morphological subgroups show a high female preponderance.

Meningiomas arise in some typical locations that may be associated with neurological syndromes; therefore, olfactory groove meningiomas lead to early anosmia, whereas parasagittal meningioma may be followed by paraplegia mimicking a spinal location. Large meningiomas of the cerebral convexities may produce ipsilateral hemiparesis, and a well-documented but rare event is the intraventricular location of this tumor.

Gross meningiomas are well demarcated (Fig. 3.2.16) and firm, often adherent to the meninges and/or bone. Some tumors are lobulated. So-called infiltration of the dura mater and the bones of the skull is of uncertain significance with regard to malignant behavior. Some meningiomas grow as flat masses – en plaque.
3.2 Brain Tumors

The main histological feature of the meningioma is its tendency to "cover": virtually all structures, single cells, small vessels or minute calcifications are surrounded by layers of covering cells. Thus, a wealth of concentric onion bulb formations can be seen in quite a number of meningiomas. A second, almost constant feature is the meningioma cell with round to oval pale nucleus and frequently with central clearing. Notwithstanding those more common features there are many subtypes, the most common being the endotheliomatous (meningotheliomatous), fibrous, transitional, and angiomatous varieties. Meningiomas with abundant formation of calcifications are described as psammomatous; they are an example of high female and site prevalence. They occur in females typically in the 60–70 age group and are mostly located in the thoracic spinal cord. Further rarer subtypes are the cystic meningioma, the secretory variant with PAS-positive secretory products (pseudopsammoma bodies), the lymphoplasmacyte-rich meningioma and the metaplastic meningioma usually with focal mesenchymal differentiation. All these subgroups are classed as grade I in the WHO classification if there are no overt signs of advanced growth. There are few subtypes that by their histological nature are classed as grade II. The chordoid meningioma in parts resembles the chordoma and the clear cell meningioma, whose "empty" cytoplasm contains glycogen. Rhabdoid and papillary meningioma are classed as grade III, but they are both rare.

Thus, there are three grades. Most common meningiomas are classed as grade I; grade II meningiomas may be any of the aforementioned with signs of higher proliferation, especially mitotic activity. They are called atypical meningiomas. Together with the chordoid and clear cell subgroups described they form the grade II group of meningiomas in the WHO classification. Highly proliferating or invasive meningioma of any type or papillary and rhabdoid subtypes are included in grade III. Grade III meningiomas of any subtype are named anaplastic or malignant meningioma.

The differential diagnosis of meningiomas includes mesodermal and vascular tumors. Benign and malignant mesodermal tumors occur in the meninges and occasionally in the brain. Somewhat more frequent are hemangiopericytomas of the meninges, formerly known as hemangiopericytic meningiomas. They correspond mostly to grade III in the WHO classification.

Another neoplasm that is found in the leptomeninges with diffuse spread is primary diffuse melanosis of the brain, a condition with a poor prognosis.

3.2.1.4.12 Vascular Tumors

There are two true vascular tumors in the intracranial space; namely, the hemangiopericytoma, already alluded to in connection with the meningiomas and the hemangioblastoma Lindau. The hemangiopericytoma does not differ from specimens in other locations of the body, both with regard to morphology and to biological behavior, apart from the fact of its intracranial site with imminent pressure (Fig. 3.2.17). The angioblastoma Lindau is found in the fossa posterior, seldom in the brain stem and spinal cord. It accounts for 1–2% of intracranial tumors. Its first symptoms often appear in the 30+ age group, but earlier onset is not uncommon.

When growing within the hemispheres of the cerebellum, angioblastomas tend to undergo cystic transformation. Only small tumors grow regularly in a compact fashion. The histology of angioblastoma consists of a wealth of

Fig. 3.2.16a,b Meningiomas are tumors of the cerebral coverings that grow within the intracranial space and may compress considerably the adjacent brain, but often do not invade the brain or spinal cord (a). Histologically, onion bulb formations and psammoma bodies can often be found. The cells contain the intermediary filament vimentin (b)
vessels of different sizes; mostly, however, capillaries and interstitial cells. The latter may contain fat droplets. Thus, the histological picture is uniform: endothelial cells, basement lamina (reticulin-stained), and interstitial cells.

All hemangiopericytomas are considered to be classed as grade II or frequently grade III. Angioblastoma Lindau is classed as grade I. It is a matter of convention whether or not cerebellar angioblastoma might always be considered as the forme fruste of the von Hippel–Lindau phakomatosis.

3.2.1.4.13 Germ Cell Tumors
Germ cell tumors are found in midline locations within the nervous system. One of the more conspicuous neoplasms of this group is the germinoma. It arises in the pineal site and is the most frequent tumor at this site. Furthermore, germinomas may be detected in the hypothalamic region and elsewhere in the midline (formerly known as ectopic pinealoma). Germinomas, like other germ cell tumors, are more common in children and young people, and there is a clear male preponderance in teratomas and germinomas.

Germinomas present with two cell types. Large cells that occasionally show mitotic figures are the true tumor cells. Small cells occurring in clusters or diffusely intermingled with the tumor cells lead to the characteristic picture (Fig. 3.2.18). Other germ cell tumors, such as embryonal carcinomas or choriocarcinomas, have the morphologies of their gonadal or extragonadal forms elsewhere.

Teratomas are tumors that differentiate along more than one germ line be it ecto-, meso- or entodermal. Their mature form has formations that are found in fully differentiated tissues, whereas the immature form consists fully or partly of immature fetal tissue. Mature teratomas are considered benign; their immature counterparts are less so, but can obviously undergo tumor “maturation.” In addition, teratomas with malignant transformation have been described that in addition contain sarcoma or carcinoma. Yolk sac tumors also resemble the specimens found in gonadal sites; some of their constituents express alpha fetoprotein. The latter tumors have an unfavorable course.

3.2.1.4.14 Tumors of the Pituitary
Tumors of the pituitary are pituitary adenomas and their very rare malignant forms are known as pituitary carcinomas and craniopharyngiomas. Pituitary adenomas are endocrinologically active or silent tumors, possibly leading to acromegaly or Cushing’s syndrome, etc. They belong to the more frequent intracranial tumors (8–12%), there is no clear cut monophasic age peak, and there is equal distribution between males and females.

Pituitary adenomas either form sheets of monomorphic small round cells (Fig. 3.2.19) or may exhibit some papillary formations. Craniopharyngiomas occur in children and adults, the male–female ratio is balanced (Fig. 3.2.20). In addition, few cysts occur in this site, the most common being Rathke's cleft cyst.

Pituitary adenomas are classified as endocrinologically active if they produce prolactin or growth hormone (frequently) or ACTH (seldom) or other hormones (extremely seldom). The pertinent cell populations in the tumors may be identified by special stains, immunohistochemistry or electron microscopy. But a one-to-one correlation from morphology to endocrinological chang-
3.2 Brain Tumors

3.2.1.4.15 Miscellaneous

Metastases to the brain from distant carcinomas are frequent (Fig. 3.2.21). Most often the brain is the metastatic goal of tumors of the lungs, breast, kidney, gastrointestinal tract, and as a direct extension of the pharynx. Obviously, a tumor with high metastatic potential to the brain is the chorionepitheliom, which, however, is infrequent as a primary tumor. A similarly high rate of brain affiliation is observed in malignant melanoma of the skin and other localizations.

Malignant lymphomas may stem from cerebral or subarachnoidal seedings or arise primarily in the brain (Fig. 3.2.22). Both malignant lymphomas and carcinomas are prone to inducing neoplastic meningitis (leukemic or carcinomatous).

On the opposite side of the spectrum of intracranial space-occupying lesions there are a variety of cysts (Fig. 3.2.23), some of which have already been mentioned. Most are malformative cysts such as the enterogenous cyst, bronchogenic cyst, and colloid cyst of the third ventricle. Some hamartomas, the so-called glioma nasi, and the cysts of the dermoid or epidermoid may be gathered within the same rubric. Since these are not true tumors, no grading is given.

There are several categories in the latest 2007 WHO Classification of Tumours of the Nervous System (Table 3.2.1) that are not specifically addressed in the text, as they are rather uncommon or contentious. Further information can be found in the cited or other textbooks.

es should not be expected. Craniopharyngiomas contain bands of partly stratified epithelium; two forms, papillary and adamantinomatous, may be distinguished and have slightly different histological features and varying age distribution and recurrence rates, the latter forming wet keratin and calcifications, the former almost exclusively occurring in adults.

Pituitary adenomas and both forms of craniopharyngiomas are classed as grade I. Pituitary carcinomas, which are extremely rare, receive grade IV. Rathke’s pouch cleft is not a proper tumor, but may be considered as a forme fruste of a craniopharyngioma.

Craniopharyngiomas are often cystic and show several regressive features visible to the naked eye.

Metastases to the brain from distant carcinomas are frequent (Fig. 3.2.21). Most often the brain is the metastatic goal of tumors of the lungs, breast, kidney, gastrointestinal tract, and as a direct extension of the pharynx. Obviously, a tumor with high metastatic potential to the brain is the chorionepitheliom, which, however, is infrequent as a primary tumor. A similarly high rate of brain affiliation is observed in malignant melanoma of the skin and other localizations.

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Fig. 3.2.19 Pituitary adenomas, hormonally either active or inactive, consist of a dense population of small cells that are poorly delineated and form monomorphic sheets

Fig. 3.2.20 Craniopharyngioma are often cystic and show several regressive features visible to the naked eye

Fig. 3.2.19

Fig. 3.2.20

Fig. 3.2.19

Fig. 3.2.20
Selected Reading

20. Lekanne D, Bianchi AB, Groen NA, Warringa UL, Seizinger BR, Hagemeier A, van Drunen E, Bootsma D,
Brain Tumors

3.2.2 Epidemiology of Brain Tumours

FLEMING GJERRIS

3.2.2.1 Basics

The treatment of primary brain tumours in adults and children is a challenge for neurosurgeons, paediatricians and neuro-oncologists. It is important to have a thorough knowledge of the frequency, taxonomy and prognosis of brain tumours. Epidemiology of intracranial (brain) neoplasms is thus a study of the occurrence of brain tumours in a distinct population or region [1, 2]. The compilation of all the different cases within one region is dependent on the organisation of the medical services, on neuropathological traditions, on tumour taxonomy, on the availability of cancer and mortality registration systems, and finally on the different rules in a single country. The neuropathological classification of primary brain tumours is described in Sect. 3.2.1. During the last 20 years, modern imaging methods such as roentgen computed tomography (CT) and magnetic resonance imaging (MRI) have been of great help in the verification and planning of treatment or follow-up of patients with brain tumours.

3.2.2.2 Definitions

3.2.2.2.1 Definitions and Age Limits

- A brain tumour is an intracranial neoplasm verified by histology, operation, autopsy or by imaging methods, and arises from the brain itself or from the meninges, and grows inside the skull. Tumours located in the skull only, i.e. dermoids and granulomas, are not included. Arteriovenous malformations of the brain are not neoplasms and should not be incorporated into the classification of brain tumours.

- The age limits used for adults are the age groups above 14 years of age, i.e. 15–99 or more.

- The age limits for children are the 15 year groups from 0 to 14 years of age.

- Supratentorial location is the space above the tentorial incisura and includes the anterior and medial fossa of the skull and the brain above the tentorium.

- Infratentorial location is the posterior fossa space, including the cerebellum, brainstem and the adjacent parts of the skull base.

- Imaging verification by CT or MR in the supratentorial area should only be performed for deep-seated tumours, i.e. in the basal ganglia or pineal area and in the posterior fossa for brain stem tumours, mostly due to the rather high risk related to a biopsy. In all
other intracranial regions a tumour should always be verified by histology in an attempt to plan and apply the best treatment.

- Prevalence and incidence are the two major measures of disease frequency.
- Prevalence is the number of persons alive with a brain tumour in a population divided by the total population at risk within that time; for example, in Denmark 2,500 persons out of 5.3 million people = 50 per 100,000 per year. The prevalence depends on two factors, i.e., incidence and duration of the disease, so a variation in prevalence may reflect a change in incidence or outcome or both.
- The cumulative incidence is observed for an equal period of time and is the probability of developing a brain tumour in a population. It is defined as the number of new brain tumours during a period of time (generally 1 year) divided by the population at risk within that time (Fig. 3.2.24). The incidence rates are usually expressed per 100,000 persons of a standardised European population. As an illustrative example, Denmark has 4.4 million adults and about 1 million children below 15 years of age. The annual incidence is 440 per 4.4 million adults = 10 per 100,000 adults, and 35 per 1 million children = 3.5 per 100,000 children.
- The incidence density is the average risk of developing a brain tumour in a population, i.e., the number of new brain tumours per year divided by the population at the beginning of the time interval, e.g., 400 per 5.3 million = 9 per 100,000 per year. The incidence density is used when persons are observed for different lengths of time.
- Mortality (death) rate is the number of persons dying of a brain tumour during a period of time divided by the population at risk within that time.

### 3.2.2.2 Further Epidemiologic Concepts

The frequency of brain tumours can be investigated by cohort or case-control studies [1, 2, 7].

The cohort study is a follow-up (retrospective) investigation or a prospective analysis in which groups of individuals are identified and followed over time [5, 6].

The case-control study identifies persons with brain tumours, uses a similar age group of individuals without brain tumour as controls and evaluates survival, disability rate and social events. These are retrospective in nature and compare a sample of cases with exposures of interest, i.e., diet and vaccinations [4]. The retrospective (case-control) study identifies children by whether or not they have a brain tumour. Thus, a case-control study might be based on only 50 children with a specific brain tumour and a similar number of controls. The advantage, besides its low cost, is that it provides an opportunity to explore multiple hypotheses. If parental exposure is a risk factor for brain tumours in children, it is necessary to determine how much of the increased risk reflects exposure before conception, during pregnancy and after birth.

Correlational (ecological) studies explore the rate of brain tumours in a population area and compare this with a geographic distribution of suspected risk factors. The principle goal is to find the causes of a brain tumour so that preventive measures may be implemented. Only prospective studies can provide accurate information about exposure, but are incredibly expensive. For example, for every 100,000 children under the age of 15 years investigated, only 3 or 4 children will manifest a brain tumour each year [6, 17].

The occurrence of brain tumours in populations is not an indiscriminate phenomenon. It depends on many causes, e.g., biology, exposure and the dose–response relationship. Brain tumours can be induced in experimental animals via the intracerebral or other routes of different compounds, e.g., aromatic hydrocarbons and nitrosoureas [12, 13], which exert their carcinogenicity in different ways. Foetal animals are more susceptible to chemical oncogenesis than adult animals. Adult persons in some occupations are at increased risk of central nervous system tumours, e.g., lead smelters and petrochemical workers [13].

Different risk factors are described, of which only a few are mentioned here, e.g., immunosuppression, postnatal irradiation, viral exposition, gender and gene disorders. People who are immunosuppressed are at risk of developing lymphomas or sarcomas in the brain. Reports of central nervous system tumours have implicated therapeutic radiation as a risk factor [6], e.g., irradiation of the head for a malignant brain tumour during childhood appears to result in an increased risk of meningiomas and other intracranial tumours. In laboratory animals, viral infections increase the risk of brain tumours, and

**Fig. 3.2.24** European incidence rates standardised according to age of brain and CNS tumours, by sex, Great Britain, 1975–2003; modified from [15], with permission.
younger the age at inoculation, the greater the incidence of multiple tumours [4]. Polio vaccine contaminated with simian virus-40 (SV-40) can be oncogenic. SV-40 is a papovavirus with which some live polio vaccines were contaminated. Increased occurrence of ependymomas and plexus papillomas has been described in animals after SV-40 contamination, but has not been found in children vaccinated for polio with SV-40-contaminated vaccine [4]. Men are at greater risk of brain tumours than women [15]. Compared with male/female ratio in the paediatric population, the incidence figures only disclose a very slight preponderance in boys [5, 6]. Some genetic factors are known, e.g. von Recklinghausen's neurofibromatosis (Table 3.2.6).

The reader can calculate the frequency of brain tumours using the above given numbers and can compute the incidence figures for adults and children in their own country, if stable bio-statistical figures for the population, adults and children are known. For elaboration of these definitions; see the following textbooks of epidemiology [1, 2, 7, 16, 19, 20].

The reason why a specific brain tumour might develop is unknown in most cases.

### 3.2.2.3 Epidemiology of Brain Tumours in Adults

Brain tumours are not very common, and many more than 50% of all brain tumours are metastatic (most common are from cancer of the lung [50%], breast [15%], melanoma [10%] and kidney [8%]), and the number is still increasing due to longer survival in patients with a cancer like the breast, kidney and prostate, or better diagnostic methods such as MRI (Sects. 3.2.5.6. and 3.2.6.3).

#### 3.2.2.3.1 Incidence Rates of Primary Brain Tumours

Over the years 1980 to 2000, incidence rates of primary brain tumours have increased in adults [8, 15], caused by either improved diagnoses or a real change in incidence (Fig. 3.2.24). The rise found in persons above the age of 64 years is only a very modest increase, probably caused by better diagnostics using CT and MRI. In 2003 in the UK the crude incidence rate (Fig. 3.2.25) per 100,000 of the population was 8.5 for males and 7.2 for females and the age-standardised rate in Europe per 100,000 of the population was 7.9 for males and 5.1 for females, numbers that are similar over the world. The different age peaks are well illustrated in Fig. 3.2.24.

Primary intracranial tumours are not among the most common tumours and constitute only 2–3% of all malignancies, with an incidence of 8–10 per 100,000 inhabitants in Europe and North America [14]. In adults, brain tumour figures from cancer registry studies are dependent on the rate of notification, which is high in many European countries and North America. However, a lack of clarity regarding the criteria for tumour definitions, the considerable variation in age ranges that are accepted as childhood, and the selection of materials, make comparison of incidence, classification, and survival difficult in many series. Statistical surveys very often include spinal tumours, but the low incidence of primary spine tumours implies only a slight increase in the total number, especially in children. The incidence rates for different primary brain tumours are fairly similar all over the world; an exception is a very high rate of pinealomas in Japan and the high rate of lymphomas in AIDS patients.

In adults glioblastomas and meningiomas are the most frequent and the distribution of the different types is shown in Table 3.2.7. A number of gene disorders or familial syndromes are shown in Table 3.2.6.

<table>
<thead>
<tr>
<th>Gene disorder</th>
<th>Tumour type</th>
<th>Place</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Hippel-Lindau’s disease</td>
<td>Haemangioblastoma</td>
<td>Cerebellum, brain stem, spinal cord</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Astrocytoma, optic – chiasmal glioma</td>
<td>Midline, chiasmal area</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>Schwannoma, meningioma, glioma</td>
<td>Cerebellopontine angle, overall intracranial</td>
</tr>
<tr>
<td>Tuberose sclerosis</td>
<td>Subependymal giant cell astrocytoma</td>
<td>Third and lateral ventricles</td>
</tr>
<tr>
<td>Sturge-Weber disease</td>
<td>Plexus papilloma</td>
<td>Ventricular system</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>Medulloblastoma</td>
<td>Cerebellum</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>Medulloblastoma, glioblastoma</td>
<td>Cerebellum, cerebral hemispheres</td>
</tr>
<tr>
<td>Gardener’s syndrome (familial gliomas)</td>
<td>Glioma</td>
<td>Brain</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Glioma</td>
<td>Brain</td>
</tr>
</tbody>
</table>
3.2.2.3.2 Distribution in Connection with Location and Histology

3.2.2.3.2.1 Overall Remarks on Location and Histology

Primary brain tumours are classified according to their localisation. The intracranial space is for convenience divided into the supratentorial and infratentorial spaces. In adults 80–85% of the tumours will be placed in the supratentorial space and 15–20% in the posterior fossa.

Histology rather than the anatomical location defines brain tumours today. The different classifications are described in Chap. 3.2.1 and the WHO classification has been used for many years [9]. The pathological classification is based on the tissue of origin and the morphological criteria for malignancy are anaplasia, invasiveness, recurrence and metastatic growth. All the different histological types of brain tumours are shown in Tables 3.2.7 and 3.2.8. Tumours, mostly neuroepithelial, are divided by degree of malignancy according to histological features into four malignancy groups, I–IV, where grade I includes juvenile astrocytomas and ependymomas, grade II diffuse astrocytomas, ependymomas and oligodendrogliomas, grade III anaplastic astrocytomas, ependymomas and oligodendrogliomas, and grade IV glioblastomas.

3.2.2.3.2.2 The Supratentorial Space

3.2.2.3.2.2.1 Sellar, Chiasmal and Pineal Region

These midline tumours account for 8–12% of all intracranial neoplasms. Pituitary adenomas (6–8%) are the most common followed by craniopharyngiomas (5%), pinealomas and chiasmal gliomas. Pinealomas occur mostly in young adults, i.e. germinomas. Ependymomas and papillomas are found in the third ventricle.

3.2.2.3.2.2.2 The Cerebral Hemispheres and Lateral Ventricles

The most frequent tumours are astrocytomas, glioblastomas, ependymomas and oligodendrogliomas. Glioblastomas are slightly more common in males. Meningiomas are benign tumours, arising from the arachnoid membrane and found all over the inside of the dura. They are seldom found in the lateral ventricles. Meningiomas are doubly frequent in females as in males. Atypical meningiomas are uncommon and often associated with recurrence. Ependymomas and giant cell astrocytomas are found in the ventricles.

3.2.2.3.2.3 The Infratentorial Space

3.2.2.3.2.3.1 Cerebellum and Fourth Ventricle

The most common tumours are astrocytomas, grades II to III, ependymomas, haemangioblastomas and dermoids.

3.2.2.3.2.3.2 Brain Stem

These tumours are rather uncommon in adults and are mostly astrocytomas grades II to III.

3.2.2.3.2.3.3 Cerebellopontine Angle

Cerebellopontine angle tumours are most often meningiomas and schwannomas.

---

**Table 3.2.7** Histological types and frequency of the most common primary brain tumours

<table>
<thead>
<tr>
<th>Histology</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma multiforme</td>
<td>20–25</td>
</tr>
<tr>
<td>Astrocytoma, anaplastic</td>
<td>3–5</td>
</tr>
<tr>
<td>Astrocytoma, juvenile or diffuse, low grade</td>
<td>18–20</td>
</tr>
<tr>
<td>Ependymoma, low grade or anaplastic</td>
<td>3–5</td>
</tr>
<tr>
<td>Oligodendroglioma, low and high grade</td>
<td>2–4</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>2–4</td>
</tr>
<tr>
<td>Meningioma</td>
<td>15–18</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>6–8</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>6–8</td>
</tr>
<tr>
<td>Pinealoma, low and high grade</td>
<td>1–2</td>
</tr>
<tr>
<td>Angioblastoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Papilloma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Epidermoid</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Primitive neuroepithelial tumours (PNET)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Lipoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Other types</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

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**Fig. 3.2.25** Numbers of new cases and age-specific incidence rates of brain and other CNS tumours, by sex, UK, 2003; modified from [15], with permission.
3.2.2.4 Epidemiology of Brain Tumours in Children

In children brain tumours are the second most common type of tumour after leukaemia, i.e. about 25%. The natural history of a brain tumour includes a continual growth of the tumour, which means that almost every child will sooner or later come to medical attention. This also means that detection biases are infrequent. The rate of histological verification is in many older publications as high as 85–90%, but autopsy has decreased in many European countries during the last two decades. In specific non-eloquent locations, i.e. the basal nuclei and brain stem, many tumours are verified by CT or MRI only. Metastasis to the brain is very uncommon in children.

3.2.2.4.1 Incidence Rates

The frequency of brain tumours in childhood reported in the previous literature is mostly based on materials from single departments, i.e. paediatric and neurosurgical clinics, neuropathological institutes or on reports referring to selected histological tumour types and only give a limited view of the epidemiological patterns. The annual incidence rates all over the world differ a little, probably due to registration matters. The rates for the Scandinavian countries, UK, The Netherlands and North America are very close. Other studies use the age of 20 as the upper age limit for childhood. First, acceptance of this high upper age limit will cause inclusion of supratentorial tumours, typically found in adults, and secondly, comparison between individual studies in some countries is difficult as most population statistics take the end of the 14th year as the upper age limit of childhood [3, 5]. Materials based on cancer registry studies or population materials

<table>
<thead>
<tr>
<th>Location</th>
<th>Histology</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td>Pituitary adenoma</td>
<td>Craniopharyngioma</td>
<td>Craniopharyngioma</td>
</tr>
<tr>
<td>Sellar</td>
<td>Craniopharyngioma</td>
<td>Glioma, optic chiasm</td>
<td>Glioma, optic chiasm</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>Glioma</td>
<td>Ependymoma</td>
<td>Ependymoma</td>
</tr>
<tr>
<td>Pineal region</td>
<td>Pineoblastoma</td>
<td>Pinealoma/pineocytoma</td>
<td>Germinoma, teratoma</td>
</tr>
<tr>
<td>Meningioma</td>
<td></td>
<td></td>
<td>Astrocytoma</td>
</tr>
<tr>
<td>Cerebral hemi-</td>
<td>Glioblastoma</td>
<td>Astrocytoma, juvenile/diffuse</td>
<td></td>
</tr>
<tr>
<td>spheres</td>
<td>Astrocytoma, low grade</td>
<td>Astronyctoma, anaplastic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Astrocytoma, anaplastic</td>
<td>Spongioblastoma</td>
<td></td>
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<tr>
<td></td>
<td>Oligodendroglioma</td>
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</tr>
<tr>
<td>Lateral ventricles</td>
<td>Ependymoma</td>
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<td></td>
<td>Meningioma</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Ependymoma</td>
<td></td>
<td></td>
</tr>
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<td>Astrocytoma, pilocytic</td>
<td>Medulloblastoma</td>
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</tr>
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<td>Astrocytoma, pilocytic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angioblastoma</td>
<td>Angioblastoma</td>
<td>Dermoid cyst</td>
</tr>
<tr>
<td>Fourth ventricle</td>
<td>Meningioma</td>
<td>Medulloblastoma</td>
<td>Ependymoma</td>
</tr>
<tr>
<td></td>
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have shown an annual incidence of brain tumours of between 2.2 and 3.5 per 100,000 in children below 15 years of age, with an average incidence of 3.5 per 100,000 for boys and 2.5 per 100,000 for girls [10, 11]. Other reports show differences both in location and histological typing, mostly due to varying age ranges for childhood [6, 21]. The age peak of brain tumours in childhood is illustrated in Fig. 3.2.25.

Three epidemiological studies of brain tumours in children in Denmark for the years 1935–1959, 1960–1984 and 1980–1996 have shown that the number of tumours or different tumour types did not change during the first 50 years, but increased during the last 10 years of study [5, 6, 17]. The increased incidence rate of brain tumours in children is found in several countries. It is uncertain whether the increase is biologically real or is due to improved diagnostic methods, but the data strongly suggest that the incidence rate of brain tumours among Danish children aged 0–4 years has truly increased. Statistics from Denmark, Germany, Sweden and the UK indicate that improved diagnostic methods are unlikely explanations for the registered increases in incidence rates [10, 11, 17]. The most pronounced increase was seen for astrocytomas and primitive neuroectodermal tumours [11, 17].

3.2.2.4.2 Distribution in Connection with Location and Histology

3.2.2.4.2.1 Overall Remarks on Location and Histology

Thirty years ago intracranial tumours in children were described as being far more frequent in the infratentorial than in the supratentorial compartment, and in particular tumours of the cerebral hemispheres were reported less frequently. Later reports from Sweden, the UK and Denmark show that supratentorial tumours now constitute about 45% of all childhood intracranial tumours [6, 11]. Many authors have found identical rates of supratentorial and infratentorial tumours, but they had an upper age limit for childhood of 17 years, which implies a rise in the number of supratentorial tumours [6]. The only well-known cause of brain tumours in children is heredity, as shown in Table 3.2.6. Half of the tumours in the supratentorial space are located in the midline and the other half in the lateral space. In children 75% of posterior fossa tumours are localised in the cerebellum or fourth ventricle, 20% in the brain stem and less than 2% in the cerebellopontine angle. Nearly the same distribution is found in cancer registry materials in Europe and North America [14, 17]. The most distinct differences in intracranial tumour types between children and adults are shown in the Table 3.2.8.

Histology and anatomical location define brain tumours in children today, the International Classification of Diseases for Oncology (ICD-O) is in use. The majority of the tumours (80%) originate from neuroepithelial tissue. Astrocytomas are the most common, followed by medulloblastomas, ependymomas and oligodendrogliomas. In the most malignant ones differentiation between medulloblastomas, ependymoblastomas and sarcomas can be almost impossible, and many neuropathologists prefer to classify many of them as PNET (primitive neuroectodermal tumours). PNET are highly malignant and particularly seen in the cerebral hemispheres in infants. Pituitary adenomas, schwannomas and meningiomas are very uncommon in childhood [5, 6, 18].

3.2.2.4.2.2 Supratentorial Space

3.2.2.4.2.2.1 Sellar, Chiasmal and Pineal Regions

Tumours of these regions account for more than 10% of all intracranial neoplasms in children. Craniopharyngiomas constitute about 5% of all childhood brain tumours, pinealomas about 2% and chiasmal gliomas between 2 and 4%, and they often manifest during the first 5 years of life with a familial predisposition.

3.2.2.4.2.2.2 Cerebral Hemispheres and Lateral Ventricles

The cerebral hemispheres are the second most common site (20%) and 40% of all intracranial neoplasms in infants are found here. They are usually astrocytomas, ependymomas, oligodendrogliomas, glioblastomas and PNET (Table 3.2.8). Meningiomas are very uncommon.

3.2.2.4.2.2.3 Infratentorial Space

3.2.2.4.2.3.1 Cerebellar Tumours

Approximately 45% of childhood brain tumours arise in cerebellum. Juvenile and diffuse astrocytomas are the most frequent, followed by medulloblastomas, ependymomas, haemangioblastomas and plexus papillomas.

3.2.2.4.2.3.2 Brain Stem Tumours

These tumours are low grade or anaplastic astrocytomas. They are most common in the pons, infiltrating the cranial nerve nuclei and growing intrinsically along the long fibre tracts. Often, exophytic masses protrude into the fourth ventricle, which might enable biopsy or partial removal.

3.2.2.4.2.3.3 Cerebellopontine Angle Tumours

Cerebellopontine angle tumours are seldom seen in children [5, 6]. It is mostly acoustic schwannomas (nearly always in the 10–14 years age group), epidermoids, dermoids and lipomas.
3.2 Brain Tumors

3.2.2.5 Special Remarks

Primary brain tumours represent 2–3% of all cancers, with a yearly incidence of 8–10 per 100,000 adults, 20 per 100,000 adults above the age of 64 years and 3.5 per 100,000 children. With the estimated increase in incidence in children, an average annual number of 40 new primary brain tumours per one million children is to be expected in a future European child population. Eighteen of these will be placed in the supratentorial area, 18 in the cerebellum and 3–4 in the brain stem or cerebellopontine angle. CT and MRI make it possible to establish the location and size of the tumour, and probably also to get an impression of the tumour type in question.

Far and wide, knowledge of the epidemiology and a uniform standardised classification system for primary brain tumours in both children and adults are necessary tools for the correct treatment of the individual, for the evaluation of the long-term prognosis in different tumour types, and for a comparison of rates of tumours among different centres and countries. It also provides the possibility of analysing difficult cases over a long period, to evaluate and identify different types of exposure, and to treat high-risk groups. Cancer registry studies have shown that a low incidence of a type of brain tumour corresponds to a poor prognosis and that joint European efforts in multicentres and follow-up studies are necessary.

After decades of research, we know a little more about the epidemiology and causes of primary brain tumours. Trends in brain tumour incidence have been influenced by technological advances in imaging and subsequent increased detection, especially in elderly people and children. Molecular epidemiologic studies of common genes and their possible interaction with different types of environmental exposure will hopefully provide new information on the incidence and causes of primary brain tumours.

Selected Reading

3.2.3 General Principles of Surgery on Brain Tumors

CHRISTIANTO B. LUMENTA

3.2.3.1 Indications for Surgery

The indication for surgery depends on the location of the tumor: it must be easily approachable and removable. Other important factors are the size and the growth factor of the tumor, and whether or not hydrocephalus is present. The Karnofsky performance scale and the age of the patient also have to be taken into consideration.

In an infiltratively growing glioma palliative surgery is indicated, while curative surgery can be performed in low grade, non-glial tumors like meningioma, neurinoma, etc.

The surgeon should decide on the radicality of the surgery, i.e., stereotactic biopsy, partial, subtotal or total extirpation of the tumor.

3.2.3.2 Aim of Surgery

The aim of surgery is:
- To remove as much as possible of the tumor
- To improve the quality of life
- To postpone the clinical worsening
- To improve the conditions for adjuvant therapies

3.2.3.3 Results of Surgery

The results of surgery correlate significantly with the techniques used:
- Operating microscope
- Navigation system
- Endoscope
- Intraoperative imaging
- Intraoperative neurophysiologic monitoring

Another important type of equipment is microsurgical instruments.

3.2.3.4 Microsurgical Instruments

- Craniotomy instruments (high speed drill system), retractor system, micro-instruments: forceps, scissors, knives, dissectors, micro irrigation systems, etc.
- Ultrasonic aspirator allows a demolition followed by extraction of the tumor tissue.
- Instruments used very frequently are a monopolar instrument for cutting and a bipolar instrument for hemostasis.
- Similar to the instruments that are used very frequently, laser also plays also a role in cutting, shrinking and hemostasis in specific tumors. The common types are Nd-YAG, CO₂, holmium and argon laser.

3.2.4 Stereotactic Biopsy

CHRISTIANTO B. LUMENTA,
HARTMUT GUMPRECHT, MATTHIAS J. KRAMMER

3.2.4.1 Introduction

Stereotactic techniques are employed to collect biopsies from a brain lesion for diagnostic evaluation by means of minimally invasive techniques. Mathematical calculations are used to define a target point within the three dimensional space of the brain. The calculation of a target point relates to a Cartesian coordinates system. This mathematical concept identifies a point in space by its relationship to three planes intersecting at right angles to each other and intersecting at a common point. The concept forms the basis for identifying a stereotactic target by the three coordinates: lateral (x) anterior-posterior (y), and vertical (z) [7].

Historically, at the end of the 19th century, Professor Zernov, as one of the first, constructed the encephalometer [27], an apparatus designed to calculate the surface anatomy of the brain. In 1908, Horsley and Clarke published a report on the application of a stereotactic apparatus in animals [10]. Using mathematical calculations and a frame fixed to the head of the animals, a target point could be defined. Spiegel and co-workers introduced stereotactic operations as a clinical method in humans in 1947 [22]. As a fundamental modification they used intraoperative X-rays to visualise intracerebral landmarks like the third ventricle to define a target point. In 1952, Spiegel presented an atlas of the human brain for stereotactic surgery that illustrated the relevant anatomical structures. The basis for target point calculation was the commissura posterior. Later, the necessity of two intracerebral benchmarks, the commissura anterior and posterior, was postulated [23]. Visualisation of intracerebral structures was realised by pneumoencephalography [20, 21]. Over the years, various stereotactic systems were developed [1, 5, 9, 14, 18, 19].

With the introduction of computed tomography (CT) into clinical use [11] it was possible to visualise pathological structures and a target point directly. This expanded the indications for stereotactic procedures.

The development of a fiducial system was the breakthrough in CT-based stereotaxy. This fiducial system consists of three sets of rods, arranged in an N-shaped configuration and containing all the information for
three-dimensional targeting of each two-dimensional CT plane. The height of the slice, the z coordinate, could be determined by the position of the diagonal centre rod relative to the vertical rod. The BRW system incorporated this principle first [5].

The most popular stereotactic system in Europe is based on the “centre of arc” principle, designed by Lars Leksell [14, 15]. A semicircular arc with a moveable probe carrier is attached to the base ring. The arc can swing in an anterior–posterior direction and an intracranial target can be approached from any entry point on the patient’s head.

### 3.2.4.2 Technique of Frame-Based Stereotactic Biopsy

Nowadays, CT- and MRI-compatible stereotactic frames are available. In our department we use an arc-centred stereotactic system manufactured by Zeppelin Surgical Instruments®, Pullach, Germany. This equipment is easy-to-handle and consists of a base frame, the Z-posts, the fiducial plates and the arc with the targeting probe (Fig. 3.2.26). The fiducial plates are equipped with N-shaped rods as described previously (Fig. 3.2.27). The image slices are acquired parallel to the base frame. If the

![Fig. 3.2.26a,b](image) The stereotaxy apparatus consists of a base frame, the Z-posts, the fiducial plates and the arc with the targeting probe

![Fig. 3.2.27](image) The fiducial plates are equipped with N-shaped rods, as described in the text

![Fig. 3.2.28](image) Calculation of the X- and Y-values directly from the image slice
frame is attached rigidly to the CT couch, the values of X (lateral position) and Y (anteroposterior position) can be calculated directly from the image slice (Fig. 3.2.28). The Z-value (distance from the base frame to target point) is calculated by measuring the distance of the diagonal rod to the vertical rod (Fig. 3.2.29). The rods on the fiducial plate are arranged like a 90° triangle. Therefore, the red line (C) is equal to the green line (B), which marks the distance to the frame base (A), the Z-value. If the frame is not fixed to the CT table, the values for X, Y and Z are calculated using a mathematical formula. Alternatively, various types of computer software are available that allow the calculation of a trajectory with sophisticated 3D computer graphics. The advantage of software calculation is the virtual simulation of the trajectory. Relevant brain areas (Fig. 3.2.30) can be spared, with assessment of the three-plane view.

After calculation of the target point, the values of the coordinates are transferred to the stereotactic apparatus. We perform a 0.5-cm skin incision and then a twist.
Biopsies can be taken from pathological structures in almost any supra- or infratentorial region of the brain. Normally, the shortest distance from the skull to the target point should be used, sparing eloquent brain areas and critical vascular structures. Lesions within the basal ganglia and most brain stem lesions can be reached using a coronal approach.

### 3.2.4.3 Indications

The indication for a stereotactic biopsy is the intention to obtain a histopathological diagnosis of an unknown cerebral tumour in patients in whom an open tumour resection is not the “first choice” therapy. Included in this group are patients with lesions in critical brain areas like the basal ganglia, the brain stem and the motor- or language-related cortex, as well as lesions with a diffuse spread, multifocal lesions with suspected metastatic disease, brain-related disease or lymphoma, as well as AIDS-related pathological brain lesions. The need for histological differentiation between tumour relapse and radionecrosis is also an indication for stereotactic biopsy. Even a cerebral abscess can be treated by stereotactic biopsy. First, an extraction of the infectious material should be performed for further examination of the abscess and then a catheter should be placed for abscess irrigation.

### 3.2.4.4 Complications

The complications of stereotactic biopsy are haemorrhage, deterioration of the neurological status, seizure and infection. Bleeding can occur at the entry site in terms of a subdural or epidural haematoma, along the trajectory and at the biopsy site. Neurological deficits may occur when the lesion or a bleeding is directly localised in an eloquent area.
brain area like the basal ganglia, the brain stem, the motor or visual cortex and the speech area. Furthermore, new neurological deficits can be elicited by miscalculation of the trajectory crossing relevant brain structures. We prefer general anaesthesia to local anaesthesia because the patient cannot move and possibly displace the frame and can be sedated in the case of a surgery-related seizure. We do not administer a prophylactic anticonvulsant loading dose. The risk of a superficial or deep infection in stereotactic biopsy is very low.

In general, the risk of complications [2, 6, 12, 26], like bleeding, transient or permanent neurological deficits or even death, is low. The mortality rate for the biopsy of supratentorial lesions is below 1% and approximately 4% for brain stem tumours. Therefore, stereotactic biopsy is a safe and reliable diagnostic tool, with a diagnostic potential reported in the literature ranging from 83 to 93% [4, 13, 17, 24, 25].

**Selected Reading**

10. Horsley V; Clarke RH (1908) The structure and the function of the cerebellum examined by a new method. Brain 31:45
3.2.5 Supratentorial Brain Tumors in Adults

MANFRED WESTPHAL

3.2.5.1 Neuroepithelial Tumors

3.2.5.1.1 Basics

Neuroepithelial tumors arise from the glial component of the brain. The largest group consists of the astrocytomas, followed by the oligodendroglialomas. Mixed entities exist. Ependymomas are comparatively rare and tend to occur more frequently in children. Glial tumors are classified according to the WHO system [6].

Grade I astrocytomas are synonymous with pilocytic tumors and occur mostly in children. Their preferred location is the optic chiasm and the optic pathway including the hypothalamus. The other preferred location is the cerebellum and tumors there tend to be cystic. Another variant is the brain stem glioma, which is frequently a grade I astrocytoma.

Grade II astrocytomas, synonymous with the diffuse astrocytoma, occur anywhere in the hemispheres and are typical of young adulthood. These tumors tend to progress over time to grade III astrocytomas (anaplastic astrocytomas) or grade IV astrocytomas (glioblastomas). The underlying mechanism is the sequential progressive acquisition of genetic aberrations.

Grade III astrocytomas tend to occur anywhere in the brain and are more frequent in younger adults.

Grade IV astrocytomas (glioblastomas) have their peak incidence in the sixth and seventh decades of life. They either originate from lower grade lesions or arise de novo anywhere in the brain.

Grade II oligodendroglialomas occur anywhere in the brain, have a different set of genetic aberrations from astrocytomas and also progress to grade III tumors over time (anaplastic oligodendrogliomas). They tend to occur in adulthood with peak incidences before the sixth decade.

Mixed gliomas or oligoastrocytomas contain both components and occur in grades II and III tumors. The genetic distinction between the different tumor types [5] and the existence of the mixed variant has raised the question as to whether there are different kinds of tumor stem cells.

Ependymomas come as grade I (synonymous with subependymoma), grade II, and grade III (anaplastic ependymomas) [16]. They can be found throughout the ventricular system and in adults are more frequent in the lateral ventricles and in the third ventricle, whereas in children they tend to be in the infratentorial compartment (Fig. 3.2.34). They are the most frequent intramedullary tumor.

3.2.5.1.2 Epidemiology

There is limited epidemiological information about gliomas in Europe [15, 17]. However, extrapolating data from regional registries and the North American databases [1], around 30,000 new cases of malignant glioma can be expected in Europe every year. The numbers for low-grade gliomas are much lower, but due to longer life expectancies, the prevalence increases accordingly. As there are incongruences between the inclusion of pediatric patients and age cut-offs for the epidemiological data collections, and in addition no European standard for the separation between WHO grade I and II, any number from any regional cancer registry in Europe is meaningless.

Fig. 3.2.34a–c Anaplastic ependymoma in a 16-month-old boy that arose from the roof of the fourth ventricle. a,b MRI with gadolinium preresection and c postresection
There are no etiological clues to the origin of these tumors, not environmental, nutritional or occupational. A hereditary component has only been very vaguely implied and familial gliomas are very rare [17].

3.2.5.1.3 Symptoms
Gliomas become symptomatic with a broad range of symptoms. Low-grade tumors (WHO II) tend to lead to seizures, including the whole spectrum of possible seizure types. As these tumors grow slowly, they will rarely produce a focal neurological deficit before becoming symptomatic with a seizure. Higher grade tumors also cause seizures, but due to their more rapid growth and more aggressive behavior, they frequently lead to progressively and rapidly evolving focal neurological deficits. Depending on the location this could be dysphasia, hemiparesis, a visual field deficit or cognitive problems, just to name a few. With increasing size, the tumors will cause intracranial hypertension, which in turn will lead to decreasing levels of consciousness, brain stem compression with central dysregulation of blood pressure, and other vegetative functions. Singultus is already a grave sign of advanced raised intracranial pressure or brain stem compression.

3.2.5.1.4 Complications
Except for the occasional pilocytic astrocytoma, gliomas are eventually fatal. The intrinsic property of the glioma cells to migrate through the brain will lead to invasion and eventually to involvement and functional impairment of vital structures, excluding any further therapeutic option once all possible therapies have been applied. During the disease, a period of profound disorientation may occur, necessitating continuous care and supervision. Systemic metastases of gliomas are the exception. Whereas glioblastomas have been seen in transplanted organs donated by glioblastoma patients, lifetime development of extracranial metastases has only been reported for a number of anaplastic oligodendrogliomas, which tend to metastasize to the lung and bone marrow.

3.2.5.1.5 Diagnosis
When a patient is suspected of harboring a glioma based on the neurological symptoms mentioned above, the first step will be imaging, and it is mandatory today that an MRI scan is performed because it allows a highly probable estimate of the histological diagnosis to be obtained using today’s routine modalities, such as spectroscopy [8]. Also, MRI is helpful with distinguishing a glioma from other lesions, especially metastases, which tend to frequently occur as multiple lesions. With the refinement of the MRI techniques, there is no real need for any other modality, such as PET or SPECT, in the initial setting. Those modalities may be useful for monitoring therapy. If a tissue diagnosis is required for a nonresectable tumor, this will be obtained by stereotactic biopsy [7]. Immunohistochemistry, and to an increasing extent, molecular genetics, will secure the differential diagnosis. There is no role for electrophysiology in the establishment of the correct diagnosis, nor are there tests for serum or CSF.

3.2.5.1.6 Therapy
Therapy for gliomas is interdisciplinary. Most tumors will be resected as radically as is safely possible, but some are primarily unresectable (mostly midline tumors) and these will be biopsied to obtain a proper tissue diagnosis before they go on to conservative, nonsurgical treatments.

3.2.5.1.6.1 Conservative Treatment
Apart from treating the tumor, it may be necessary to treat collateral edema. This is done with dexamethasone at an initial dose of 4 × 4 mg/day, which then tapers according to the improvement or stabilization of the neurological status. It is frequently possible, and should be the goal, to get patients off steroids completely after successful treatment; however, there may be a need to reinitiate therapy in the case of symptomatic recurrence.

Seizure prophylaxis with anticonvulsive drugs is mandatory in those patients who become symptomatic with a seizure. The prophylaxis may be tapered and eventually withdrawn after a tumor is removed. The predictive value of EEG is questionable. There is a wide range of drugs that only in the past 5 years has seen several new additions [4]. Most commonly, valproic acid will be used, but other substances, like phenytoin and carbamazepine, are also still used. Prophylaxis should be as short as possible. In the case of slowly progressing low-grade glioma, the nature of the seizures may change and an adaptation of anticonvulsive therapy may become necessary, sometimes leading to complex combinations.

Non-surgical tumor therapy rests on radiotherapy and chemotherapy. Radiation regularly follows the resection of a high-grade glioma and 54 Gy are applied in 1.8-Gy fractions over 6 weeks to the tumor area plus a 2-cm margin. Chemotherapy is also offered to patients who have recurrences or progression not eligible for further surgery, or those patients who have nonresectable tumors that are histologically confirmed by stereotactic biopsy (Fig. 3.2.35) [2]. A wide range of chemotherapeutics has been used, but all with marginal efficacy in the newly diagnosed patient, as well as in the situation of recurrence. Chemotherapy in general is regarded as salvage therapy, but nevertheless is frequently given as the last resort. Recently, the combination with radiotherapy in the treat-
ment of newly diagnosed patients has been shown to extend survival has become the standard and a subgroup analysis showed that the efficacy is mostly due to cases in which there is hypermethylation-mediated silencing of the MGMT gene [3, 13].

3.2.5.1.6.2 Surgical Therapy
The role of surgery for gliomas, low-grade as well as high-grade, has been questioned for a long time, but evidence has now been produced as a collateral result from the phase III trial with fluorescence-guided resection of newly diagnosed glioblastoma [12], showing that the extent of resection correlates with survival [11a]. Prior studies coming to that conclusion were mostly retrospective or uncontrolled or even meta-analyses [9, 10]. Technically, there are few limitations of surgical resection, as any area in the brain can be easily accessed. However, there are definite functional/anatomical limitations due to the direct involvement of functionally important structures, and in particular, tumors crossing the midline or involving the basic ganglia, as well as the cerebral peduncles, are not good candidates (Fig. 3.2.35). In general, not only resectability (anticipated morbidity) has to be considered, but also the wish of the patient and his or her general condition including age, Karnofsky performance score, and collateral diseases. The principles of resection are standardized and include microsurgery, minimal invasiveness, image guidance, and where applicable, intraoperative monitoring by electrophysiological means or awake surgery.

For pilocytic astrocytomas of the optic system, partial resection may be an option to obtain decompression of frontobasal structures and reconstitute the CSF pathways (Fig. 3.2.36). Residuals from pilocytic astrocytomas have been known to remain stable for long periods and even spontaneously regress (see sections on pediatrics).

A surgical resection is by definition incomplete because of the invasive nature of the disease, but in surgical candidates it is frequently possible to resect all contrast enhancement of a WHO grade III or IV lesion (Fig. 3.2.37) or all of the hypointensity in the case of seemingly well-delineated low-grade gliomas, of which there seems to be a truly locally confined subtype [11].

With regard to low-grade gliomas, only those that seem to be compact will be good candidates, but not the diffusely infiltrating variants (Fig. 3.2.38a). Frequently, the indication will be associated with the attempt to control seizures (Fig. 3.2.38b).

As for high-grade gliomas, the resection can be supplemented with intracavitary drug application [14] or experimental therapies. In newly diagnosed patients this will be followed by standard external beam radiotherapy. In the situation of recurrence, any decision regarding reoperation follows the same rules as for the initial treatment, but has to take into account the course of the disease, the time to recurrence, and the judgment by the patient as to whether the first operation was seen to be a beneficial measure.

3.2.5.1.7 Differential Diagnosis
In the case of doubt about the nature of a lesion, there are now numerous neuroradiological techniques that allow distinctions to be made, and if there is still insufficient information or nonresolvable controversy, a stereotactic biopsy can be performed [7]. For noncontrast-enhancing lesions, the major differential is an encephalitic lesion or a postencephalitic state.
Fig. 3.2.36 Incomplete resection of an optic pathway astrocytoma (WHO I) that is followed up with no further therapy. The goal was the disobliteration of the CSF pathway, which was achieved without incurring visual, endocrine or diencephalic problems.

Fig. 3.2.37 Subependymal glioblastoma of the posterior thalamic region (top row) that was debulked via a transventricular approach (bottom row) with actual improvement of a pre-existing moderate hemiparesis.
that are symptomatic, progressive or cause mass effect are removed with an attempt at a gross total resection. Lesions that are incidental, stable, and asymptomatic can be watched or undergo a stereotactic biopsy, after which the histological diagnosis determines further treatment options. Low-grade lesions are followed at regular intervals. High-grade lesions are radiated after biopsy or gross total removal. For glioblastomas, radiation is combined with chemotherapy with temozolomide.

For contrast-enhancing lesions, the differential diagnosis between glioblastoma and metastasis may be difficult (Fig. 3.2.39), or lymphoma and very rarely an acute inflammatory lesion in the context of multiple sclerosis. In deep-seated lesions, a stereotactic biopsy should be performed. A brain abscess or granulomatous disease is rarely mistaken for a glioma (Fig. 3.2.40). MR spectroscopy can distinguish between those and tumors.

3.2.5.1.8 European Standard of Care for Neuroepithelial Tumors
For diagnosis and treatment planning, enhanced MRI and preferably MR spectroscopy are necessary. Lesions that are symptomatic, progressive or cause mass effect are removed with an attempt at a gross total resection. Lesions that are incidental, stable, and asymptomatic can be watched or undergo a stereotactic biopsy, after which the histological diagnosis determines further treatment options. Low-grade lesions are followed at regular intervals. High-grade lesions are radiated after biopsy or gross total removal. For glioblastomas, radiation is combined with chemotherapy with temozolomide.

When lesions recur, reoperation can be indicated in patients with a good quality of life and in lesions that do not pose an additional risk during resection; however, European practice is rather inhomogeneous with regard to this condition.
Fig. 3.2.39  a Typical gadolinium-enhanced MRI of a glioblastoma. b Irregular cystic lesion with contrast-enhancing margins that turned out to be the metastasis of a urothelium carcinoma

Fig. 3.2.40  Cystic, contrast-enhancing lesion in the brain stem that was believed to be a malignant glioma, but which increased in size within a few days and turned out to be an abscess
Selected Reading


3.2.5.2 Meningiomas

3.2.5.2.1 Basics

Meningiomas arise from the arachnoid cover cells of the brain. They can occur anywhere around the brain and may also be located in the ventricles. They are classified according to the WHO system [24].

Grade I meningiomas make up 80% of this type of tumor. There are at least nine histological subtypes, which, however, have not been shown to be relevant to prognosis [24].

Grade II meningiomas (atypical meningiomas) tend to have a higher cellularity and increased signs of proliferative activity, and tend to have a higher incidence of recurrence.

Grade III meningiomas (anaplastic meningiomas, papillary meningioma) are aggressive malignant tumors with a tendency to metasasize.

Genetically, it was found that deletions on chromosome 22 or losses of the whole chromosome are an early event in the disease. Genetic progression to more aggressive types is possible over time in repeatedly recurring cases, but is not the rule, as in astrocytomas, and has to be considered a rare event [22].

3.2.5.2.2 Epidemiology

Meningiomas are more frequent in women (2.5:1 female-to-male ratio). They typically occur in the older age group with a peak incidence in the sixth decade and beyond. There are also pediatric meningiomas, but they tend to occur more frequently in boys and have a preferential ventricular location. There is limited epidemiological information about meningiomas in Europe. However, extrapolating data from regional registries and the North American databases are available.

Many affected patients will be able to live nearly normal lives with the disease, but with the necessity of being under continuous surveillance.

Ionizing radiation has been the most definitive factor associated with the etiology of meningiomas [30]. A hereditary component has been discussed [14], but it is definitely present in patients with type 2 neurofibromatosis [23].
3.2.5.2.3 Symptoms
Meningiomas have a broad range of symptoms. Depending on their location, they cause seizures [3] (temporomesial, periorlandic), focal neurological deficits, symptoms of obstructive hydrocephalus, visual field impairment or behavioral disorders (large frontobasal tumors). Many meningiomas are asymptomatic and are found incidentally.

There is no specific neurological symptom or syndromic complex associated with meningiomas.

3.2.5.2.4 Complications

3.2.5.2.4.1 Hormonal Influence
Meningiomas are more frequent in women and there is the as yet unresolved problem of how the increased levels of steroid hormone receptors lock into the biological behavior of meningiomas [34]. Consequently, there is debate on the role of hormonal replacement therapy in postmenopausal women with regard to the growth, progression or recurrence of meningiomas [16, 37].

3.2.5.2.4.2 Pregnancy
In the course of a pregnancy one has to be aware of rapidly expanding lesions that may even hemorrhage intratumorally, leading to an emergency situation for mother and fetus (Fig. 3.2.41) [38].

3.2.5.2.4.3 Associated Stroke
Encasement of the carotid artery and subsequent severe stenosis or even complete obliteration may lead to stroke (Fig. 3.2.42).

3.2.5.2.4.4 Optic Nerve Involvement
Encasement of the optic nerve will lead to blindness (Fig. 3.2.42).

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Fig. 3.2.41 Thirty-one-year-old woman in the 32nd week of gestation who became unconscious with a generalized seizure and had to undergo emergency tumor removal combined with a cesarean section

Fig. 3.2.42 Progressive recurrent meningioma with encasement of the left optic nerve that originated from the residual of a much larger tumor. Slow progression of this lesion eventually led to blindness in the left eye. The tumor was treated with radiosurgery
3.2.5.2.4.5 Spinal Cord Compression
Meningiomas at the craniocervical junction that may have gone unnoticed for a long time can lead to acute paraplegia in the situation of a whiplash injury (Fig. 3.2.43).

3.2.5.2.4.6 Cancer Metastases
Possibly in relation to the unresolved hormonal dependence, there is also a relationship with breast cancer metastases, which appear to be able to preferentially hone in on meningiomas. Therefore, in any incidentally discovered meningioma in a woman who is affected with breast cancer there is an additional reason for it to be removed to prevent that from happening (Fig. 3.2.44).

3.2.5.2.5 Diagnosis
The suspected diagnosis will be established from neuroimaging and it is mandatory today that an MRI scan is performed to allow the relevant information to be obtained in all three planes, which will allow the assessment of the invasion or involvement of neighboring structures such as the venous sinuses or cranial nerves [19]. Men-

Fig. 3.2.43 Meningioma of the craniocervical junction which could be removed without sequelae. MRI with and without Gd (left and middle) in the sagittal and coronary plane (right)

Fig. 3.2.44 Coincidence of metastasis from mammary carcinoma and meningioma. Meningioma of the craniocervical junction caused bilateral leg weakness and hypoesthesia
Meningiomas are homogenously enhancing lesions that as a rule have a broad attachment to the dura of the convexity or the skull base. They may be calcified, which may be seen on an additional CT scan. Surrounding intracranial edema may be present, indicating breakdown of the arachnoid plane. This may be present in some cases all around the meningioma, but is most pronounced around the secretory variant (Fig. 3.2.45) [7]. MR spectroscopy may give additional clues [11].

Angiography is no longer part of the routine evaluation of meningiomas. If it is performed for specific reasons, blood supply from the external carotid artery will be found as a rule. Should the blood supply come from the internal carotid, other differential diagnoses have to be considered: either a more malignant variant of meningioma, like papillary meningioma or meningiosarcoma, or also hemangiopericytoma (see Sect. 3.2.5.2.9).

### 3.2.5.2.6 Therapy

Therapy for meningiomas is mostly surgical [1, 2]. Most tumors will be resected as radically as is safely possible [9] and radicality is still captured according to the Simpson [32] grading system. Some meningiomas are primarily unresectable (mostly skull base tumors) and these will be treated by combined surgical and radiosurgical strategies [6, 9].

#### 3.2.5.2.6.1 Conservative Treatment

An incidental meningioma that has been definitively asymptomatic after a thorough case history has been established may be observed with neuroimaging at appropriate time intervals, which should be 6 months in young adults and up to a year in patients over 70. Thereafter, the intervals will be adjusted according to the emerging growth characteristics. This is different when the incidental discovery is a fortuitous event, as in a suprasellar meningioma that has not yet caused symptoms, but shows displacement and compression of the optic chiasm or analogous cases in the posterior fossa. Early treatment should be advised.

While observing an asymptomatic meningioma, stable disease may be present for a long time. Special attention has to be given to the perimenopausal period, during which proliferation dynamics can change.

Seizure prophylaxis with anticonvulsive drugs can be necessary in some patients who became symptomatic with a seizure. As long as the tumor causing the seizure activity is still in place, it needs to be continued.

Radiosurgery has its established role in the treatment of residual tumors at the skull base [6] or as primary treatment of well-contained cavernous sinus meningiomas that are limited to that compartment or optic sheath meningiomas [4]. Frequently, radiosurgery will be combined with surgical resection within the limits of what is safely possible [36].

Endovascular embolization, used alone, has not found its way into the established treatment schemes. It may be used preoperatively in selected cases [5, 28, 29].

There is no role for chemotherapy in grade I and II tumors. In these cases, when there is no surgical option and all other measures, such as radiosurgery, have been exhausted, experimental treatment with hydroxy-urea can be attempted, which has shown anecdotal efficacy, but has never been proven to be efficacious in a controlled clinical trial [25, 26]. Likewise, all hormone-based treatments have not been efficacious [12]. For anaplastic tumors, there are limited reports on chemotherapy, but the success is limited and temporary stabilization is the maximum achievement [9, 10, 20].

#### 3.2.5.2.6.2 Surgical Therapy

The role of surgery for meningiomas is well established. Resection of meningiomas with Simpson grade I resections should lead to a definitive cure in most cases [2].

The principles of resection are standardized and include microsurgery, minimal invasiveness, image guidance, and where applicable, intraoperative monitoring by electrophysiological means. The paradigm to obtain maximal radicality, even with the help of bypass surgery and intracranial grafting for severed cranial nerves, has been left behind [6]. Nevertheless, there are complex skull base lesions that may require interdisciplinary ap-
proaches involving ophthalmic surgeons, maxillofacial surgeons or ENT colleagues for what can be considered the removable part. Nonresectable portions of tumor, either in the wall of major sinuses or at the skull base, will be left for close observation. They may remain unchanged for many years. Should regrowth or progression be clearly documented, a focal radiation should be offered to the patient and the planning should occur between both the radiotherapist and the neurosurgeon as an interdisciplinary effort.

3.2.5.2.6.2.1 Surgical Resection of Convexity Meningiomas
The incision is planned so that the entire area of the tumor origin is exposed. Dura is removed together with the tumor and replaced with grafted periosteum.

3.2.5.2.6.2.2 Surgical Resection of Sphenoid Wing Meningiomas
Usually, a pterional approach is taken and the Sylvian fissure split. The exophytic part is removed, including the dura, and bone is drilled as far as possible, sometimes removing the lateral wall of the orbit and opening the superior orbital fissure. Reconstruction uses methyl methacrylate or titanium mesh and periosteum (Fig. 3.2.46).

3.2.5.2.6.2.3 Sagittal and Falcine Meningiomas
Exposure of the sinus anterior and posterior to the lesion is planned to go far enough laterally on both sides so that the interhemispheric space can be entered from both sides. In the case of an obliterated sinus, after removal of the exophytic part of the tumor, the sinus will be secured and divided anterior and posterior to the tumor, and the infiltrated part removed, including a generous portion of the falk. When there is no involvement, the inferior sagittal sinus should be spared, as it may serve as important collateral. In the case of involvement of only the external sheath of the sinus, this will be sharply dissected and then coagulated. If there is growth throughout the whole wall and anticipated removal would leave a hole too large to be easily grafted with periosteum, the infiltrative part is left behind and watched. In the case of further growth, two alternative approaches might be taken. One is to wait until the sinus is obliterated, which usually occurs slowly with concomitant formation of sufficient collaterals. Then, the residual tumor can be taken out en bloc. The other less preferable approach is treatment with focal irradiation.

3.2.5.2.6.2.4 Frontobasal Meningiomas
The approaches taken vary according to the lesion and its extension and include anything from a small frontobasolateral craniotomy to large pterional, orbitofrontozygomatic and even bifrontal transbasal approaches. Most suprasellar meningiomas and olfactory meningiomas can be approached via a pterional craniotomy. Most suprasellar meningiomas and olfactory meningiomas can be approached via a pterional craniotomy. Most suprasellar meningiomas and olfactory meningiomas can be approached via a pterional craniotomy. Care should be taken to coagulate and scrape any dura to minimize the incidence of recurrences. When extending towards the optic canal, this might need to be opened to allow mobilization of the nerve and removal of affected dura. In the case of compression of the chiasm any displacement of neural structures should be minimal but the tumor should be debulked from the inside to gradually decompress the neural structures. Large olfactory meningiomas may penetrate the skull base requiring replacement of the cribriform plate with a bone graft taken as split bone from the lamina externa of the bone flap (Fig. 3.2.47) [8].

3.2.5.2.6.2.5 Adjuncts to Surgical Resection

3.2.5.2.6.2.5.1 Preoperative Embolization
This has a value in cases where significant blood supply comes from areas which will only be exposed late during surgery. These are few cases and the experience with them is mixed [5, 28, 29]. Should it be used, there needs to be increased awareness for swelling which is dangerous
in cases where brain stem compression is already present or herniation is imminent in the case of large bifrontal or temporal lesions which already have significant amounts of edema.

3.2.5.2.6.2.5.2 Radiosurgery
Radiosurgery is mostly used in combination with surgery although sometimes also as primary modality [13]. Treatment planning and field control for radiation has made significant advances in the last decades and high intensity radiation can now be safely administered to even very critical regions like the cavernous sinus which has complex neighborhood relationships to the optic and hypothalamic structures [18]. The debate, whether single dose radiosurgical treatment by gamma knife or LINAC or whether a fractionated regimen are better is still undecided and intensity modulated schedules are too early in the follow up period to comment [9, 36].

3.2.5.2.7 Differential Diagnosis
There are almost no durally attached intracranial tumors which can be mistaken for meningioma. The only other tumor resembling meningioma is hemangiopericytoma which has as differentiating characteristics destruction of bone, frequently a very inhomogeneous structure, blood supply from the internal carotid and always pronounced edema [15].

Lymphomas and metastases can occur in principle anywhere, thus also as dural neoplasms [21, 31, 33, 35]. The overall medical history of the patient needs to be considered when shape and other structural characteristics suggest that kind of differential diagnosis.

3.2.5.2.8 Prognosis
The prognosis of meningiomas is generally favorable. Most patients can expect to be cured or at least in long term control of their disease. The disease may locally progress with little therapeutic options and that is in particular the case for optic nerve meningiomas which cannot be resected and are only partially controlled by radiotherapy.

Recurrence rates are low for convexity grade I meningiomas but high for meningiomas of the skull base or midline.

Atypical meningiomas (WHO grade II) need closer monitoring and stringent follow-up but may have the same good prognosis as grade I tumors, only with the necessity of several therapeutic interventions over the lifetime.

Anaplastic meningiomas have a poor prognosis [27]. Even with all combined modalities like resection, radiation and chemotherapy the median survival in most published series is less than four years particularly due to the tendency to metastasize [17, 27].

3.2.5.2.9 Hemangiopericytoma
This tumor is not an exclusively dural neoplasm but deserves special consideration in this context because dural manifestation represents a major subgroup. The tumor often mimics meningioma but shows more bone erosion and blood supply from the internal carotid as well as edema. Treatment is similar to meningiomas and ranks resection as the major means to reduce tumor. These tumors have, however, a high rate of local recurrence but show some degree of increased local control after resection and local irradiation. Chemotherapy is frequently used especially after metastases are found. The prognosis is better than for anaplastic meningiomas but is still unfavorable in the long run.
Selected Reading

3.2.5 Lymphomas

3.2.5.3.1 Basics
The origin of primary lymphomas of the central nervous system (PCNSL) have for a long time been a matter of debate. It is still not agreed from where the cell of origin is derived, but it is agreed that expansion and progression is intracerebral. Most are of the B cell type [7]. T cell lymphoma is rare [9].

In addition, there are increasing numbers of CNS lymphoma associated with immunosuppression, either in the context of an HIV infection or in patients who have received an organ transplant [2].

3.2.5.3.2 Epidemiology
Primary lymphomas of the CNS are most common in the older age groups. There is an increasing incidence that has given rise to much debate about the possible causes, none of which, however, could be firmly established. The last reported incidence describes PCNSL constituting 6% of all primary intracranial neoplasms [7].

3.2.5.3.3 Symptoms
Lymphomas usually become symptomatic with seizures or a rapidly progressive focal neurological deficit. The symptoms are not generally different from any other parenchymal intracerebral lesion and none is specific to or pathognomonic for lymphoma.

3.2.5.3.4 Complications
Most complications of PCNSL are associated with treatment. Lymphomas are by their nature frequently associated with perifocal edema. Although lymphoma can often be suspected from the imaging characteristics (see below) or an associated disease context (see above), unfortunately, steroids are often given as a reflex to the edema seen on the T2-weighted MRI. This may lead to disappearance of the lesion (ghost tumors) and no diagnosis can be made. Without such a diagnosis, however, the appropriate therapy cannot be started. Stopping the steroids will allow the lesion to reappear, but more aggressive clones may already have been selected.

While there is still ongoing debate regarding the roles of whole brain radiation treatment (WBRT) in the treatment of PCNSL, it is acknowledged that in older patients, in addition to or synchronous with, chemotherapy, it appears to cause unacceptable neurocognitive deficits. This complication is avoided by not including WBRT in elderly patients [4, 5].

3.2.5.3.5 Diagnosis
The suspected diagnosis will be established from neuroimaging and it is mandatory today that an MRI scan be performed. Lymphomas are characteristically located in the periventricular white matter (Figs. 3.2.48, 3.2.49), but may also have extensive cortical presentation. They are usually primarily hyperintense and characteristically homogeneous in appearance; thus, they can be mistaken for meningioma when located cortically. They have, however, unclear “foggy” margins (Fig. 3.2.49) and are almost never necrotic or cystic. Contrast enhancement is also homogeneous. Multiple lesions are possible. There are patients with only arachnoidal enhancement. The PCNSL is truly a neuroradiological chameleon that is almost certainly diagnosed when presenting with a typical appearance, but then there is such a broad range of possible appearances, that in rare instances it can mimic almost any other lesion [6]. When PCNSL is suspected, no steroids should be given before tissue diagnosis. Histology is usually es-

Fig. 3.2.48 Gadolinium-enhanced T1-weighted MRI of a typical left-sided paraventricular, deep white matter lesion with homogeneous enhancement, no necrosis and fuzzy edges, which was biopsied and proven to be PCNSL.
3.2.5.3.6 Therapy

Therapy for CNS lymphomas is nonsurgical except when space occupation removal is felt necessary [1]. Different regimens for chemotherapy and radiation and combinations thereof have been evaluated over the last few decades. The most accepted regimens are based on risk adaptation and aggressive chemotherapy, both intraventricular and systemic, and additional radiation, depending on the performance of the patient [4, 8]. Methotrexate features prominently in the current regimens, but there are current extrapolations from the treatment for systemic lymphoma with monoclonal antibodies and also blood–brain barrier disruption [10], which may have specific implications for this tumor type as it has a physiology that accounts for different pharmacokinetics than those known from intrinsic brain tumors [11].

Surgical removal adds no additional benefit to the current chemotherapy regimens [1].

3.2.5.3.7 Differential Diagnosis

Lymphomas need to be distinguished from metastases and sometimes from anaplastic gliomas. Also, inflammatory lesions, and especially large foci of multiple sclerosis, have to be excluded because therapy is very different from that of lymphoma. Careful evaluation of the case history and additional investigations like CSF chemistry for inflammatory lesions or MR spectroscopy may help to distinguish between different entities.

3.2.5.3.8 Prognosis

The prognosis of lymphomas is still considered unfavorable. However, there is a tendency toward increasing survival with the more intense, risk-adapted therapy regimens, new reagents based on experience gained from systemic lymphomas or derived from insights into tumor physiology, and even long-term remission with an acceptable quality of life has been observed [3, 10, 11].

3.2.5.3.9 European Standard for the Treatment of PCNSL

- When the presence of PCNSL is suspected, no steroids are given before tissue diagnosis is established.
- Tissue diagnosis is established by stereotactic biopsy.
- Risk-adapted chemotherapy protocols of variable intensity are the current gold standard of treatment.
- Surgical resection for lymphoma is unusual and is the consequence of highly individual circumstances.

Selected Reading


3.2.5.4 Germ Cell Tumors

3.2.5.4.1 Basics
Germ cell tumors occur mostly in the pediatric population. They originate from embryonal tissue and are generally divided into proper germ cell tumors and the so-called non-germinomatous germ cell tumors, which include yolk-sac tumors, teratoma, teratocarcinoma, embryonal carcinoma, and choriocarcinoma [11].

3.2.5.4.2 Epidemiology
Germ cell tumors are rare. There are regional differences with the highest incidence apparently in Japan. The peak incidence is in Asia, where they constitute 2% of all intracranial tumors, but only 0.2% to 0.5% elsewhere [11]. There is a slight predominance of germinomas in males, but no gender difference for the other tumors.

No environmental clues have been described and no genetic syndromes are associated with this tumor group.

3.2.5.4.3 Symptoms
Germinomas arise usually in the pineal region and/or in the suprasellar region, particularly in relation to the pituitary stalk. Therefore, the symptoms are those of chronic or even acute hydrocephalus from compression of the Sylvian aqueduct, hormonal disorders, with diabetes insipidus and pituitary insufficiency, or visual disorders caused by chiasmal compression. It has been proposed that the combination of diabetes insipidus with a pineal lesion, even in the absence of neuroradiological evidence of hypothalamic involvement, is certain to be associated with germinoma [13]. This has to be questioned as the combination has also been seen with histologically proven pineocytoma, leaving the cause of germinoma unresolved (Fig. 3.2.50).

Fig. 3.2.50 Biopsy-proven pineocytoma in a 1.5-year-old boy with diabetes insipidus in whom germinoma was suspected, but no treatment was started before tissue diagnosis, which turned out to be different from the initial assumption.
The other group, the non-germinomatous germ cell tumors, frequently produce high levels of hormones like alpha feto-protein or beta human chorionic gonadotropin (HCG), which can lead to precocious puberty.

### 3.2.5.4.4 Complications
As with most other entities, many complications may arise from therapy. Initially, acute hydrocephalus occurs due to pressure on the Sylvian aqueduct. This may force immediate intervention, but should not lead to implantation of a shunt, as this can be complicated by systemic metastases [1]. Hemorrhage may occur spontaneously or in conjunction with stereotactic biopsy [14].

As the pineal region tumors are extremely heterogeneous, endoscopic or stereotactic biopsy may provide an inadequate sample [6], and therefore mixed tumors are either underestimated (pineocytoma instead of pineoblastoma) or overestimated (germinoma instead of mature teratoma with germinomatous components (Fig. 3.2.51).

Treatment for germinomas includes radiotherapy, which in most cases includes the whole brain or even the spinal cord in craniospinal radiation and the neurocogni-

![Fig. 3.2.51](image)

*Fig. 3.2.51* Mixed teratoma with germinoma in a young man. Because of its heterogeneity the lesion was approached for open resection, which was abandoned when during the procedure a frozen section showed a germinoma. Later, a teratoma with immature features was seen in additional specimens and after radiation, the tumor maintained a formidable size, most likely constituting a mature teratoma for which patient and family refused further treatment.

### 3.2.5.4.5 Diagnosis
A major component of the diagnostic procedure is neuroimaging. It is mandatory today that an MRI scan be performed, especially to obtain information on the displacement of the Sylvian aqueduct in the sagittal plane and the relationship with the quadrigeminal plate. As for the features of the lesion itself, there are no specific clues or characteristics that allow diagnose a germinoma, a non-germinomatous germ cell tumor or a pineal parenchymal tumor to be diagnosed with any certainty [8].

An additional cranial CT might be useful for determining the extent of calcification. Simultaneous lesions in the pineal region and the suprasellar cistern very strongly hint at pure germinoma (Fig. 3.2.52). A lesion confined to the suprasellar cistern may also be a granuloma and may need to be biopsied to establish the diagnosis (Fig. 3.2.53). Lesions within the pineal region cannot be subclassified based on the morphology alone, as all germinomas and non-germinomatous germinomas may be partly cystic, present with perilesional edema, and have patchy contrast enhancement (Fig. 3.2.52). The only clue pointing toward a possible teratoma is extreme heterogeneity (Figs. 3.2.51, 3.2.54).

Biochemical markers in serum or CSF may be very helpful in establishing the final diagnosis.

Cerebrospinal fluid markers and cytology can only be obtained when there is clearly no sign of CSF pathway obstruction. Otherwise, when serum samples show ambiguous results and CSF sampling is required, CSF might be obtained during stereotactic or endoscopic biopsy, which has taken on a significant role in recent years, as it also allows ventriculostomy at the time of biopsy and allows the necessity of any shunting to be circumvented [10, 15].

### 3.2.5.4.6 Therapy
Therapy for germinomas and non-germinomatous germ cell lesions is complex and requires an interactive interdisciplinary team [4, 5]. The most important element is a safe and representative tissue diagnosis, which can be obtained by stereotactic or endoscopic biopsy, but will be most reliable when the lesion is surgically excised whenever possible and is not a pure germinoma [2].

If a pure germinoma can be assumed to be present, radiation will be initiated as the first line of therapy [7], but may be preceded by chemotherapy to further increase the efficacy of radiation, which may then be confined to
the involved field [7]. Rapid and sustained resolution is to be expected (Fig. 3.2.55).

For non-germinomatous germ cell tumors, there is first combinatorial chemotherapy and radiation. Should there still be tumor present, surgery should be performed to remove the remaining solid part. Afterward, another chemotherapy regimen should be given to consolidate the treatment [7]. The treatment efficacy greatly improved when the experiences gained from the treatment of adult germ cell tumors were combined with the pediatric experience.

Focal radiation has been frequently mentioned over the last decade, particularly as an alternative to surgical removal, which was considered to carry too high a risk. It cannot be denied that radiosurgery has its place in the treatment of many tumors and also plays some role in recurrent or otherwise exhaustively treated pineal region tumors [3]. The argument, however, cannot be that surgery is too risky, as in those centers in which this highly standardized operation is performed regularly, the morbidity is very low when using the classical supracerebellar, infratentorial approach (Fig. 3.2.56) [2].

3.2.5.4.7 Differential Diagnosis

In the pineal region, pineal parenchymal tumors such as pineocytoma or pineoblastoma need to be distinguished. They have no markers, but the neuroimaging appearance overlaps with the other tumor types so that in any case a biopsy, preferably a resection for a marker negative tumor is advised, providing enough sample to not miss the intermediate type, which may easily progress to an aggressive lesion (Fig. 3.2.56). Pineocytomas may also be cystic and thus not distinguishable from pineal cysts, which in turn may cause aqueductal compression and even hemorrhage (Fig. 3.2.57).

Fig. 3.2.52 Hypothalamic granuloma with severe water and electrolyte imbalance and eating disorder as well as mental alterations

Fig. 3.2.53 Germinoma with inhomogeneous appearance, which is located in the pineal region as well as in the suprasellar region, with additional manifestation in the fourth ventricle. The simultaneous suprasellar and pineal location is very typical of germinoma
Fig. 3.2.54  Very inhomogeneous tumor in the quadrigeminal cistern apposed to the pineal gland that turned out to be a mature teratoma and was completely resected

Fig. 3.2.55  Typical biopsy-proven germinoma filling the whole third ventricle, which responded well to standard treatment
In the suprasellar region, granulomas are more frequent than elsewhere (Fig. 3.2.52). They are also marker-negative and indirect inflammatory signs in the CSF are absent or ambiguous. They may respond to steroids, but the response may be slow; therefore, a lack of response does not exclude that possibility.

**Fig. 3.2.56** a Axial and b sagittal Gadolinium-enhanced T1-weighted MRI showing a cystic pineal parenchymal tumor of intermediate differentiation, which was completely resected by c, d the supracerellar approach

**Fig. 3.2.57** Pineal cyst with signs of hemorrhage and chronic hydrocephalus due to compression of the Sylvian aqueduct

### 3.2.5.4.8 Prognosis

The prognosis for pure germinomas is generally excellent with correct treatment and long-term control or cures are frequent. As for the mature teratomas, the prognosis is also excellent when completely resected. With the anaplastic non-germinomatous germ cell tumors, the prognosis
is uncertain because no large series with homogeneous treatment regimens have been published. There is reason to believe, though, that with appropriate combinations of chemotherapeutics, surgery and radiation the prognosis improves and long-term control is possible [5].

3.2.5.4.9 European Standard for the Treatment of Germ Cell Tumors

• Upon detection of a pineal tumor, serum and possibly CSF markers should be obtained.
• Hydrocephalus is treated by third ventriculostomy, strictly avoiding shunting.
• Tissue diagnosis is made from biopsy or after open surgical resection.
• Resection techniques have been refined and are safe.
• Germinomas are treated with radiation therapy, which may be preceded by chemotherapy.
• Non-germinomatous germ cell tumors are resected when mature and treated by a combination of surgery, chemotherapy, and radiation when immature. The same holds true for pineal parenchymal tumors.

Selected Reading


3.2.5.5 Tumors of the Sellar Region

3.2.5.5.1 Basics

Sellar tumors originate from the proper contents of the sella, which is the pituitary gland, or from developmental residues there, or from the surrounding structures. The first group is thus the adenomas from the anterior lobe, which are either hormonally active or nonfunctional. The second type of tumor is the craniopharyngioma and tumors from the surrounding structures, which are mostly meningiomas or metastases and will be dealt with in that context elsewhere (Sects. 3.2.5.2 and 3.2.5.6).

Hormonally active tumors secrete prolactin, growth hormone, the adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH) or gonadotrophins (LH/FSH). Mixed hormone secretion is also known but rare. The inactive adenomas may still produce subunits of some hormones or inadequately processed precursor molecules. Pituitary adenomas are mostly restricted to the sellar area, but, without being histologically anaplastic in some cases, may also grow invasively into the cavernous sinus and compromise its contents. Anaplastic adenomas and pituitary carcinomas are rare and usually develop after a long history of recurrence and repeated multimodal treatment. Many different classification schemes exist, but only one was adopted by the WHO [6].

Craniopharyngiomas arise from residuals of the craniopharyngeal duct. They are frequently cystic and locally invasive. They occur in the sella, in the sella with extensive suprasellar extension, but also originate higher
up all along the pituitary stalk and at the base of the infundibulum. Histologically, they are made up of Rathke pouch epithelium and are classed as grade I according to the WHO, with only extremely rare instances of anaplasia [5].

### 3.2.5.5.2 Epidemiology

Pituitary adenomas occur throughout life, although the proportion of children and patients over 70 affected is rather small.

Craniopharyngiomas occur typically in children and then with a second incidence peak later in the seventh decade.

No environmental clues have been described and no genetic syndromes are associated with either of these tumor groups.

### 3.2.5.5.3 Symptoms

For sellar tumors, there are some common, nonspecific symptoms and then there are symptoms that are specifically related to the endocrine activity of a tumor. The nonspecific symptoms are visual field disturbances caused by tumors compressing the optic chiasm from below. Also, compression of the optic nerves may cause severe loss of visual acuity and even blindness. A sudden hemorrhage into a tumor is a feared complication and immediately results in emergency treatment to rescue the patient from optic nerve compression and subsequent loss of vision. The other major common symptom for all sellar lesions large enough to exert pressure on the pituitary stalk or the gland itself is that of pituitary insufficiency, which is particularly dangerous when it affects the adrenal axis, perhaps eventually leading to an Addison crisis. Any mild compression of the gland due to a tumor that results in a lack of inhibitory control of the prolactin secretion can result in reactive hyperprolactinemia, which is different from hyperprolactinemia due to an active adenoma. This will lead to infertility or amenorrhea in women and loss of libido in men.

Hormonally active pituitary adenomas have their characteristic symptoms depending on the hormone secreted. Prolactinomas cause infertility in females and amenorrhea, and when large with excessive hormone production, even galactorrhea. In males the most frequent presenting sign of prolactinomas is impotence, and with excessive prolactin secretion, gynecomastia.

Growth hormone-producing adenomas typically present with acromegaly in the adult and with gigantism in children or teenagers.

Adrenocorticotropic hormone-producing adenomas cause hypercortisolism and this leads to the development of Cushing's disease.

Thyroid-stimulating hormone-secreting tumors result in hyperthyroidism, whereas gonadotropin-secreting tumors also cause fertility problems.

Craniopharyngiomas most often present with partial pituitary insufficiency and visual problems due to suprasellar extension and optic nerve/chiasm compression. There may be delayed puberty as well as impairment of pituitary/hypothalamic function, such as diabetes insipidus or eating disorders.

### 3.2.5.5.4 Complications

Hemorrhage into a large pituitary adenoma, which is also called pituitary apoplexy, can cause immediate loss of vision, headache, and severe impairment of pituitary function including diabetes insipidus [12].

Extension of very large adenomas or craniopharyngiomas into the third ventricle may lead to obstructive hydrocephalus because of the blockade of the foramen of Monro. This can lead to acutely raised intracranial pressure with herniation.

Suprasellar extension into the third ventricle with hypothalamic compression may also cause severe imbalances of water and electrolytes. Hypo- or hypernatremia may result, with the related disturbances of consciousness and even severe brain edema may be a feared complication.

Extensive suprasellar and retrosellar extension may affect the integrity of the mammillary bodies, either in the untreated state or later in the context of therapy leading to apathy and memory loss.

There are also severe complications from insufficient treatment of hormonally active tumors. Longstanding severe Cushing's disease causes hypertension, muscle wasting, and osteoporosis. Long-standing acromegaly causes severe diabetes with all the late effects and cardiomegaly with, eventually, fatal cardiomyopathy.

The most feared treatment-related complication in ACTH-producing pituitary adenomas is the development of Nelson's syndrome after adrenalectomy for Cushing's disease, which has fortunately become extremely rare, but was more frequent during the days of insufficient transphenoidal surgery and poor endocrine diagnostics where adrenalectomies were performed.

### 3.2.5.5.5 Diagnosis

A major component of the diagnostic procedure is neuroimaging. It is mandatory today that an MRI scan be performed, especially to obtain information on the relationship with the optic chiasm and the pituitary stalk and possible invasion of the cavernous sinus. An additional cranial CT might be useful for determining the extent of calcification, especially for craniopharyngiomas.

Adenomas are homogeneously enhancing, well-demarcated tumors that may just be visible in the pituitary and cause stalk deviation (Fig. 3.2.58) or fill the whole sella...
lumen or extend into the suprasellar region (Fig. 3.2.59). They are only rarely cystic. In extreme cases they can extend to all neighboring structures and invade the cavernous sinus as well as the anterior skull base (Fig. 3.2.60).

Craniopharyngiomas are much more frequently cystic or multicystic. The cysts can be extremely heterogeneous in their imaging properties ranging from hyperintense to hypointense, depending on the contents (Figs. 3.2.61, 3.2.62). Calcifications are frequent. At least in primary tumors, the pituitary can often be seen in the sella, displaced or compressed into one corner.

Hormonally active adenomas are diagnosed due to their endocrine syndromes [7]. All pituitary hormones can be easily measured; therefore, serum diagnostics are

![Fig. 3.2.58 Pituitary microadenoma contained in the sella with stalk deviation to the side of the tumor](image)

![Fig. 3.2.59 Large inactive pituitary adenoma with extensive suprasellar extension, leading to the choice of a primarily transcranial approach](image)
Fig. 3.2.60 Very large human growth hormone-secreting adenoma with diffuse infiltration of the perisellar structures that was resistant to multimodal treatment.

Fig. 3.2.61 Typical suprasellar craniopharyngioma, which has a very heterogeneous appearance on MRI, not only with a mix of cystic and solid components, but also cysts with variable signal intensities.
conservative treatment for pituitary adenomas is constantly undergoing changes because of the increasing availability and efficacy of medical therapies [11]. Prolactin-secreting adenomas are mostly treated by dopamine agonists that need to be taken for many years, or even for life. This leads in most cases to complete long-term control, but there are still reasons mostly related to patient compliance and side effects why surgery is warranted [2]. Human growth hormone-secreting adenomas are nowadays also treated with drugs first. Somatostatins have been developed into long-acting agents so that treatment can be managed by most patients. Long-term control is possible, but intolerance to treatment or insufficient response still requires surgical intervention.

routine. Measuring the prolactin levels is mandatory in large, newly diagnosed tumors because the levels will determine further decisions and will clearly distinguish between reactive hyperprolactinemia and prolactinoma.

Only for ACTH, is there the possibility of ectopic hormone production in small cell lung carcinoma or other potentially paraneoplastic endocrine-active tumors. As at the same time, these adenomas may really be microadenomas that cannot be seen, even on high-resolution MR, catheterization of the petrosal sinus may be helpful in establishing at least by virtue of a central to peripheral gradient the diagnosis of central Cushing’s disease versus an ectopic syndrome [4].

**3.2.5.6 Therapy**

**3.2.5.6.1 Conservative Treatment**

Therapy for pituitary adenomas is constantly undergoing changes because of the increasing availability and efficacy of medical therapies [11]. Prolactin-secreting adenomas are mostly treated by dopamine agonists that need to be taken for many years, or even for life. This leads in most cases to complete long-term control, but there are still reasons mostly related to patient compliance and side effects why surgery is warranted [2]. Human growth hormone-secreting adenomas are nowadays also treated with drugs first. Somatostatins have been developed into long-acting agents so that treatment can be managed by most patients. Long-term control is possible, but intolerance to treatment or insufficient response still requires surgical intervention.

**Fig. 3.2.62** Almost exclusively cystic, mainly intrasellar, craniopharyngioma
Medical treatment is insufficient for the other hormonally active adenomas, and there is no medical treatment for inactive adenomas or craniopharyngiomas.

3.2.5.5.6.2 Surgical Treatment
Pituitary adenomas are safely removed by selective microsurgical transsphenoidal adenomectomy [1]. Large suprasellar extensions may rarely require additional or primary transcrtanial intervention (Fig. 3.2.59 [1]).

Craniopharyngiomas are approached using the transsphenoidal approach when the tumor is intra- or intra-/suprasellar [3], but frequently using the transcranial approach when there is major involvement of the third ventricle and hypothalamus. As the tumors are highly individual in their extension, there are many approaches that need to be taken, which range from pterional through bifrontal to transcallosal/transventricular. Literature series report effective gross total resection in 50–70% of cases.

Recurrent tumors can frequently be reoperated, but thereafter radiotherapy must be considered.

3.2.5.5.6.3 Radiotherapy
Pituitary adenomas can grow invasively into the cavernous sinus, rendering them uncontrollable by surgery alone. In these cases, residual tumors or any tumor that shows signs of regrowth can be treated by conformal radiosurgery, either with single high-dose stereotactic radiosurgery by Gamma knife or LINAC, or in a fractionated regimen. Radiosurgery plays an increasing role in the overall management [8].

Craniopharyngiomas should also be irradiated upon recurrence and some groups already advocate radiation as the primary treatment without even risking initial surgery, which may incur morbidity due to hypothalamic injury. For mostly cystic craniopharyngiomas, instillation of radionuclides for interstitial radiation is successfully used by some centers.

3.2.5.5.7 Differential Diagnosis
In addition to intrinsic and extrinsic tumors, inflammatory lesions occur in the sella. Hypophysitis is rare and is characterized by the same symptoms as an intrasellar adenoma. It can also extend to the suprasellar plane and cause visual symptoms, and therefore the diagnosis is frequently made after surgery and not with imaging [9, 10]. Granulomas are even rarer and typically in closer proximity to the pituitary stalk. Likewise, germinomas may occur along the pituitary stalk and the diagnosis should be suspected when there is an additional lesion in the pineal region.

Metastases can occur just as often in the sella or parasellar region as anywhere else. They tend to be locally invasive and frequently destruct bone. The diagnosis is more likely when an underlying primary tumor is known.

Meningiomas tend to have a broad attachment to the bony surroundings of the sella and also frequently show dural involvement over the tuberculum sellae or the sphenoid plane.

3.2.5.5.8 Prognosis
The prognosis for endocrine active pituitary adenomas is excellent, except for giant adenomas, which at the time of presentation are already invasive (Fig. 3.2.60). Inactive adenomas usually present later and with larger sizes; therefore, in these cases, recurrence is more frequent. Even with local invasiveness, the prognosis for long-term control is good when radiotherapy is included in the therapeutic strategies.

Craniopharyngiomas have a tendency to recur even after gross total resection because of the invasive nature of the capsule, which may have digit-like processes into the surrounding parenchyma, which in the case of hypothalamic extension cannot be removed with any kind of safety margin. Therefore, there is a need for irradiation in subtotally resected or recurrent tumors [13, 14]. This, however, does not result in complete control in all cases and progression may still occur, but 10 year survival is over 90% in most series when combination therapy is used and patients are regularly followed up.

3.2.5.5.9 Generally Accepted Standard Treatment in Europe

3.2.5.5.9.1 Pituitary Adenomas
Prolactin and growth hormone-secreting tumors are first treated medically. Surgery is only indicated when medical therapy fails or the patients wish to circumvent their need for constant medication. All other adenomas are resected microsurgically, either transnasally or via the transcranial route when there is extensive suprasellar or parasellar extension. There is increasing use of the endoscope in transnasal surgery. Invasive tumor residuals or recurrences are treated by fractionated conformal radiotherapy.

3.2.5.5.9.2 Craniopharyngiomas
There is no consensus on the treatment of craniopharyngiomas. Small intrasellar lesions are resected transsasally. The majority of the suprasellar cystic craniopharyngiomas will also be resected. When residual tumor is present, resection is followed by radiation. In cases of radiologically complete resection radiotherapy may be withheld to wait and see whether there will be recurrence. Some centers advocate biopsy and radiation as the primary treatment. Also, interstitial radiation (brachytherapy) is given in some centers to treat cystic lesions.
### Selected Reading


### 3.2.5.6 Metastases

#### 3.2.5.6.1 Basics

Metastases are the most frequent intracranial tumor entity. With increasingly improved control of systemic disease, there are a growing number of patients who will fail in the intracranial compartment during the course of the disease [2]. Brain metastases are hematogenic because there is no lymphatic system. It is speculated that a specific set of cell surface adhesion molecules is necessary for a tumor to metastasize to the brain. Not all primary tumors have equal potential to spread to the brain. Metastases may be singular (only one metastasis known in the body) or solitary (only one metastasis known in the brain). Multiple lesions may be present. When they are all of a similar size, just one metastatic event is assumed (synchronously metastasizing), or when they are very different in size a metachronous event is postulated.

#### 3.2.5.6.2 Epidemiology

With the increasing incidence of cancer in an aging population and increasingly successful systemic therapies, the incidence of brain metastases is rising and it can roughly be assumed that there are ten times as many brain metastases as primary brain tumors. The annual occurrence for the European Union is therefore estimated to be roughly 300,000 cases.

#### 3.2.5.6.3 Symptoms

Metastases become symptomatic with a broad range of symptoms. Depending on their location, they cause seizures (temporomesial, perirolandic), focal neurological deficit, symptoms from obstructive hydrocephalus, visual field impairment, or behavioral disorders (large frontal tumors). Many metastases are asymptomatic when found and are discovered in the context of staging or routine follow-up for known disease. Twenty percent of metastases are found without a known primary and a clue as to where to look for a primary tumor is often only obtained after tissue diagnosis of the metastasis.

#### 3.2.5.6.4 Complications

Hemorrhage into a large metastasis may have the same symptoms as a spontaneous intracerebral hemorrhage with a sudden neurological deficit, loss of consciousness or even herniation. Hemorrhage is not pathognomonic for a specific histology, but can occur with almost any histology.

Shedding of cells on the surface of metastases exposed to CSF spaces may lead to spread within the CNS compartment and subsequent meningeal carcinomatosis (Fig. 3.2.63).

Extensive metastases may lead to increased protein concentrations in the CSF and consecutive malresorptive hydrocephalus.

#### 3.2.5.6.5 Diagnosis

A major component of the diagnostic procedure is neuroradiology. Metastases may show contrast enhancement of varying intensity, and when centrally necrotic mimic
glioblastoma (Figs. 3.2.64, 3.2.65). Multiplicity is always a strong indicator for metastases (Fig. 3.2.66). It is mandatory today that an MRI scan be performed, in particular to obtain information about the extent of disease, which may be already untreatable by the time of diagnosis when ten or more lesions are present. CT shows the lesions as well, but especially in the infratentorial compartment or the brain stem, MRI is superior (Fig. 3.2.67).

When there is a known tumor in the case history, the diagnosis is easier to suspect. Most often the diagnosis

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**Fig. 3.2.63** Meningeal carcinomatosis in a patient with proven temporal metastasis from a bronchial adenocarcinoma

**Fig. 3.2.64** Typical appearance of a superficial metastasis; in this case, from a known renal cell carcinoma that had caused severe neuropsychological disturbances, which were rapidly resolving after complete removal

**Fig. 3.2.65** Largely cystic, centrally hypointense metastasis from a mammary carcinoma that, without specific case history, could also be taken for glioblastoma
Fig. 3.2.66 Metachronous metastases from colorectal cancer with coexisting large and small lesions.

Fig. 3.2.67 Adenocarcinoma of the lung with one cystic, symptomatic lesion in the right temporal region, which is shown on the CT (top left) as well as on the MRI (top right). The infratentorial lesion shows much better on the MRI scan.
is made from tissue obtained either from a stereotactic biopsy or from resection.

### 3.2.5.6.6 Therapy

Treatment in general has to take into account the general status of the disease, options to treat or control the underlying disease, and the life expectancy, including quality of life.

#### 3.2.5.6.6.1 Conservative Treatment

Chemotherapy plays only a limited but slowly growing role in the treatment of brain metastases [5]. Mainly, small cell lung carcinomas and some metastases from mammary carcinoma lend themselves to chemotherapy.

For surgically untreatable cases there is whole brain radiation with or without chemotherapy [3, 10].

#### 3.2.5.6.6.2 Surgical Treatment

Resection of metastases has been shown in controlled studies to be of benefit, which is enhanced when radiotherapy is added [6, 7]. Resection is warranted in all lesions over 3 cm, lesions that are easily accessible and those that are surrounded by symptomatic extensive edema [12]. Also, infratentorial lesions that threaten to cause obstructive hydrocephalus are surgical indications, and can be considered even in complex locations like the pineal gland where resection immediately restores CSF pathways (Fig. 3.2.68). Up to three lesions can easily be removed in one surgical setting, even in the infratentorial and supratentorial compartments with repositioning of the patient.

Removal of brain metastases should be attempted in toto, possibly even with a small cover of perilesional white matter as a safety margin. The ability to do so also determines the choice of additional treatment. Resection in toto is clearly impossible in large cystic lesions, which therefore have a higher tendency toward local recurrence, and in those cases additional radiation, either as whole brain or in the field involved, may be desirable.

#### 3.2.5.6.6.3 Radiotherapy

As an alternative to surgery, stereotactic radiosurgery (SRS) has frequently been used [1, 4]. The lesions are ideally spherically shaped and when less than 3 cm an ideal volume for focused irradiation. Multiple lesions can be treated in one setting. When the appropriate dose which may vary depending on the underlying histology is delivered, control is excellent, but the resolution of brain edema takes much longer than after surgical removal. SRS may be used in combination with surgery [8, 11] or whole brain radiotherapy [9].

Whole brain radiation is given when widespread disease is present and there is no other option. This may have severe neurocognitive sequelae.

#### 3.2.5.6.7 Differential Diagnosis

Because of the contrast enhancement and central necrosis, metastases mimic high-grade glioma. Because of the spherical shape and the ring-like marginal enhancement, there can also possibly be uncertainty between metastasis and brain abscess. This is currently easily resolved with an ADC sequence in the MRI, which can very reliably distinguish between these entities.

#### 3.2.5.6.8 Prognosis

The prognosis for patients with metastases is generally poor as most patients will succumb to their underlying disease.
When the systemic disease can be controlled, and this appears to be increasingly the case, aggressive treatment of brain metastases may provide durable control and it is therefore indicated as much as aggressive treatment of gliomas is indicated. When widespread, untreatable cerebral involvement is present, survival falls within the range of 4–6 weeks (Fig. 3.2.69).

### 3.2.5.6.9 European Standard for Cerebral Metastasis

- When the patient is known to have cancer, thorough staging has to precede any discussion of therapeutic options. Cranial MRI is mandatory.
- Control of the systemic disease is desirable when treatment of CNS metastasis is to be considered. There has to be a life expectancy of at least 6 months.
- Treatment of brain metastases is interdisciplinary and includes microsurgical resection, diagnostic stereotactic biopsy followed by radiation (whole brain or SRS), and chemotherapy, or any combination.
- Shunting is to be avoided and in cases of obstructive hydrocephalus, third ventriculostomy may be indicated.

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**Selected Reading**


3.2.6 Infratentorial Brain Tumours in Adults

Infratentorial brain tumours represent about 15% of adult and about 60% of paediatric brain tumours. Those that include the group of medulloblastomas will be discussed in Sect. 3.2.9.1. Tumours of the posterior fossa constitute a continuing challenge to the neurosurgeon due to the limited access options as well as the delicate anatomy of the cranial nerves and the brain stem nuclei and fibre tracts.

3.2.6.1 Neuroepithelial Tumours

JÜRGEN KIWIT

The oncological basics are discussed in Sect. 3.2.5.1. In general, all neuroepithelial tumours of the cerebral hemispheres can be found infratentorially as well. The WHO classification [6] is widely accepted, but is basically a morphological classification of tumours. Histological features determine the grading system, and there is general acceptance that the morphological grade of malignancy corresponds to the patient’s prognosis. WHO grade I tumours are considered benign lesions with low proliferative potential and possible cure after surgery. WHO grade II tumours infiltrate the surrounding brain, brain stem or cerebellum, have low mitotic activity, but tend to progress to a more malignant phenotype. WHO grade III and IV tumours show histological signs of malignancy, are mitotically highly active and have a universally fatal clinical course. Cytogenetic and molecular genetic classification systems that are prognostically valid and correspond to the origins of those tumours rather than to morphological criteria will someday replace this classification system.

Table 3.2.9 gives an overview:

<table>
<thead>
<tr>
<th>Table 3.2.9 Neuroepithelial tumours of the cerebellum and brain stem</th>
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<tbody>
<tr>
<td>I Glial tumours</td>
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<tr>
<td>1. Astrocytic tumours</td>
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<td>2. Oligodendroglial tumours</td>
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<td>3. Mixed gliomas</td>
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<tr>
<td>II Neuronal and mixed neuronal-glial tumours</td>
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<tr>
<td>1. Gangliocytoma</td>
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<td>2. Ganglioglioma</td>
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<td>3. Desmoplastic infantile astrocytoma/ganglioglioma</td>
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<td>4. Dysembryoplastic neuroepithelial tumour</td>
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<td>5. Central neurocytoma</td>
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<td>6. Cerebellar liponeurocytoma</td>
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<tr>
<td>7. Cerebellar paraganglioma (only case reports)</td>
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<td>III Non-glial tumours</td>
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<td>1. Embryonal tumours</td>
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<td>2. Choroid plexus tumours</td>
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<td>Choroid plexus papilloma</td>
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<tr>
<td>Choroid plexus carcinoma</td>
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</table>
3.2.6.1.1 Definition
Tumours arising from various neuroglial cells in the central nervous system. The traditional naming of neuroepithelial tumours corresponds to the presumed cell of origin, but concepts of tumourigenicity are rapidly changing. Rather than dedifferentiation from local cells it seems that glioma stem cells are capable of tumour initiation and tumour renewal. These stem cells have been characterized as CD133-positive; the CD133-negative cells, in contrast, show limited proliferative ability and no tumourigenicity. Glioma stem cells harbour extensive similarities to normal neural stem cells and recapitulate the genotype, gene expression patterns, and in vivo biology of human gliomas [8]. This might be the explanation for the infiltrative nature, chemoresistance, and immunological masking of these tumours. On the other hand, tumours from different brain regions might have explicit distinct genetic signatures [10].

3.2.6.1.2 Aetiology/Epidemiology
There are no reliable data regarding neuroepithelial tumours in Europe. About 8/100,000 individuals per year will develop primary supratentorial brain tumours. Infratentorial tumours represent about one tenth of these patients. In the paediatric population, posterior fossa tumours are much more frequent.

3.2.6.1.3 Symptoms
Signs and symptoms are related to neuroanatomy. They include headaches, general malaise, loss of appetite, nausea, vomiting, gait ataxia and dysarthria, and may develop over weeks and months. Obstruction of the ventricular foramina or the aqueduct may lead to acute increased intracranial pressure caused by occlusive hydrocephalus.

3.2.6.1.4 Clinical Course
All patients with infiltrating gliomas of the posterior fossa (except pilocytic astrocytoma) will eventually die due to the invasive nature of these tumours.

3.2.6.1.5 Diagnostic Procedures
3.2.6.1.5.1 Recommended European Standard
- Careful medical history
- Neurological examination including long fibre tracts
- Cranial nerve function (II–XII)
- Motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs)
- Cerebellar function including formal vestibular testing
- Magnetic resonance imaging (MRI)
- Trans-oesophageal ultrasound to detect a patent oval foramen if surgery in the sitting position is planned (large tumours or those in the upper cerebellar vermis are best operated on via a supracerebellar, infratentorial approach)
- Blood count, clotting times, electrolytes, liver function tests, creatinine, electrocardiography
- Audiogram (VIII) and acoustic evoked potentials (AEPs) in selected cases
- Visual field testing (perimeter) – only in cases of large tumours with hydrocephalus

3.2.6.1.6 Therapy
3.2.6.1.6.1 Conservative Treatment
- Whole brain radiotherapy (WBRT) with a fractionated technique
- Dexamethasone (3×8 mg daily), tapering according to clinical status
- PCV (procarbazine, CCNU and vincristine) therapy in patients with anaplastic oligodendroglioma with 1p 19q deletions
- Temozolomide in cases of MGMT (methylguanine methyltransferase) gene silencing

3.2.6.1.6.2 Surgical Treatment
- Suboccipital craniotomy and tumour removal in cerebellar/vermis tumours
- Open biopsy or partial removal in dorsal exophytic brain stem gliomas
- Stereotactic biopsy in diffuse brain stem tumours (pons)

3.2.6.1.7 Differential Diagnosis
- Cerebellar abscess/inflammation
- Intra-axial metastases
- Ischaemic infarction of the cerebellum or brain stem
- Demyelination (e.g. multiple sclerosis)

3.2.6.1.8 Prognosis
Malignant neuroepithelial tumours in the posterior fossa carry a serious prognosis, and malignant brain stem gliomas are always fatal within a few weeks or months, despite therapy. Chemotherapy has not influenced survival in the last 40 years; however, molecular genetic typing of gliomas can help to define individuals who might benefit from adjuvant chemotherapy like temozolomide [3]. Low-grade tumours may show very slow progression and
patients can survive for years. There is no benefit to be gained from radiotherapy for this group. The subgroup of pilocytic astrocytoma carries an excellent prognosis after surgery, and the 10-year survival has been reported to be over 90%.

3.2.6.1.9 Surgical Principles

3.2.6.1.9.1 Suboccipital Craniotomy
- Make a midline linear skin incision for a large craniotomy extending laterally to the sigmoid sinus and cranially to the transverse sinus. In cases affecting only one cerebellar hemisphere perform a unilateral suboccipital craniectomy. If possible, retain the bone flap for reinsertion. Carry out the microsurgical opening of the dura. In the midline (cerebellar vermis or ventricular) approach, incise the dura of the suboccipital midline sinus bilaterally and carefully ligate the sinus. Protection of the cerebellar hemispheres with cotton or cellulose net (e.g. Tabotamp®) and opening of the cisterna magna may be necessary.
- In cases involving the cerebellar vermis or fourth ventricle, identify the posterior inferior cerebral artery (PICA) and strictly confine to the midline. Opening the foramen of Magendie is usually no problem. Never coagulate near the medulla oblongata or foramen of Luschka, as sacrifice of even the smallest vessels may lead to serious neurological deficits.
- Do not attempt to achieve primary dural closure as it usually does not work. Use a dural graft with running sutures to try to achieve watertight closure. Attempt to reinsert the original bone flap and fix with either miniplates/screws or clamps like Craniofix®

3.2.6.1.9.2 Technique
- Rigid fixation in a Mayfield clamp
- Continuous MEP and SEP monitoring in cases involving the brain stem
- Wax the emissary veins to avoid air embolism
- Avoidance of cerebellar retraction by CSF release
- Avoidance of bipolar coagulation close to the ventricular floor
- Strictly no bipolar coagulation around the medulla and foramen of Luschka
- Piecemeal removal of the tumour
- Watertight closure of the dura with a dural graft

3.2.6.1.9.3 Useful Additional Therapeutic Considerations
- Precordial or trans-oesophageal ultrasound to detect air embolism
- Palacos® closure of the bone defect and tight fixation if the original bone cannot be replaced

3.2.6.1.9.4 Possible Surgical Complications
- CSF leakage (in approximately 10% of cases)
- Postoperative haemorrhage (approximately 1–2%)
- Postoperative hydrocephalus (1–3%)
- Wound infection (1–2%)

3.2.6.2 Cerebellopontine Angle Tumours

JÜRGEN KIWIT

Cerebellopontine angle (CPA) tumours occupy the space between the petrous bone laterally, the pons and medulla medially, and the cerebellar hemispheres posteriorly. Tumours in this region are nearly always benign. They represent a major challenge to the surgeon as they are closely related to the cranial nerves. Large tumours have to be operated on using the “windows” between the cranial nerve groups. The arachnoid membranes, and most importantly, the smallest nerve vessels, have to be strictly preserved. Never coagulate small bleeders in this area. A small cotton pad and a lot of patience will do. Positioning of the patient is dependent on the extent of the tumour. Small CPA tumours are best operated on in the supine position with the head fixed and rotated to the contralateral side. The cerebellar hemisphere will come down after opening of the subarachnoid space and CSF release, thus avoiding any retraction of the cerebellum. Tumours measuring up to 2 cm can be safely operated on in this position. Larger tumours should be operated on in a sitting position, the head being rotated to the ipsilateral side without tilt. The advantage of this position is the free drainage of blood and the good exposition of the petrous vein and upper CPA. Retraction is usually necessary, and this positioning may be impossible in cases of patent oval foramen or in cardiovascularly compromised patients.

3.2.6.2.1 Acoustic Neurinoma

3.2.6.2.1.1 Synonyms
- Acoustic neuroma
- Vestibular schwannoma
- Vestibular neurilemmoma

3.2.6.2.1.2 Definition
Tumours arising from the vestibular branches of the vestibulo-cochlear nerve (VIII), usually displacing the cochlear and facial nerve anteriorly. They are always histologically benign and can be classified according to Koos into four categories (Table 3.2.10) [7]:
- Grading is closely related to symptoms and treatment results.
3.2.6.2.1.3 Aetiology/Epidemiology

About 1/100,000 individuals per year will develop symptomatic vestibular schwannoma, the tumour accounting for 6–8% of all intracranial tumours. The true prevalence, however, is likely to be higher. Incidental acoustic neurinomas can be found in up to 7/10,000 tumours in a large series of MRIs [1]. Although the exact mechanism of tumourigenesis is not fully understood, a malfunction of a tumour suppressor gene coding for schwannomin/merlin on chromosome 22q12 is responsible for the development of vestibular schwannomas. This seems to be true of the development of spontaneous unilateral tumours as well as for the bilateral tumours found in neurofibromatosis type II.

3.2.6.2.1.4 Symptoms

A declining hearing ability is the most common symptom that leads to the diagnosis of acoustic neurinoma. Usually, hearing declines over time, but 5–15% of patients complain of sudden or fluctuating hearing loss, most likely due to compromised blood flow to nerve and cochlea. Only 5% of patients presenting with acoustic neurinoma have normal hearing and speech discrimination. Rotational vertigo may be an early symptom; however, the gradual decline in vestibular function is usually well compensated by the contralateral labyrinthine system and central brain information processing. The facial nerve has a larger stretching tolerance than the cochlear portion of the eighth nerve; hence, facial weakness in small and even larger tumours is uncommon. Only 10% of patients, even those with large tumours (including Koos III and IV) present with unilateral facial weakness. More often facial dyasiaesthesia (up to 20%) can be observed due to cranial extension of the tumour contacting the trigeminal nerve.

3.2.6.2.1.5 Clinical Course

A considerable number of acoustic tumours will not grow or will grow at an extremely slow pace, considering the probably very high incidence of tumours. A second group might show slow growth defined as 0.2 cm/year on axial imaging studies. A third group might exhibit rapid growth of > 1 cm/year.

3.2.6.2.1.6 Complications

Complications in the natural course of the disease are rare, cystic tumours might deteriorate rapidly due to cyst filling or intratumoural haemorrhage. Large tumours will at some stage compress the fourth ventricle and aqueduct leading to occlusive hydrocephalus.

3.2.6.2.1.7 Diagnostic Procedures

3.2.6.2.1.7.1 Recommended European Standard

- Careful medical history including history of hearing dysfunction
- Neurological examination including long fibre tracts
- Cranial nerve function (II–XII)
- Audiogram (VIII) and AEPs
- Speech discrimination score measurements
- Facial nerve function (VII) according to the House/Brackmann scheme including electromyography [4]
- Cerebellar function including formal vestibular testing
- MRI
- CT scan using the bone window technique to watch for bone erosion, widening of the internal acoustic meatus and relation of the jugular bulb to the meatus
- Trans-oesophageal ultrasound to detect a patent oval foramen if surgery in sitting position is planned (tumours larger than 2 cm)
- Blood count, clotting times, electrolytes, liver function tests, creatinine, electrocardiography

3.2.6.2.1.7.2 Additional Useful Diagnostic Procedures

- Digital subtraction angiography (DSA) only in very large tumours or suspected glomus tumours
- MEPs and SEPs in very large tumours compromising brain stem function
- Visual field testing (perimeter) only in cases of large tumours with hydrocephalus

3.2.6.2.1.8 Therapy

3.2.6.2.1.8.1 Conservative Treatment

- Observation with serial imaging in elder patients as well as in “incidentalomas”
- Radiosurgical treatment (e.g. Gamma Knife®) with 12–13 Gy to the 50% isodose line
- Fractionated stereotactic radiotherapy (e.g. LINAC – linear accelerator, frameless system) with up to 17 Gy to the 80% isodose line

3.2.6.2.1.8.2 Surgical Treatment

- Suboccipital retro-mastoid craniotomy and tumour removal
3.2.6 Infratentorial Brain Tumours in Adults

3.2.6.2.9 Differential Diagnosis
Intracanalicular tumours are uniformly acoustic neurinomas, but meningiomas of the anterior internal meatus can mimic morphology and symptoms of these tumours (see Fig. 3.2.70). In contrast to acoustic neurinomas, the facial and cochlear nerves are displaced posteriorly and are easily identified.
- Meningioma of CPA
- Glomus tumour
- Epidermoid
- Extra-axial metastasis

3.2.6.2.10 Prognosis
Tumour control rate after radiosurgery is 95–98%; surgical tumour control is reported to be 90–95%. Hearing preservation in radiosurgery is reported to range from 60 to 70% compared with 80% in Surgical Centres of Excellence. Facial nerve function is better after radiotherapy compared with microsurgery for these tumours, i.e. 90 versus 80% in small tumours.

3.2.6.2.11 Surgical Principles
3.2.6.2.11.1 Suboccipital Retro-Mastoid Craniotomy
- A retro-mastoid linear skin incision is made, and a 3-cm craniotomy performed, extending laterally to the sigmoid sinus and cranially to the transverse sinus. The dura is opened microsurgically, avoiding sinus lesions. The cerebellar hemisphere is protected with cotton or cellulose net (e.g. Tabotamp®), the arachnoid cisterns are opened, and in large tumours it may be necessary to open the cisterna magna. The anterior inferior cerebellar artery (AICA), nerves VII and VIII and the internal auditory artery (IAA) are identified.
- The posterior meatus is opened and bone removed with a high-speed drill. The canalicular dura is opened and the tumour removed piecemeal removal without bipolar coagulation; the bleeding will stop when tumour is removed. Meticulous haemostasis, irrigation and functional control of the facial and cochlear nerves are ensured by monitoring.

3.2.6.2.11.2 Technique
- Rigid fixation in a Mayfield clamp
- Continuous facial EMG monitoring (m. orbicularis oculi, m. orbicularis oris)
- Continuous acoustic evoked potential registration
- Suboccipital retro-mastoid craniotomy extending to the sigmoid sinus
- Wax the mastoid cells to avoid CSF leakage; wax the emissary veins to avoid an air embolism
- Avoidance of cerebellar retraction by CSF release
- Avoidance of bipolar coagulation close to the cranial nerves and meatus
- Identification of the facial (VII) and cochlear (VIII) nerves
- Piecemeal removal of the tumour without any traction on the nerve
- Watertight closure of the dura with a dural graft

Fig. 3.2.70 a Acoustic meningioma of the right cerebellopon- tine angle operated on in the supine position (with the head turned to the left). b Acoustic meningioma. 1 = facial nerve (VII), 2 = superior vestibular nerve (VIII) partially surrounded by the tumour, 3 = cochlear nerve (VIII), 4 = inferior vestibular nerve (VIII), 5 = internal auditory artery, 6 = tumour
3.2.6.2.11.3 Useful Additional Therapeutic Considerations
- Precordial or trans-oesophageal ultrasound to detect air embolism
- Palacos® closure of the bone defect and tight fixation

3.2.6.2.11.4 Possible Surgical Complications
- CSF leakage, either through the wound or through air cells opened intraoperatively via the Eustachian tube (approximately 10%)
- Postoperative haemorrhage (approximately 1–2%)
- Postoperative hydrocephalus (1–3%)
- Wound infection (1–2%)

3.2.6.2.12 Special Remarks
There has been considerable debate on what is the best treatment option for small tumours, but the trend clearly favours radiosurgery due to the minimal treatment time, lower complication rate and excellent preservation of facial function. However, there is a small risk of delayed radiation-induced oncogenesis, with five cases of radiation-related secondary malignancies having been reported. Looking at the large treatment numbers, the possible risk to a patient probably lies below 1:1,000.

3.2.6.2 CPA
Meningioma/Petro-Clival Meningioma

3.2.6.2.2.1 Synonym
CPA meningioma.

3.2.6.2.2.2 Definition
Tumours arising from the meningeal cells of the petrous dura/arachnoid and growing into the cerebellopontine angle and/or the clivus region. These tumours may reach large dimensions without causing any clinical symptoms and signs and are generally difficult to operate on. They tend to displace the cranial nerves posteriorly, which facilitates early identification of nerves, but makes removal difficult. The surgeon has to operate through the natural “windows” between the jugular foramen nerve group (IX, X, XI) caudally and the internal auditory meatus group (VII, VIII) as well as the trigeminal nerve (V) cranially (Fig. 3.2.71).

3.2.6.2.2.3 Aetiology/Epidemiology
About 6/100,000 individuals per year will develop meningioma, the tumour accounting for 13–26% of all intracranial tumours. However, these data refer to supratentorial meningiomas, while posterior fossa meningiomas represent only 10% of this group. The true prevalence, therefore, should be between 0.5 and 1 per 100,000 individuals. The most common cytogenetic alteration in meningiomas is a loss of chromosome 22 in 60–70% of histologically benign WHO grade I tumours. Progression to more aggressive forms of meningioma is associated with deletion of 1p, 6p, 10q 14q and 18q in atypical meningiomas and 9p (CDKNA) for anaplastic meningioma. Women are affected more often than men with a female:male ratio of 2:1, and most tumours occur in the sixth or seventh decade of life.

3.2.6.2.2.4 Symptoms
There is no most common symptom leading to the diagnosis of posterior fossa meningioma. These tumours grow slowly and may stay asymptomatic for years. They can affect any cranial nerve leading to symptoms from nausea, vertigo, diminished hearing to facial weakness or facial dysesthesia. Very rarely, the space-occupying mass has

Fig 3.2.71 a Petro-clival meningioma of the left side. Note the tumour stretching the lower cranial nerves and displacing the posterior inferior cerebellar artery (PICA) caudally. b Lower cranial nerves on the left after complete tumour removal
grown to such an extent that it compromises the foramina Luschka and Magendie, leading to acute hydrocephalus requiring emergency surgery.

3.2.6.2.5 Clinical Course
Petro-clival meningiomas are slow-growing, but progressively devastating tumours. In very old patients, observation and regular clinical and imaging controls might be appropriate. In younger patients, surgical removal is the preferred treatment option.

3.2.6.2.6 Complications
Complications in the natural course of the disease are rare; patients may suffer from lower cranial nerve lesions predisposing to aspiration pneumonia. Rarely, hydrocephalus has to be treated when acute/subacute CSF obstruction is observed.

3.2.6.2.7 Diagnostic Procedures
3.2.6.2.7.1 Recommended European Standard
- Careful medical history
- Neurological examination including long fibre tracts
- Cranial nerve function (II–XII)
- Audiogram (VIII) and acoustic evoked potentials (AEPs)
- Cerebellar function including formal vestibular testing
- Magnetic resonance imaging (MRI)
- CT using the bone window technique to watch for bone erosion, infiltration of the dura and neighbouring bone, and widening of the internal acoustic meatus
- Trans-oesophageal ultrasound to detect a patent oval foramen if surgery in the sitting position is planned (in tumours larger than 3 cm)
- Blood count, clotting times, electrolytes, liver function tests, creatinine, electrocardiography
- Digital subtraction angiography (DSA) to assess blood supply particularly for the tentorial branches of the internal carotid artery (ICA)

3.2.6.2.7.2 Additional Useful Diagnostic Procedures
- Motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) in very large tumours compromising brain stem function
- Visual field testing (perimeter) only in cases of large tumours with hydrocephalus
- Speech discrimination only in cases of affected hearing
- Facial nerve EMG only in cases of large tumours affecting facial nerve function

3.2.6.2.8 Therapy
3.2.6.2.8.1 Conservative Treatment
- Observation with serial imaging in older patients as well as in “incidentalomas”

3.2.6.2.8.2 Surgical Treatment
- Suboccipital retro-mastoid craniotomy and tumour removal

3.2.6.2.9 Differential Diagnosis
- Acoustic neurinomas
- Glomus tumour
- Chordoma
- Epidermoid
- Extra-axial metastasis

3.2.6.2.10 Prognosis
Depending on the WHO grade, benign meningiomas recur in 7–20% of cases, atypical meningiomas (grade II) in about 33% and anaplastic tumours graded WHO III in about 60–80% of all cases. Histological subtyping (meningothelial, fibroblastic, transitional etc.) plays no major role in the prognosis. Patients harbouring malignant meningiomas with brain invasion have short survival times down to only 2 years.

3.2.6.2.11 Surgical Principles
3.2.6.2.11.1 Suboccipital Retro-Mastoid Craniotomy
- A retro-mastoid linear skin incision is made, and a craniotomy is performed, extending laterally to the sigmoid sinus and cranially to the transverse sinus. The dura is opened microsurgically, avoiding sinus lesions. The cerebellar hemisphere is protected with cotton or cellulose net (e.g. Tabotamp®), the arachnoid cisterns are opened, and in large tumours it may be necessary to open the cisterna magna. The PICA, AICA, internal auditory artery (IAA) and cranial nerves can usually be easily identified.
- The posterior tumour capsule between cranial nerve groups is opened, the petrosal and other veins are protected, and cerebellar retraction is avoided if possible. The arachnoid membranes on cerebellum and brain stem are preserved.
- The tumour is removed piecemeal without bipolar coagulation; the bleeding will stop when the tumour has been removed. Meticulous haemostasis, irrigation and functional control of the cranial nerves are ensured by monitoring. If feasible, the dural attachment of the tumour should be removed, and if necessary a dural graft with watertight closure with running sutures should be performed. Otherwise there will be coagulation of the tumourous dural attachment.

3.2.6.2.11.2 Technique
- Rigid fixation in a Mayfield clamp
- Continuous facial EMG monitoring (m. orbicularis oculi, m. orbicularis ori)
- Continuous acoustic evoked potential registration
3.2 Brain Tumors

3.2.6.3 Metastases

JÜRGEN KIWIT

3.2.6.3.1 Definition
Metastases of the posterior fossa are neoplasms that originate in tissues outside the central nervous system and then spread to the cerebellar hemispheres, the brain stem or the subarachnoid space. In solitary lesions, such tumours should not be automatically diagnosed as metastases only because the patient is harbouring a malignancy. Appropriate treatment of curable benign tumours may be missed. In contrast, multiple posterior fossa lesions in widespread metastatic disease can usually be assumed to be of cancerous origin. In general, patients with metastatic disease to the posterior fossa have a very bad clinical prognosis with survival of only a few weeks or months.

3.2.6.3.2 Aetiology/Epidemiology
Metastases to the brain are the most common intracranial tumours in adults. Twenty to 40% of all cancer patients will develop brain metastases accounting for at least 100,000 to 150,000 new cases per year in Germany. Eighty percent of those will develop metastases to the cerebral hemispheres, 15% to the cerebellum and about 5% to the brain stem. The true incidence may be much higher, as MRI can detect even extremely small metastases with no clinical symptoms and signs. The most common primary tumours are lung (50%), breast (20%), melanoma (10%) and colon carcinoma (5%+). Principally, every malignancy can metastasise to the brain or the meninges. Most patients harbour multiple metastases at the time of the first diagnosis, but solitary metastases may also occur.

3.2.6.3.3 Symptoms
Brain stem tumours may cause cranial nerve signs when small and are generally detected early in the clinical course. Cerebellar tumours may reach a considerable size before becoming symptomatic; they often present with acute signs and symptoms of occlusive hydrocephalus and may require emergency surgery.

3.2.6.3.4 Clinical Course
The clinical course of metastatic disease to the posterior fossa is always devastating.

3.2.6.3.5 Diagnostic Procedures

3.2.6.3.5.1 Recommended European Standard
- Careful medical history including previous cancer treatment
- Neurological examination including long fibre tracts
- Cranial nerve function (II–XII)
- Magnetic resonance imaging
- CT using the bone window technique in cases involving bone
- Trans-oesophageal ultrasound to detect a patent oval foramen if surgery in the sitting position is planned (large tumours)
- Blood count, clotting times, electrolytes, liver function tests, creatinine, electrocardiography

3.2.6.3.5.2 Additional Useful Diagnostic Procedures
- Motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) in very large tumours compromising brain stem function
- Visual field testing (perimeter) only in cases of large tumours with hydrocephalus
3.2.6.3.6 Therapy

3.2.6.3.6.1 Conservative Treatment
- Radiosurgical treatment (e.g. Gamma Knife®) with up to 20 Gy is the treatment of choice for single brain stem metastases [2]
- Whole brain radiotherapy (WBRT) using a fractionated technique
- Dexamethasone (3 × 8 mg daily), tapering according to clinical status

3.2.6.3.6.2 Surgical Treatment
- Suboccipital craniotomy and tumour removal

3.2.6.3.7 Differential Diagnosis
In widespread metastatic disease and multiple posterior fossa lesions diagnosis of cerebellar/brain stem metastasis might be assumed. In solitary lesions stereotactic biopsy or removal should be considered.
- Neuroectodermal tumours
- Lymphoma
- Cerebellar or brain stem abscess

3.2.6.3.8 Prognosis
The tumour control rate after radiosurgery is about 90%, but survival is no more than 10 months after treatment. Even aggressive multimodal therapy, including surgery, stereotactic radiation and WBRT does not lengthen survival by more than 13 months [5].

3.2.6.3.9 Surgical Principles

3.2.6.3.9.1 Suboccipital Craniotomy
- A midline linear skin incision is made, and a large craniotomy is performed, extending laterally to the sigmoid sinus and cranially to the transverse sinus. In small cerebellar metastases a unilateral suboccipital craniectomy is carried out. If possible, retain the bone flap for reinsertion. The dura is opened microsurgically. In the midline (cerebellar vermis or ventricular) approach, incise bilaterally the suboccipital midline sinus and carefully ligate the sinus. The cerebellar hemispheres are protected with cotton or cellulose net (e.g. Tabotamp®). It may be necessary to opening the cisterna magna. Microsurgical removal of metastases is usually not very demanding and technically quite easy (Fig. 3.2.72).

3.2.6.3.9.2 Technique
- Rigid fixation in a Mayfield clamp
- Continuous MEP and SEP monitoring in cases involving the ventricular floor
- Wax the emissary veins to avoid an air embolism
- Watertight closure of the dura with a dural graft

3.2.6.3.9.3 Useful Additional Therapeutic Considerations
- Precordial or trans-oesophageal ultrasound can be used to detect an air embolism in the sitting position
- Palacos® closure of the bone defect and tight fixation if reinsertion of the original bone flap is not feasible

![Fig. 3.2.72](image_url) a Left solitary cerebellar metastasis of lung cancer on coronal contrast-enhanced MRI. b Left solitary cerebellar metastasis of lung cancer on coronal contrast-enhanced MRI after removal
3.2 Brain Tumors

3.2.6.3.9.4 Possible Surgical Complications

- CSF leakage (in approximately 10% of cases)
- Postoperative haemorrhage (approximately 1–2%)
- Postoperative hydrocephalus (1–3%)
- Wound infection (1–5%)

Selected Reading


3.2.6.4 Pathologies of the Cranio-Cervical Junction

BERNARD GEORGE

The cranio-cervical junction (CCJ) is a complex region with many important neurovascular structures in and around osteoligamentous elements achieving the mobility as well as the stability of the junction between the head and the neck. Pathological changes affecting this region are various and numerous. Their treatment is often challenging. The goal must be as radical a treatment as possible with preservation or restoration of CCJ stability.

3.2.6.4.1 Definition

The CCJ includes:

- The lower part of the intracranial cavity with the lower third of the clivus, occipital condyle and posterior margin of the foramen magnum (occipital bone)
- The upper part of the cervical spine with the atlas and odontoid. The inferior limits are the body, laminae, and spinous process of C2.

3.2.6.4.2 Anatomy

The CCJ is embryologically made from multiple segments of ossification, some of which connect together [8]. In fact, the upper part with the lower clivus and condyle corresponds to a piece of spine rather than to a piece of the skull. It can be named C0.

It is important to realize that the first two joints, C0–C1 and C1–C2, are much more anteriorly located than the lower cervical joints (C3–C7). In fact, they are almost entirely located before the neuraxis on the side of the odontoid. Therefore, the CCJ has two main walls:

- The anterior wall with the clivus, the anterior arch of the atlas and the odontoid. This wall is reached directly via the transoral approach.
- The lateral wall with the occipital condyle and lateral mass of the atlas and the two joints C1–C2 and C0–C1. On top of the occipital condyle the jugular tubercle is placed, which is the medial wall of the jugular foramen. This lateral wall is directly reached via the lateral approach (Figs. 3.2.73, 3.2.74).

There is a third wall, the posterior one, which is weak and does not participate in the mobility and stability of the CCJ. It includes the squama of the occipital bone and the posterior arch of the atlas. It is reached via the standard posterior midline approach and can be removed without almost any consequences.

The anterior midline (transoral) approach, as well as the posterior midline approach, has the same lateral limits, which are the vertebral arteries.

As a consequence of this anatomical presentation, there is no intervertebral foramen and the C1 and C2 nerve roots merge behind the joints (and not in front as is the case lower in the neck). Thus, there is a wide free space lateral to the neuraxis behind the joints.

Anatomical relations between the bony structures are in fact modified during head movements, especially the rotation. During head rotation, the atlas follows the
head movement and the C0–C1 joint does not participate. On the contrary, the axis does not follow the head, which rotates around the axis of the odontoid process and the C1–C2 joint moves a great deal. The vertebral artery (VA), which runs along the C1–C2 joint, is stretched on one side and compressed on the other. This is important to understand with regard to two occurrences:

- Positioning of the patient for surgery
- Intermittent compression of the VA, generally during rotation (Bow Hunter’s syndrome).

Many variations and congenital anomalies can be observed at this level. The most common types may involve the bone: fusion of different, normally separate pieces and a supplementary piece of bone. The VA may also be the site of anomalies. Besides the variation in diameter with a dominant VA on one side and a minor (hypoplastic or atretic) VA on the other side (40%), a duplication with an intradural course of the VA, a persistent congenital anastomosis with the carotid artery (pro-atlantal artery) and an extracranial origin of the posterior inferior cerebellar artery (PICA) are most commonly observed.

Calcification or ossification of the atlanto-occipital membranes sometimes turns the groove of the VA on the posterior arch of the atlas into a tunnel and makes VA exposure more difficult.

### 3.2.6.4.3 Pathologies

Different pathologies may involve different structures. Excluding intra-axial lesions, pathologies may develop into either the intradural or the extradural space and the bony structures. They may be of different types [6, 7]:

- Vascular: essentially aneurysm of the VA or the PICA, or much more rarely, dural arteriovenous fistulas. The

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**Fig. 3.2.73a,b** Coronal a MRI and b CT showing the lateral wall of the CCJ with: 1 atlas; 2 axis; O occipital condyle; T jugular tubercle; star internal jugular vein above and below the transverse process of C1; arrow vertebral artery

**Fig. 3.2.74** a 3D CT showing the location of the C0–C1 and C1–C2 joints (circles) and of the C3–C4 and C4–C5 joints (stars). b Angio-CT showing the course of the vertebral artery around the C0–C1 joint. c Axial MRI showing the limit of the vertebral artery groove (arrow)
control of VA branches supplying highly vascularized tumors, especially glomus jugulare tumors, and revascularization of the distal VA in some cases of proximal occlusion, must also be considered in the vascular field.

- Inflammatory and infectious: tuberculosis and rheumatoid arthritis are commonly observed at the CCJ level. They may have the features of pseudotumors, with cysts or a pannus compressing the neuraxis.

- Degenerative: spondylosis of the C0–C1 or the C1–C2 joint is not frequent. The main problem for degenerative as well as for some inflammatory processes is to distinguish them from real tumors, so that aggressive surgical resection is adequately proposed.

- Malformative: the CCJ is the site of many different bony malformations, sometimes associated with malformations of the nervous system (Chiari malformation, syringomyelia).

All these pathologies may simulate a tumor producing symptoms related to permanent or intermittent compression of the nervous or vascular structures and present features of pseudotumors on imaging studies. Carrying out a biopsy before deciding on surgical resection is sometimes a good option.

Tumors at the CCJ level are most commonly meningiomas for intradural ones and chordomas for those involving the bone or the extradural space (Tables 3.2.11, 3.2.12). Intradural tumors to which the name foramen magnum tumors is generally given mostly include meningiomas and neurinomas. In fact, these tumors may also be partially or totally extradural. This is rarely observed for meningioma (10% and 3% respectively); it is more frequent in cases of neurinomas (49% and 37%). Besides these two main types of tumors, intradural extra-axial tumors may be hemangioblastomas, epidermoid cysts or ependymomas. Extradural tumors are mostly represented by bone tumors. If metastasis is excluded, chordomas are most frequently observed. Then primary bone tumors may be of different types, including for the most frequent ones, osteoid osteomas, aneurysmal cysts and plasmocytomas [1]. Chordomas are often located on the midline, but frequently extend laterally and even sometimes bilaterally [3]; therefore, requiring combined or staged surgical approaches (Tables 3.2.11, 3.2.12)

All these pathologies may require surgical treatment for two main reasons

- Decompression of the nervous parenchyma (upper spinal cord, medulla oblongata, and lower cranial nerves) or much more rarely of the VA.
- Instability of the CCJ.

Sometimes the two factors are simultaneously observed and need to define a particular strategy in one or several surgical stages with one or several combined approaches.

### 3.2.6.4.4 Surgical Approaches

When dealing with a CCJ pathology, the surgeon must be able to apply any of all the main surgical approaches leading to the CCJ.

<table>
<thead>
<tr>
<th><strong>Table 3.2.11</strong> Tumors of the cranio-cervical junction area. Personal series (Hopital Lariboisière, 2006)</th>
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<tbody>
<tr>
<td><strong>Intradural</strong></td>
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<tr>
<td>Meningioma</td>
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<tr>
<td>Neurinoma</td>
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<tr>
<td>Others</td>
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<tr>
<td>Pseudotumors</td>
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<tr>
<td><strong>Extradural</strong></td>
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<tr>
<td>Meningioma</td>
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<td>Neurinoma</td>
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<tr>
<td>Chordoma</td>
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<td>Sarcoma</td>
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<tr>
<td>Metastasis</td>
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<td>Osteoid osteoma</td>
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<td>Others</td>
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<tr>
<th><strong>Table 3.2.12</strong> List of the main pathologies involving the bony structures of the cranio-cervical junction level</th>
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</thead>
<tbody>
<tr>
<td><em>Neoplastic</em></td>
</tr>
<tr>
<td><strong>Benign:</strong></td>
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<tr>
<td>- Aneurysmal cyst</td>
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<tr>
<td>- Fibrous dysplasia</td>
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<tr>
<td>- Osteoid osteoma</td>
</tr>
<tr>
<td>- Osteoblastoma</td>
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<tr>
<td>- Giant cell tumor</td>
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<tr>
<td>- Histiocytosis</td>
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<tr>
<td>- Osteochondroma</td>
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<tr>
<td><strong>Malignant:</strong></td>
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<tr>
<td>- Plasmocytoma</td>
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<tr>
<td>- Metastasis</td>
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<tr>
<td>- Hodgkin’s</td>
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<tr>
<td>- Chordoma</td>
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<tr>
<td>- Chondrosarcoma</td>
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<tr>
<td><em>Developmental and acquired</em></td>
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<tr>
<td><strong>Infections:</strong></td>
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<tr>
<td>- Tuberculosis</td>
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<tr>
<td><strong>Inflammatory:</strong></td>
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<tr>
<td>- Rheumatoid arthritis</td>
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<tr>
<td>- Ankylosing spondylitis, psoriasis</td>
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<tr>
<td>- Scleroderma</td>
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<tr>
<td>- Synovial cyst</td>
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<tr>
<td>- Amylosis</td>
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<tr>
<td><strong>Metabolic:</strong></td>
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<tr>
<td>- Morquio’s syndrome</td>
</tr>
<tr>
<td><strong>Genetic:</strong></td>
</tr>
<tr>
<td>- Down’s syndrome</td>
</tr>
<tr>
<td>- Osteogenesis imperfecta</td>
</tr>
<tr>
<td>- Achondroplasia</td>
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<tr>
<td>- Neurofibromatosis</td>
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<tr>
<td><em>Congenital</em></td>
</tr>
<tr>
<td><strong>Clivus segmentation</strong></td>
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<tr>
<td><strong>Proatlas remnant</strong></td>
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<tr>
<td><strong>Condylar invagination</strong></td>
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<tr>
<td><strong>Condylar hypoplasia</strong></td>
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<tr>
<td><strong>Atlas assimilation or fusion</strong></td>
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<tr>
<td><strong>Axis fusion</strong></td>
</tr>
<tr>
<td><strong>Odontoid hypoplasia</strong></td>
</tr>
<tr>
<td><strong>Ossiculum terminale</strong></td>
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</tbody>
</table>
3.2.6.4.4.1 Anterior Approaches
The CCJ has an anterior wall that can be reached via the transoral approach. This approach, with all its variations (upper extension with transpalatal splitting and the transmaxillary combined Le Fort approach, and lower extension with the transglossal and transmandibular approaches) is useful for any midline lesion located before or in this anterior bony wall [4, 9]. It is a straightforward approach, deep, and therefore needs long instruments, but with no structures on the way; only the mucosa and prevertebral muscles have to be divided and laterally retracted. It has lateral limitations with the two VAs and for the upper opening, the jugular veins and internal carotid arteries (ICAs). It is certainly not indicated for lesions located behind the anterior bony wall and moreover for intradural lesions. In fact, to reach these lesions via the transoral approach, it is necessary to destroy the anterior bony wall, thus creating a previously non-existent instability. This problem can be avoided using lateral approaches. Then, closure of the dura is often difficult to achieve, with a high risk of CSF leak and meningitis.

3.2.6.4.4.2 Posterior Approaches
The posterior wall is rather weak compared with the anterior and lateral ones. It has little importance in CCJ instability. The direct route to this wall is the standard posterior midline approach, very well known by every neurosurgeon. It leads directly to the posterior midline of the CCJ area by splitting in between the two parts of the posterior cervical muscles dividing the avascular midline. It may be used for any extra- or intradural midline posterior lesion. It is limited laterally by the end of the VA groove in the posterior arch of the atlas and anteriorly by the neuraxis.

3.2.6.4.4.3 Lateral Approaches
The lateral wall of the CCJ consists mainly of the two joints, C0–C1 and C1–C2. It is in fact an anterolateral wall, since the line of these joints is at the level of the C2 vertebral body. There is no pedicle and no intervertebral foramen at the CCJ level; the C1 and C2 spinal nerve roots merge posterior to the joints, while lower spinal nerve roots merge anterior to them. Therefore, lateral approaches are directed to these joints, either turning around the posterior aspect of them (the posterolateral approach) or going straight to them (the anterolateral approach) [2, 5–7].

The posterolateral approach (Fig. 3.2.75) is in fact the lateral extent of the midline posterior approach, so that the VA groove is exposed and the resection of the occipital bone and posterior arch of the atlas reaches the posterior aspect of the occipital condyle and lateral mass of the atlas. The patient’s position can be sitting, prone or lateral; the skin incision is either vertical on the midline and curved at the occipital protuberance down to the mastoid process, or oblique vertical from the top of the ear toward the posterior midline at the C5–C6 level. The bone is exposed subperiosteally so as to keep intact the periosteal sheath surrounding the VA. Then the bone can be safely removed above and/or below the VA. Following the course of the VA, the surgeon may penetrate into the subarachnoid space at the foramen magnum, first along the lateral aspect and then the anterior aspect of the medulla oblongata (MO). These spaces lateral and anterior to the MO are generally enlarged owing to tumoral development, making it still easier to access them.

This posterolateral approach is therefore essentially designed for intradural tumors or for extradural pathologies that have developed behind the lateral wall of the CCJ. The lateral opening is extended toward this lateral wall, especially in cases of lesions anterior to the neuraxis. However, it is the exception that some drilling of the lateral mass of the atlas and/or of the occipital condyles has to be done.

The anterolateral approach (Fig. 3.2.76) is similar to that used lower in the neck to expose the transverse processes and the VA. At the CCJ level the anterolateral approach goes to the C1 and C2 transverse processes and to the suboccipital (V3) VA segment. The field is opened between the medial aspect of the sterno-mastoid muscle (SM) and the lateral edge of the internal jugular vein. To get more space it is often useful to detach the SM and occasionally the posterior cervical muscles from the occipital bone. For this, the patient is in the supine position with the head slightly extended and rotated toward the opposite side. The skin incision follows the upper 10 cm of the medial limit of the SM up to the tip of the mastoid process, then follows the mastoid process and the superior occipital crest toward the occipital protuberance. Once the field between the SM and the internal jugular vein is opened the accessory nerve (CN XI) must be identified and dissected, then retracted inferiorly with the fat pad covering the depth of the field.

The transverse process of the atlas can be palpated 15 mm below and before the tip of the mastoid process. It is freed from all the small muscles attached to it, thus providing a view of the C1–C2 and above C1 segments of the VA with the posterior arch of the atlas interposed between them. Transposition of the VA out of the transverse foramen permits exposure of the CCJ lateral wall with the two joints C0–C1 and C1–C2. More rotation of the head contralaterally brings the posterior part of the atlas and CCJ into view, while less rotation permits running in front of the joints and reaching the anterior wall of the CCJ (anterior arch of the atlas, the vertebral body of C2 and the odontoid process).

This approach can be extended as necessary inferiorly to lower levels in the neck as the same anterolateral approach permits exposure and control of the entire cervical spine. It can also be extended superiorly to the jugular
Fig. 3.2.75  a Schematic drawing of the skin incision and opening of the posterolateral approach (top). Operative view (bottom) of the posterolateral approach. The arrow indicates the midline. Star vertebral artery; M mastoid process; C2 lamina of C2; C1 posterior arch of the atlas. b Schematic drawing and operative view of the posterolateral approach after bone resection (occipital bone and posterior arch of the atlas). 2 lamina of C2; A lateral mass of the atlas; star vertebral artery; O occipital condyle; T jugular tubercle; S sigmoid sinus
Infratentorial Brain Tumours in Adults

foramen and the posterior fossa. In this case a complementary opening of the posterior fossa via a retro-sigmoid approach is realized. The last possible extension is toward the petrous bone above the jugular foramen. This may be necessary in large tumors of this region, such as paragangliomas.

Most of the time, the anterolateral approach is applied for tumors invading the bony elements of the anterior and lateral wall. It means that CCJ stability is already compromised and will be even more impaired after surgery; therefore, a stabilization procedure generally needs to be considered in the management of these patients, either in the same surgical stage or in a separate one. Circumstances must be quite exceptional to make a patient unstable who is preoperatively stable. It generally means that something was wrong in the strategy and the chosen surgical approach was not appropriate.

Morbidity related to the exposure should be minimal. VA injury should remain the exception. If there is any reason to think that it may occur, the VA size should be considered: minor VA can be sacrificed without any consequences; equal or dominant VA should be tested by preoperative balloon occlusion. If the choice is to include the ligation of the VA in the surgical planning (for instance to achieve a more radical tumoral resection) revascularization (saphenous vein bypass from the carotid artery) has to be considered in case of balloon occlusion test failure.

Another morbidity may be related to damage of the accessory nerve (CN XI), especially owing to retraction of the SM muscle being too hard. At this level, a lesion to the sympathetic trunk very rarely leads to Horner’s syndrome.

Morbidity in relation to the injury of other nerves (CN IX,X, XII) may be due to tumor resection, but not to exposure of the CCJ.

Selected Reading

3.2 Brain Tumors

3.2.7 Tumor of the Orbit

WERNER-ERWIN HASSLER, UTA SCHICK

3.2.7.1 Introduction

A broad variety of tumors and pseudotumors can involve the small, well-defined orbit. Two-thirds of the lesions are benign and one-third are malignant. The proportion of malignant tumors is inverse to age due to the higher incidence of orbital metastases and lymphomas. In childhood more dermoid cysts and orbital capillary hemangiomas are seen. Neurosurgeons encounter more neural tumors such as meningiomas and optic pathway gliomas, ENT or head and neck surgeons more secondary lesions such as mucoceles and paranasal sinus neoplasms. Ophthalmologists experience a greater incidence of thyroid-related orbitopathies and inflammatory pseudotumors. Only a few specialized centers have an overview of the broad variety of these rare lesions and possible minimally invasive surgical approaches.

3.2.7.2 Symptoms

- Proptosis 92%
- Visual field defect/loss of visual acuity 74%
- Diplopia, strabism 66%
- Pain 34%
- Lacrimation 23%
- Conjunctival edema 22%

Proposis can be caused by any type of orbital process. Visual acuity is often reduced by malignant and inflammatory/infectious processes (79%), as well as by optic nerve gliomas (67%); it is less commonly reduced by meningiomas (45%). Pain is a prominent feature of inflammatory/infectious disorders (96%) and meningiomas (70%).

The mean duration of symptoms before diagnosis is 4.2 months for malignant tumors, 15 months for gliomas, and 28 months for meningiomas. The mean age at manifestation is 19 years for optic gliomas, which is considerably lower than for schwannomas (42 years) or meningiomas (54 years).

3.2.7.3 Topographical Distribution

- Intracanal (optic nerve): optic nerve glioma, optic nerve sheath meningioma
- Intracanal: cavernoma, schwannoma, metastases, lymphoma, lymphangioma
- Extraconal: dermoid cyst, pleomorphic adenoma of the lacrimal gland, pseudotumor
- Subperiosteal: mucocele
- Sphenoid wing, bony orbit: meningioma, osteoma, malignant tumor, fibrous dysplasia
- Orbital apex, superior orbital fissure, cavernous sinus: meningioma, cavernoma
- Lacrimal gland, duct system: pleomorphic adenoma, carcinoma
- Muscles: endocrine orbitopathy, rhabdomyosarcoma
- Preseptal, lids: lymphomas, infections, lipoma

The intracanal space is delimited by the conus, which connects the four rectus muscles to each other. The extraconal compartment surrounds the muscular conus like a tube. The subperiosteal compartment is defined as the space between the periosteum and the bony orbit.

3.2.7.4 Histology

3.2.7.4.1 Meningioma

The most common orbital tumor is a meningioma arising from the medial portion of the sphenoid wing, the anterior clinoid process, or the optic nerve sheath. They manifest themselves with gradual loss of visual acuity, accompanied by optic nerve atrophy or proptosis. The peak incidence is between the ages of 30 and 50. Patients with optic nerve sheath meningiomas should undergo...
decompression of the optic canal, intracranial tumor re-
section, and postoperative irradiation of the intraorbital part.

The goals of surgery for sphenoo-orbital meningiomas are good cosmetic and functional results, good tumor control, and minimal morbidity. Aggressive resection in the cavernous sinus and superior orbital fissure is not recommended. Surgery should be performed as early and as radically as possible. Radiotherapy is an option for recurrences or subtotal resections.

### 3.2.7.4.2 Vascular Lesions
We distinguish between three types of hemodynamics. Most common are arteriovenous malformations characterized by direct low flow, such as cavernous hemangiomas, and treated by complete excision. Patients with capillary hemangiomas undergo spontaneous regression. Surgery is appropriate in well-circumscribed lesions. Direct antegrade high-flow lesions like AVMs are rare; patients undergo combined endovascular and surgical treatment.

Venous flow lesions appear as distensible lesion with rich communication or nondistensible anomalies. Deep venous lesions should be treated if they cause severe pain, cosmetic disturbances or visual deterioration.

No-flow lesions have little connection to the vascular system and include lymphangiomas or combined venous lymphatic malformations. Surgery may be helpful in distinct cases with intracystic hemorrhage.

Hemangiopericytoma is a rare vascular wall tumor of adulthood. It behaves rather aggressively, is locally invasive, and undergoes malignant degeneration in 30% of cases, possibly triggering distant metastases. The prognosis is good as long as the tumor is diagnosed early and completely resected.

### 3.2.7.4.3 Optic Nerve Glioma
Pilocytic astrocytoma usually arises in childhood, particularly in children with neurofibromatosis. The initial manifestation is usually visual impairment, in small children strabismus or nystagmus.

Intraorbital tumors without useful vision or severe proptosis should be operated with transection of the optic nerve just behind the globe and prechiasmatic transection. Patients with intracranial tumors, involving the optic chiasm and hypothalamus, undergo subtotal resection, followed by chemotherapy in children below the age of 5 years, external beam radiation or seed implantation in those over 5.

### 3.2.7.4.4 Schwannoma
Schwannoma tends to develop on the sensory branches of peripheral nerves. This type of tumor is cured by complete surgical resection (Fig. 3.2.77).

### 3.2.7.4.5 Fibrous Dysplasia
Fibrous dysplasia involves the bone of the optic canal and orbital roof. Decompression of the optic canal may be indicated.

### 3.2.7.4.6 Pleomorphic Adenoma
Pleomorphic adenoma is the most common tumor of the lacrimal gland, and can be cured by total resection. Rupture of the capsule should be avoided.

### 3.2.7.4.7 Rhabdomyosarcoma
Rhabdomyosarcoma is the most common malignant orbital tumor in the first decade, is usually extraconal in the superior nasal quadrant, and may involve the conjunctiva, uvea, and the lid.

This tumor has the best prognosis among all locations (3-year recurrence-free survival rate: 91%). Anteriorly located rhabdomyosarcoma can be completely resected; posteriorly situated ones are biopsied and then treated with combined radio- and chemotherapy.

### 3.2.7.4.8 Adenoid Cystic Carcinoma
Adenoid cystic carcinoma carries a poor prognosis and produces distant metastases and local recurrence. Treatment entails enucleation of the globe or brachytherapy.

Fig. 3.2.77 Axial enhanced MRI displays a medially located schwannoma with lateral displacement of the optic nerve
3.2.7.4.9 Metastases
The primary tumor can be located in the breast, lung, prostate, GIT or kidney. Diplopia and pain are the main symptoms, and there is a short duration of symptoms until diagnosis. Treatment is palliative, as survival is poor. Confirmation by biopsy is required.

3.2.7.4.10 Lymphoma
Most are EMZL (extranodal marginal zone lymphoma) and have a good prognosis with biopsy and radiotherapy. DLCL (diffuse large cell lymphoma) is the least favorable type, and can be treated with chemotherapy. Twenty percent of EMZL and 50% of DLCL become systemic.

3.2.7.4.11 Dermoid Cysts
Dermoid cysts are of congenital origin. Complete removal is required, otherwise recurrence is likely.

3.2.7.5 Operative Approaches
The choice of approach depends on the location, size, demarcation, and histological type of the lesion (Fig. 3.2.78, Table 3.2.13).

The least atraumatic approach should be chosen. In general, we distinguish between two types of approaches: transcranial or directly extracranial. Today, the transcranial approach is no longer used in most cases.

**Table 3.2.13 Approaches to the orbit**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Indications</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral orbitotomy</td>
<td>Intra- and extracranal tumors, lateral and basal to the optic nerve; orbital apex, lacrimal gland tumors</td>
<td>Good exposure, well-tolerated procedure</td>
<td>Visible but minimal scar</td>
</tr>
<tr>
<td>Transethmoidal</td>
<td>Extracranal tumors medial to the optic nerve, traumatic injury of the optic canal</td>
<td>Well tolerated, usually used by ENT surgeons, no brain retraction</td>
<td>Limited exposure, approach through unsterile sinuses, more bleeding</td>
</tr>
<tr>
<td>Frontal transsinusoidal</td>
<td>Tumors or trauma of the frontal sinus, retention cysts, extracranal processes</td>
<td>Minimally invasive, particularly for retention cysts</td>
<td>Visible scarring, risk of infection, limited indications</td>
</tr>
<tr>
<td>Transmaxillary</td>
<td>Basal lesions, intra- or (preferably) extracranal, contraction of the maxillary sinus</td>
<td>Well-tolerated, performed in collaboration with ENT surgeons</td>
<td>Limited exposure, hemorrhage, approach through unsterile sinuses</td>
</tr>
<tr>
<td>Transconjunctival</td>
<td>Basal, medial intra- and extracranal tumors, biopsy of intracranal processes</td>
<td>Minimally invasive, ideal for cavernomas, excellent cosmetic result</td>
<td>Only for highly experienced surgeons (collaboration with ophthalmologists is recommended)</td>
</tr>
</tbody>
</table>

3.2.7.6 European Recommendations
Any patient with visual loss, proptosis, or impaired ocular motility should undergo MRI to detect or exclude an intraorbital or intracranial process.

Patients found to have one of these rare tumors should be referred to a specialized center for further treatment. Collaboration across specialties, including ENT, maxillofacial surgery, ophthalmology, and neurosurgery, improves the chances of successful treatment.
Acknowledgments

We thank Prof. Brassel, Neuroradiology, for the neuroimaging.

Selected Reading

3.2 Brain Tumors


3.2.8 Pseudotumour Cerebri

FLEMMING GJERRIS

3.2.8.1 Basics

The clinical syndrome of pseudotumour cerebri (PTC) is described by many authors, resulting today in the term idiopathic intracranial hypertension (IIH) for pseudotumour cerebri of unknown origin. There is no consensus on classification. Some authors prefer to divide intracranial hypertension into idiopathic (unknown = primary) and secondary intracranial hypertension, others into primary PTC = idiopathic intracranial hypertension and secondary PTC, where the aetiologies are multitudinous [6, 7]. When an aetiology is found, i.e. a drug or a venous sinus anomaly, the correct term is secondary PTC [7, 9]. Studies such as magnetic resonance imaging (MRI), MR-CSF flow and cerebrospinal fluid (CSF) dynamics have resulted in a better understanding of the aetiology, pathogenesis and pathophysiology of the disease [9, 11].

3.2.8.2 Idiopathic Intracranial Hypertension

3.2.8.2.1 Synonyms

Primary pseudotumour cerebri, benign intracranial hypertension, papilloedema of unknown cause.

3.2.8.2.2 Definition

Idiopathic intracranial hypertension is a condition of increased intracranial pressure (ICP) without any clinical, laboratory or radiological evidence of intracranial pathology and a completely normal composition of CSF. It is thus a diagnosis of exclusion and describes today a much more restricted group of patients than previously. The criteria are formulated in the International Headache Society’s classification of headache disorders [14].

3.2.8.2.3 Epidemiology/Aetiology

The annual incidence of IIH is 1–2/100,000 in the general population with an increase up to 3/100,000 in the age group 15–44 in women. The female: male ratio differs between 4.3:1 and 15:1. It is found in all age groups and especially in obese females of childbearing age. Several studies have attempted to find an existence of proposed associations, but apart from obesity there is no convincing evidence. The different concomitant disorders, which can give a similar clinical picture (secondary PTC) have to be outlined by CT, MRI, MRV, angiography or lumbar puncture before the diagnosis of IIH can be safely proven. Ophthalmologists should always be part of the IIH team.

3.2.8.2.4 Pathogenesis and Pathophysiology

Idiopathic intracranial hypertension may be attributed to intra- and extracellular brain oedema, increased cerebral blood volume or compromised CSF resorption. Indirect evidence of brain oedema has been provided by MR studies showing increased water content and water apparent diffusion coefficients in subcortical white matter, which may result from the convective transependymal flow of water, but a recent study of more refined MR techniques could not reproduce these findings [8, 13]. In PET studies cerebral blood flow and regional cerebral blood volume are normal, even in patients with raised ICP.

Idiopathic intracranial hypertension patients do not have increased CSF production. CT and MRI show a normal ventricular size and velocity-sensitive MR techniques demonstrate a normal CSF flow through the cerebral aqueduct. Many studies have demonstrated an increased CSF outflow resistance in 75–100% of IIH patients [9], in patients with Guillain–Barré syndrome or in intradural spinal tumours with a very high CSF protein concentration [11].

It has been proposed, that IIH patients have a defect in CSF resorption at the level of the arachnoid villi or in the capillaries in the brain cortical area, caused by some precipitating factors leading to brain water accumulation and a “stiff brain” or caused by agents or noxious events that might interfere with membrane water resorptive function (aquaporins) and brain water permeability [9]. The raised pressure on the cerebral veins could cause
cerebral vasodilatation and increased cerebral blood volume, resulting in a further rise in ICP and \( R_{out} \) until the CSF absorptive level is again in equilibrium. Venous sinus hypertension may occasionally be caused by elevated central venous pressure. Obesity correlates directly to elevated central venous pressure and a secondary raised sinus pressure in some adipositas patients, but not in all [3, 6, 13].

3.2.8.2.5 Symptoms and Signs

3.2.8.2.5.1 Symptoms

The symptoms are headache, pulsatile, often reversible tinnitus, nausea, transitory visual obscurations varying from slight blurring to total loss of light perception and double vision. The obscurations are usually related to papilloedema. Nearly 90% of the patients have headache. The headache has an episodic onset and is aggravated in the morning and by physical activity. Obesity is seen, especially in young females, often with a significant weight gain 6–12 months prior to the symptoms of increased ICP. Less common symptoms are dizziness, vomiting and paraesthesia in the hands and feet.

3.2.8.2.5.2 Signs

No focal neurological signs except for those attributable to increased ICP, i.e. papilloedema, sixth nerve palsy and enlarged blind spots are found at the time of admission.

Papilloedema is usually bilateral with blurring of the disc, diminished venous pulsation, protrusion of the optic disc and peripapillary haemorrhages or exudates. Early papilloedema is usually associated with normal visual acuity, although complaints of blurred vision may be present. Rare cases of IIH without papilloedema have been reported.

Visual field defects appear in up to 96% of patients during the course of the disease. An enlarged blind spot is the most frequent, found in nearly all IIH patients. Often field defects are arcuate scotomas. Small visual defects are often asymptomatic. When the patient becomes aware of a visual problem, the extent of the defect has often evolved. Therefore, routine follow-up of patients with IIH should consist of visual acuity testing combined with visual field examination.

The upper limit of the normal CSF opening pressure is defined as 200 mm H\(_2\)O or 15 mmHg in the lateral decubitus position. An elevated steady-state ICP has been reported in nearly all IIH patients, but many patients have long periods of normal ICP between short periods of elevated ICP. Abnormal ICP wave-forms are present. Repeated lumbar puncture after previously normal pressure may be necessary. Pressure monitoring for several hours through a lumbar drain or an intracranial transducer is recommended.

3.2.8.2.5.3 Complications

In rare cases blindness may occur rapidly within a few days, which is why visual acuity should be monitored carefully when the diagnosis of IIH is established [3, 13].

3.2.8.3 Diagnostic Procedures

3.2.8.3.1 Recommended European Standard

3.2.8.3.1.1 Neuroimaging

Computed tomography and MRI show a normal or even diminished ventricular system. MR venography may be necessary to exclude secondary PTC and is normal in IIH.

3.2.8.3.1.2 Cerebrospinal Fluid

The cerebrospinal fluid constituents (protein, sugar, cells, electrolytes) are within the normal ranges. Lumbar puncture should be performed after normal brain imaging and is of no risk in IIH patients. Post-lumbar puncture headache is not very common in IIH patients. Thirty to 120 min of lumbar pressure monitoring is necessary and sufficient to reveal an increased steady-state ICP and abnormal pressure waves. Monitoring ICP with an epidural intrathecal or a subdural lumbar transducer for at least 6–24 h is occasionally needed.

3.2.8.3.1.3 Ophthalmologic Investigations

Ophthalmoscopy, visual acuity and perimetry are necessary. All IIH patients should undergo regular testing of the visual fields with quantitative or automated perimetry. Fundus photography of the optical discs to follow the appearance over time requires collaboration with a trained ophthalmologist.

3.2.8.3.1.4 Additional/Useful Diagnostic Procedures

Measurement of \( R_{out} \) by a lumbar computerised infusion method is of considerable diagnostic value and an important parameter in the surveillance of IIH patients [2, 11]. \( R_{out} \) measurements are reliable and can be repeated several times during the course of the disease with a minimum of inconvenience to the patient [11]. Demonstrating increased CSF outflow resistance (>10 mmHg × min × ml\(^{-3}\)) with a lumbar infusion test helps to maintain the suspicion that intracranial hypertension exists despite normal CSF opening pressures.

3.2.8.3.2 Diagnosis of IIH

The clue to diagnosis is the history and imaging investigations. An algorithm for diagnosis of IIH is illustrated in Fig. 3.2.79. Clinical examination, including a general medical examination as well as thoroughly neurological and ophthalmologic examinations, is mandatory.
3.2.8.4 Therapy

3.2.8.4.1 Medical Treatment

3.2.8.4.1.1 Recommended European Standard
Standard treatment consists of carbonic anhydrase inhibitors such as acetazolamide (500–1,500 mg daily), which is very effective in most IIH cases. Side effects such as acroparaesthesias are dose-dependent. Less common are nausea, anorexia, hypokalaemia and nephrolithiasis. When acetazolamide is insufficient or intolerable the diuretic furosemide (40–120 mg/day) combined with potassium may be considered. The effect is less specific and has only a small effect on CSF production.

Repeated lumbar punctures may now be considered as obsolete and are not recommended.

3.2.8.4.1.2 Additional Therapeutic Strategies
Topiramate, a new anticonvulsant, also inhibits carbon anhydrase at clinically relevant doses. A clinical effect in IIH cases has been reported. The role of corticosteroids in the treatment of IIH is still controversial.

Weight loss reduces papilloedema, lowers CSF pressure and may be associated with relapses of IIH.

3.2.8.4.2 Surgical Treatment: Recommended European Standard
A common management error is delaying too long before surgery. Any waiting policy may be erroneous. Active surgical treatment is necessary to treat increased ICP and severe headache (most often CSF shunting) and to avoid permanent visual defects (shunting or optic nerve sheath decompression) [3, 10, 13].

3.2.8.4.2.1 Shunt Operation
Cerebral spinal fluid shunting is usually effective in IIH, but shunt dysfunctions and infections are significant problems. The lumbo-peritoneal (L-P) shunt has a rather high complication rate, and many authors prefer ventric-
ulo-peritoneal (V-P) shunting, in spite of the difficulty of cannulating a normal ventricular system [4, 5, 10].

### 3.2.8.4.2.2 Optic Nerve Sheath Decompression
Initial improvement or stabilisation of visual function has been reported in many cases, but the postoperative complication rate is rather high, i.e. seizures, infection, focal brain damage, cosmetic disfigurement, visual deterioration. The long-term efficacy is uncertain and outcome reports suggest that optic nerve sheath fenestration may be less effective than CSF shunting.

### 3.2.8.5 Differential Diagnosis
Idiopathic intracranial hypertension is still a diagnosis of exclusion. Several conditions can present with signs of raised intracranial pressure alone (Table 3.2.14).

### 3.2.8.6 Prognosis
Idiopathic intracranial hypertension is usually a self-limiting disorder with spontaneous remission in some cases. Several follow-up studies show that a few months of medical treatment in a large group of patients will improve the symptoms. Recurrence, even 5–15 years after the first attack, is described in up to 10%. A chronic course of IIH with severe headache and visual disturbances for years is not uncommon and constitutes a therapeutic problem. Visual field defects are fairly common and permanent loss of visual function is the most serious complication. Less than 5% develop blindness in one or both eyes, the risk of which is related to duration of papilloedema. In most long-term monitored patients both ICP and R_d decrease or normalise [11]. The few shunted IIH patients also have a good prognosis for both vision and headache [5, 11].

### 3.2.8.7 Surgical Principles

#### 3.2.8.7.1 Ventriculo-Peritoneal and Lumbo-Peritoneal Shunting

#### 3.2.8.7.1.1 Exposure
The basic steps in a shunting procedure are:
- Positioning of the patient
- Draping of the operative field
- Skin incisions
- Head and skull
- Insertion of the ventricular catheter
- Tunnelling of the dome, valve and the distal catheter to the jaw angle, chest and abdomen
- Insertion of the catheter into the peritoneal cavity

The different steps of CSF shunting are described in neurosurgical textbooks such as Kay and Black [10], and in a short form here.

#### 3.2.8.7.1.2 Positioning of the Patient
For a V-P shunt the patient is placed supine with the head turned to the left and with a 30° elevation. A fluffy cushion is placed under the neck and the upper part of the elevated right shoulder to flatten out the angle between the head and the chest, so that the subcutaneous tunnelling may be performed more easily. In L-P shunting the patient is placed on the side with free access to both the lumbar spine and the abdominal flank area.

#### 3.2.8.7.1.3 Draping
The skin incisions should be outlined before skin draping. The hair of the skin is cut and not shaved. The skin is washed and prepared with iodine or a similar solution.

#### 3.2.8.7.1.4 Skin Incision
The surgical drapes are placed a few centimetres from the incision sites and should not adhere to any tubes. The skin is then covered with a sticking, preferably iodinated, drapery.

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**Table 3.2.14 Most common causes of secondary pseudotumour cerebri. (Modified from [13])**

<table>
<thead>
<tr>
<th>Vascular diseases</th>
<th>Circulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cerebral venous sinus thrombosis</td>
<td>- Hypertension</td>
</tr>
<tr>
<td>- Arteriovenous malformations</td>
<td>- Congestive heart failure</td>
</tr>
<tr>
<td>CSF hyperviscosity</td>
<td>Neoplasms</td>
</tr>
<tr>
<td>- Guillain–Barré syndrome</td>
<td>- Gliomas</td>
</tr>
<tr>
<td>- Intradural or spinal cord tumours</td>
<td>- Meningeal carcinomatosis</td>
</tr>
<tr>
<td>Infection</td>
<td>- Leukaemia</td>
</tr>
<tr>
<td>- Syphilis</td>
<td>- Intradural spine tumours</td>
</tr>
<tr>
<td>- Meningitis/encephalitis</td>
<td>Others</td>
</tr>
<tr>
<td>- HIV</td>
<td>- Sleep apnoea syndrome</td>
</tr>
<tr>
<td>- Toxicity</td>
<td>- Respiratory disease with CO₂ retention</td>
</tr>
</tbody>
</table>
3.2.8.7.1.5 Head and Skull
The cranial skin incision is placed 3 cm from the midline, usually 2 cm in front of the right coronal suture. The advantages of the frontal region (non-dominant) are that the patient is supine and that the external turning points are clear (Fig. 3.2.80). The peristomeum is rongeured away, the burr hole made and the dura opened by a small crucial incision. The dural edges are thermocoagulated.

3.2.8.7.1.6 Insertion of the Ventricular Catheter
The tip of the catheter should be directed to the middle part of the zygoma and in the other plane to the middle part of the nose or the medial corner of the left eye (Fig. 3.2.80). The catheter is inserted in the right frontal horn, an approach with many advantages, i.e. short distance through the brain, access to the brain away from eloquent areas and the tip of the catheter far away from the choroid plexus. The ependyma is penetrated with the feeling of slight resistance. The catheter is fixed to the dome part with an angle connector and in some shunt types fixed to the pericranium.

3.2.8.7.1.7 The Dome and Valve
The dome and valve are placed on the pericranium of the skull, not on the soft tissue structures of the neck, and allowed to fill with CSF. The CSF flow is tested by lowering the distal end of the tube below the level of the skull. The various skin incisions are closed in two layers.

3.2.8.7.1.8 Insertion of the Catheter in the Peritoneal Cavity
The tunnelling of the catheter to the abdomen can be done either from the cranial or from the abdominal end. The abdominal skin incision is made in the midline below the xiphoid process or as a slight curvilinear incision 3 cm below and along the curvature. The subcutaneous tissue is divided, the muscle fascia opened sharply and the muscle fibres divided by blunt dissection to the peritoneum. This is elevated and opened very carefully. The catheter is pushed into the peritoneal cavity with light pressure, often to a length of 20 cm. With any hindrance, or if the catheter curls up, it is very important to start afresh. The peritoneum is secured by a purse string su-ture, and the muscle fascia, subcutis and skin are closed in the usual way.

3.2.8.7.2 The Lumbo-Peritoneal Shunt
The spine is moderately flexed to open the interlaminar spaces. A special one-piece shunt is used and the lumbar end can be placed using a percutaneous technique or by performing a small open laminectomy. The dome and peritoneal part are tunnelled subcutaneously from the lumbar spinal area to the side of the abdomen and placed in the peritoneal space.

3.2.8.7.3 Optic Nerve Sheath Decompression
If medical treatment has failed and disc swelling with visual field loss progresses, direct fenestration of the optic nerve sheaths via a medial or lateral orbitotomy is effective. The surgeon makes slits by cutting into the optic nerve sheath, which allows CSF to escape and thereby reducing the pressure around the optic nerve. The intracranial hypertension presumably persists [1]. Operative details are described in ophthalmologic textbooks.

3.2.8.8 Pseudotumour Cerebri, Secondary
A pseudotumour, like the clinical picture, is seen in chronic meningo-encephalitis, cerebral sinus thrombosis, intrathoracic lesions, polyradiculitis and spinal cord tumours. Many other causes have been described, often associated with endocrine disorders or the use or cessation of different drugs (Tables 3.2.14, 3.2.15). Extremely
careful and sufficient clinical, ophthalmologic and imaging investigations are mandatory to exclude secondary causes of pseudotumour cerebri. Sinus obstructions are revealed by MR venography (MRV) or conventional angiography in up to 40% of cases. Thrombotic material appears strongly hyperintense in the first month, and chronic thromboses or partially recanalised sinuses are best recognisable on MRV. The recognition of sinus thrombosis has crucial therapeutic implications, as management is completely different from IIH. Endovascular treatment, i.e. thrombolysis and stent placement, are promising new therapies [12]. It is outside the scope of the present chapter to give a full review of secondary pseudotumour cerebri [3, 6, 13].

### Table 3.2.15 Proposed aetiological factors of conditions similar to idiopathic intracranial hypertension. (Modified from [13])

<table>
<thead>
<tr>
<th>Exogenous factors</th>
<th>Endogenous factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Tetracyclines</td>
<td><strong>Endocrinology</strong></td>
</tr>
<tr>
<td>– Nitrofurantoin</td>
<td>– Irregular menstruation</td>
</tr>
<tr>
<td>– Nalidixic acid</td>
<td>– Pregnancy</td>
</tr>
<tr>
<td>– Sulfamethoxazole</td>
<td>– Oral contraceptives</td>
</tr>
<tr>
<td>– Penicillin</td>
<td>– Turner</td>
</tr>
<tr>
<td>– Corticosteroid treatment and withdrawal</td>
<td>– Adrenal insufficiency</td>
</tr>
<tr>
<td>– NSAID in Bartter syndrome</td>
<td>– Hyperthyroidism</td>
</tr>
<tr>
<td>– Mesalamine</td>
<td>– Hypothyroidism</td>
</tr>
<tr>
<td>– Lithium carbonate</td>
<td>– Hyperaldosteronism</td>
</tr>
<tr>
<td>– Amiodarone</td>
<td><strong>Haematology</strong></td>
</tr>
<tr>
<td>– Chlordecone</td>
<td>– Anaemia</td>
</tr>
<tr>
<td>– Cyclosporine</td>
<td>– Hypercoagulability</td>
</tr>
<tr>
<td>– Vitamin A</td>
<td><strong>Others</strong></td>
</tr>
<tr>
<td>– rhGH and IGF-1</td>
<td>– Systemic lupus erythematosus</td>
</tr>
<tr>
<td>– Others</td>
<td>– Behcet’s disease</td>
</tr>
<tr>
<td>– Acute respiratory insufficiency</td>
<td>– Sleep apnoea</td>
</tr>
</tbody>
</table>

### 3.2.8.9 Special Remarks

Idiopathic intracranial hypertension is a diagnosis of exclusion that has been puzzling health professionals for decades. The pathophysiology of IIH is not fully understood and no causal treatment exists. Research reports favour the presence of venous outflow abnormalities. Advances in diagnostic neuroimaging techniques and implications of manometry recordings particularly in relation to venous sinus pathology have demonstrated underlying causes in many of the cases conventionally classified as IIH. The disease usually resolves after a few months of medical treatment, but the risk of visual deterioration is considerable and some patients experience a chronic disabling course for years that limits their working and social capacity. When a feasible aetiology is pointed out, i.e. a drug or a venous sinus anomaly, the correct term is secondary PTC and not IIH.

### Selected Reading

3.2 Brain Tumors

3.2.9 Pediatric Brain Tumors

3.2.9.1 Infratentorial Brain Tumors in Children

MASSIMO CALDARELLI, CONCEZIO DI ROCCO

3.2.9.1.1 Introduction

Three oncotypes, astrocytoma, medulloblastoma, and ependymoma, almost exclusively encompass the field of infratentorial tumors in the pediatric age. While cerebellar astrocytoma is mainly a surgically curable disease, a combination of surgery, radiation therapy, and, to a lesser extent, chemotherapy, constitutes the basis for the management of the other two forms. Local recurrence or CSF spread is negligible for the former, whereas this is almost the rule for the latter two, unless adjuvant therapy is given after surgical excision. Tumor characteristics at diagnosis, extent of surgical excision, and age of the patient are the leading factors that influence the possibility of cure.

Clinical manifestations are common to all of them, and consist mainly of symptoms and signs of increased ICP (headache, vomiting, and lethargy), mainly due to the frequently associated obstructive hydrocephalus (80% of cases), nuchal pain, torticollis, and more rarely, signs of cerebellar deficit and isolated cranial nerve deficits; multiple cranial nerve deficits and pyramidal syndrome are suggestive of brain stem glioma. Spinal or limb pain should suggest spinal seeding.

3.2.9.1.2 Astrocytomas

Cerebellar astrocytomas constitute about 5% of all intracranial pediatric tumors and approximately one-third of those located in the posterior cranial fossa; peak incidence between 6 and 8 years, with a slight female preponderance. It is one of the few really surgically curable CNS tumors. Total resection assures 100% disease-free survivals at 10 years; however, this is the case in only 70–80% of cases, due to the invasion of eloquent areas in the remaining cases.

There are two main histological forms: pilocytic and diffuse. The first type (70%) is a pink-gray, translucent, solid and elastic mass lesion with frequent cyst formation; they are usually sharply marginated and well-demarcated from the cerebellar parenchyma, with a preferred location in the cerebellar vermis and prevalent extension toward one cerebellar hemisphere; intratumoral hemorrhage is rare. From a histological point of view, it is moderately cellular, with fibrillary cells oriented in bundles; cells are fusiform or elongated, uni- or bipolar; mitoses are absent. The second type (30%) is less well-demarcated from the cerebellar parenchyma; histologically presents pseudorosettes, hypercellularity, occasional mitoses, abundant necrosis, microcalcifications; and cyst formation is far less frequent than with the first type (25%).

3.2.9.1.2.1 Neuroimaging

The unenhanced CT appearance of pilocytic astrocytoma is of a well-demarcated, isodense or hypodense mass. Three main patterns can be recognized: a large cyst with a mural nodule; a solid tumor with cystic areas; and a cystic tumor surrounded by a thick solid neoplastic rim.

Fig. 3.2.81a,b T1-weighted a axial and b sagittal contrast-enhanced (CE) images of an infratentorial pilocytic astrocytoma. Note the typical pattern of the cystic tumor with a mural nodule and the homogenous bright contrast enhancement.
Intense, homogeneous contrast enhancement (CE) is usually seen after contrast injection. Diffuse astrocytoma presents as an ill-defined, homogeneous hypodensity, with occasional calcifications (20%).

On basal MRI pilocytic astrocytoma appears as a hypointense mass on T1-weighted images and moderately hyperintense on T2-weighted images; there is a variable cyst signal according to the protein content of the cyst fluid; and intense, homogeneous CE after Gadolinium injection (Fig. 3.2.81). On the other hand, a diffuse astrocytoma appears as an ill-defined hypointensity on T1-weighted images, a better defined hyperintensity on T2-weighted images; and there are sometimes patchy areas of CE after Gadolinium injection.

3.2.9.1.2.2 Therapy
Surgical excision is the elective treatment. In the case of cystic tumors, simple nodule excision may suffice if the cyst wall does not enhance on neuroradiological investigation; otherwise, the cyst wall must be removed together with the mural nodule. In the case of diffuse tumors, a close relationship with eloquent structures, namely the brain stem and cerebellar peduncles, can make surgical excision less radical (actually feasible in only 50–60% of cases). While survival at 25 years is over 90% in the case of pilocytic astrocytoma, this percentage decreases to only 40% in patients with diffuse astrocytoma undergoing partial resection. Recurrences should be treated with repeated surgery. Radiation therapy plays a role after partial removal in children aged 3 years or more, or after partial removal of a recurrence. Malignant transformation or CSF seeding of a benign astrocytoma is exceedingly rare.

3.2.9.1.3 Medulloblastomas
Medulloblastomas account for about 20% of all CNS pediatric tumors and approximately one-third of those within the posterior cranial fossa. The peak incidence is between 7 and 12 years (median 9 years). Boys are more affected than girls, with a sex ratio of 3.0 to 1.6. The most frequent location is the inferior cerebellar vermis with extension into the fourth ventricle. Less frequently, they are located within the cerebellar hemispheres or cerebello-pontine angle. On gross examination a medulloblastoma (MB) appears as a well-circumscribed, grey reddish mass, soft or granular; nonetheless, cerebellar invasion does occur at its edges, and possibly at the cerebellar peduncles and brain stem in about 33% of cases. On occasion, they are more firm, due to the presence of abundant connective tissue.

Histologically, MBs are composed of tightly packed, isomorphic, elongated cells, with round or oval nuclei, occasionally arranged to form pseudorosettes. Mitosis is frequent. Necrosis, calcifications, and cyst formation are uncommon. The presence of mature astrocytes or gangliocytes inside the tumor (expression of tumor multipotentiality) would be associated with a longer disease-free survival; other authors, on the contrary, deny this association, and in fact attribute a less favorable prognosis to this finding.

Two main variants are described: classic and desmoplastic. Traditionally, the latter would be characterized by a larger amount of connective tissue (an expression of mesenchymal reaction to meningeal invasion), more frequent location in the cerebellar hemispheres, less aggressive behavior, and a higher incidence in older patients. Other observations, however, indicate that the desmoplastic variant is equally distributed in the hemispheres and vermis and does not carry a better prognosis. Recently, a further variant, “multinodular,” has been described, so called for its histological appearance; it occurs prevalently in very young children, and usually bears a more favorable prognosis.

Generally, the biological behavior of MB is that of a highly malignant tumor, death occurring within 8–15 months of onset of symptomatology with no treatment or surgery alone.

3.2.9.1.3.1 Neuroimaging
Medulloblastoma is a spontaneously hyperdense mass on unenhanced CT, with peripheral edema; rare necrosis or calcifications; and marked, homogeneous CE. It is

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**Fig. 3.2.82a,b** T1-weighted a axial and b sagittal CE images of a medulloblastoma. Note the huge vermian tumor showing almost uniform contrast enhancement, with extensive infiltration of the dorsal aspect of the lower brain stem.
hypointense or isointense on T1-weighted images; shows notable decay on T2-weighted images; and is moderately to markedly hyperintense on T1-weighted images after Gadolinium injection (Fig. 3.2.82).

3.2.9.1.3.2 Therapy
Surgical excision is the first step of treatment, and should be as radical as possible to give the patient the best chance of cure. In fact survival is directly related to the extent of surgical removal, with only 30% of patients receiving partial resection still alive at 5 years, compared with 60% in the case of total removal, provided the same postoperative adjuvant treatment is given. At present, gross total resection is obtained in more than 60% of cases; operative mortality is 3–4%. Persistent hydrocephalus is observed in almost 20% of cases, in spite of gross total tumor removal. Third ventriculostomy can succeed in restoring CSF circulation in >80% of cases, VP shunting representing the treatment in the remaining cases. Routine preoperative third ventriculostomy has been repeatedly criticized, and is no longer indicated. A permanent VP shunt does not constitute an adjunctive risk for extracerebral tumor spread, as previously suggested. Adequate treatment of hydrocephalus is mandatory to prevent the side effects of chemo- and radiation therapy, which can induce cerebral edema and decompensate an apparently stable ventricular dilatation.

Tumor staging is fundamental for prognostic purposes and is based on the following criteria:

- Extent of removal (more important than tumor size at diagnosis)
- Presence of metastasis at diagnosis
- Postoperative subarachnoid tumor spread
- Negative early (within 48/72 h) postoperative CT/MRI

According to these criteria, 100% disease-free survival at 5 years is expected in patients undergoing total resection, with negative postoperative CT/MRI investigation, and with no evidence of tumor spread; this percentage is reduced to 78% in the same situation, but with subtotal resection; and to 18% in the case of subtotal resection, with positive postoperative CT/MRI, and the presence of leptomeningeal spread. According to these criteria a distinction can be made between “standard” and “high-risk” patients (partial resection, presence of metastases at diagnosis, young age). Children less than 3 years old constitute a special problem as they cannot undergo radiation therapy and are treated only with high-dose chemotherapy.

3.2.9.1.3.2.1 Radiotherapy
Radiotherapy plays a fundamental role in the treatment of MB (only one-third of patients survive 5 years without this therapy). Its major adverse effects (hypopituitarism; short stature; intellectual impairment, from learning disabilities to severe neurocognitive handicap) can be partially obviated by reducing the standard radiation dose (50–55 Gy to the posterior fossa, 35–40 Gy to the neuraxis) or by utilizing hyperfractionated irradiation in combination with chemotherapy.

3.2.9.1.3.2.2 Chemotherapy
Various chemotherapeutic drugs have been utilized over the years: vincristine, CCNU, cisplatin, busulfan, and thiopental. The role of chemotherapy in low-risk patients is still controversial; on the contrary, the survival of high-risk patients receiving chemotherapy is comparable with that of standard-risk patients. The possibility of replacing radiation therapy with chemotherapy has been investigated, but a definitive answer is still lacking. Certainly, chemotherapy plays a role in postponing for 1–2 years radiation therapy in infants and young children less than 3 years old with nonmetastatic, totally resected MBs. Less convincing are the results in infants with diffuse disease and limited resection. At present, encouraging results are obtained with high-dose chemotherapy under the cover of bone marrow stem cell rescue.

3.2.9.1.4 Ependymomas
Ependymomas represent approximately 10% of all intracranial tumors, 60% of which are located within the posterior cranial fossa; they constitute 10–15% of posterior fossa tumors. The most common location (in 60%) is the fourth ventricle, as the tumor usually originates in its floor and extends into the cisterna magna and upper cervical canal. Less frequently (in 30%), they develop in a lateral position involving the foramen of Luschka and spread into the cerebellopontine angle; very rarely, the tumor originates in the roof of the fourth ventricle. At inspection, ependymomas appear as a reddish nodular or lobulated mass, occasionally with a cauliflower appearance, mainly extra-axial, but with discrete brain stem and cerebellar infiltration. The prevalent cisternal growth accounts for the frequent involvement (compression more than infiltration) of lower cranial nerves and vascular supply to the brain stem.

From a histological point of view, the neoplastic cells are typically arranged in perivascular pseudorosettes; cytoplasm is scarce and mitoses rare. Histological classification remains controversial, the main differentiation being between ependymoma and anaplastic ependymoma (whose incidence varies widely from 7 to 89%). These tumors are often biphasic, with a prevalent benign appearance and small islands of more malignant cells.

3.2.9.1.4.1 Neuroimaging
Ependymomas are usually isodense on plain CT, with microcalcifications. Cysts and necrosis are rare. Contrast
enhancement is partial and moderate. They are usually iso- or hypointense on T1-weighted MRI, with heterogeneous CE; and typically hyperintense on T2-weighted, proton density, and FLAIR images.

### 3.2.9.1.4.2 Therapy

Ependymoma is mainly a surgical disease, and the extent of surgical resection is the single most relevant factor influencing the long-term outcome. However, despite the availability of sophisticated operative tools, like ultrasound aspiration, which enable the neurosurgeons to be more aggressive, the actual feasibility of a gross total removal remains only 50%; surgical difficulties are caused by the intimate tumor relationship with brain stem, cranial nerves, and vessels; in particular, tractions on the floor of the fourth ventricle, while attempting radical removal, can provoke life-threatening cardiocirculatory reactions (alternating tachycardia and bradycardia, elevation in blood pressure), which account for the non-negligible operative mortality and elevated morbidity.

Radiation therapy is standard adjuvant treatment in the case of partial resection and in children aged more than 3 years. Local irradiation is thought to be sufficient, as the actual occurrence of metastases is lower than originally estimated. The optimal dose is controversial, as well as the need for this therapy in the case of total resection. Chemotherapy plays a marginal role.

The prognosis of posterior fossa ependymoma continues to be poor with an overall 5-year disease-free survival of only 30–38%, which is worse than for medulloblastoma, despite its presumed better histology. Recurrences are frequent and are mainly local, with spinal spreading possible, but rare (<10%). Repeat surgery is the mainstay of treatment.

### 3.2.9.1.5 Brain Stem Gliomas

Brain stem gliomas are dealt with in Sect. 3.2.6, but some remarks must be made on aspects concerning the pediatric age. Brain stem gliomas account for approximately 8–15% of all intracranial tumors in children, and 20% of those in the posterior cranial fossa. There are two peaks of incidence, in the first and fourth decades, and 27–77% of brain stem tumors occur in the pediatric age. They may present as a symmetrical enlargement of the pons (almost 60% of localizations), or less frequently as restricted growth involving one half of the pons, medulla or midbrain.

#### 3.2.9.1.5.1 Histology

There are two main patterns: in approximately two-thirds of cases diffuse replacement of nervous tissue by small or large, fusiform, bipolar or gemistocytic astrocytes, either randomly dispersed or arranged in groups, with focal areas of anaplasia (fibrillary or gemistocytic astrocytoma, anaplastic astrocytoma, glioblastoma); in the other third the typical pattern of pilocytic astrocytoma is prevalent. From a clinical standpoint, brain stem gliomas are characterized by the association of lower cranial nerve deficits with signs of cerebellar or pyramidal tract deficits. Hydrocephalus is far less common than with other posterior fossa tumors.

### 3.2.9.1.5.2 Neuroimaging

The CT appearance of a brain stem glioma is that of diffuse brain stem enlargement with hypodense (36%), isodense (36%), or less frequently, mixed density (23%) signal. MRI appearance is that of a hypointense signal on T1-weighted images, and a hyperintense signal on T2-weighted images with variable CE. What seems most important for surgical purposes is the tumor localization:

- **Type I:** diffuse pontine tumors (55–60%) – usually hypointense on T1-weighted images and minimal or absent CE
- **Type II:** intrinsic and focal tumors (10%) – solid or cystic, localized in the pons, medulla or midbrain
- **Type III:** exophytic tumors (dorsal or lateral, 10–20%)
- **Type IV:** cervicomedullary tumors (20%)
3.2 Brain Tumors

Selected Reading


3.2.9.2 Supratentorial Brain Tumors in Children

MASSIMO CALDARELLI, CONCEZIO DI ROCCO

Brain tumors are the most frequently occurring solid neoplasms, and the second most common cause of death (following traumas) in the pediatric age. Their incidence is 2–3 new cases per year per 100,000 children, with a reported rising annual incidence of 1% in the last 20 years. In the first 2 years of life supratentorial tumors predominate, as in the adult population, over infratentorial tumors, whereas from the third year on, the latter are more frequent.

Supratentorial tumors represent approximately 40–50% of all brain tumors in children. Neuroepithelial tumors account for about 80% of cases, the remaining 20% comprising craniopharyngiomas, germ cell tumors, meningiomas, and more rare oncotypes.

For practical purposes, tumors of the cerebral hemispheres (cortex and underlying white matter) will be addressed separately from those occurring along the cerebral midline (diencephalon, hypothalamus) or within the ventricles.

3.2.9.2.1 Tumors of the Cerebral Hemispheres

Tumors of the cerebral hemispheres constitute approximately 30–40% of pediatric supratentorial tumors. Tumors of neuroepithelial origin (astrocytoma, ependymoma, and less frequently oligodendroglioma) are by far the most frequent. Among them, astrocytoma (predominantly low-grade pilocytic, fibrillary or protoplasmic) is the most frequent oncotype, followed by ependymoma, oligodendroglioma, mixed glioma, and ganglioglioma. In fact, since many pediatric tumors disclose a mixed population, histology often indicates the predominant oncotype or the most aggressive. New entities such as dysembryoplastic neuroepithelial tumors (DNET), central neurocytomas, and desmoplastic infantile gangliogliomas (DIG) have been described. Furthermore, the cerebral hemispheres may harbor embryonal tumors such as primitive neuroectodermal tumor (PNET) and atypical teratoid/rhabdoid tumor (ATRT).

Clinical manifestations vary according to tumor location and aggressiveness, and to the patient's age. Symptoms and signs of increased ICP are late, unless the tumor grows rapidly. In children less than 2 years old, irritability or lethargy, associated with macrocrania and bulging fontanel, may be the only clinical manifestation. Epilepsy is the main symptom in 40–70% of cases; while seizure semiology represents an important topographic criterion in older children and adolescents, its value is much less significant in young patients due to brain immaturity. Also, cranial asymmetry may be the revealing sign of a brain tumor. Among focal signs, motor or sensory disturbances, personality changes, deteriorating school performance, and visual field defects are the most common.

3.2.9.2.1.1 Astrocytomas

Astrocytomas are predominantly (in about 80% of cases) low-grade tumors (pilocytic and fibrillary); however, the pilocytic variant is relatively less common than those in the infratentorial compartment. Cystic forms are found in 35–60% of cases, and predominate in patients with pilocytic astrocytoma; in contrast to its infratentorial counterpart, the cyst wall contains neoplastic tissue in up to 70% of cases. Anaplastic astrocytoma and glioblastoma multiforme together account for the remaining 20%.

3.2.9.2.1.1 Neuroimaging

Low-grade astrocytomas are usually iso- or hypodense on CT, with a moderate or absent mass effect, mostly scarcely or non-enhancing after contrast agent administration. The MRI appearance (Fig. 3.2.83a,c) is that of an iso- or hypointense mass on T1-weighted images, with ill-defined borders, and hyperintense on T2-weighted images; usually there is scarce and patchy CE. Conversely, pilocytic astrocytomas, often deeply seated (in the thalamus or basal ganglia) and cystic, tend to present more distinct boundaries and marked CE, which does not represent a sign of malignancy, in contrast to what happens in adults. The CT appearance of high-grade tumors is that of a large isodense or hyperdense lesion that usually enhances homogeneously; necrosis (with post-contrast ring enhancement), cyst formation, and hemorrhage are frequent. The MRI appearance is that of an iso-/hyperintense lesion on T1-weighted images, and hyperintense on T2-weighted images; CE is usually homogeneous.
3.2.9.2.1.1.2 Management
Surgical excision is the mainstay of treatment for low-grade astrocytomas. Superficially located low-grade tumors bear a good prognosis after radical excision, with a long-term survival of 60–93% in most recent series and surgery-related mortality approaching 0%. At present, thanks to the introduction of neuronavigation, intraoperative ultrasonography, integration of functional imaging, and improvement in electrophysiological monitoring, surgical resection represents a safe option not only for superficial tumors (even when located in eloquent brain areas), but also for deeply seated tumors. Actually, most of the latter are low-grade astrocytomas, and also a subtotal resection can provide an elevated 5-year survival rate.

Postoperative radiation therapy plays a minor role, if any, after total/subtotal excision of a low-grade astrocytoma. In fact, although radiotherapy is presently much safer than before, its utilization in children less than 5 years of age should be regarded with caution, taking into account the significant immediate and later side effects of treatment. Follow-up MRI is the best way to monitor these children, and the possible tumor recurrence or progression should be managed by means of a second operation. Chemotherapy is utilized, especially in young children with a residual tumor as an alternative to radiation. There are multiple protocols including carboplatin and vincristine. Complete responses are few, whereas the rate of partial responses or stable disease is high (progression-free survival 61–75% at 3 years).

The most relevant prognostic factors in low-grade astrocytoma are the histology and the patient’s age at diagnosis. Pilocytic tumors show 5- and 10-year disease-free survival of 85% and 79% respectively, compared with 51% and 23% for nonpilocytic tumors. With regard to age, the 2-year progression-free survival has been reported to be as high as 81% in children less than 5 years of age, compared with 58% in older children. In another study, pediatric patients (<19 years old) had a 5-year survival rate of 83%, compared with 35% in those aged 20–49 years, and 12% in those aged >50 years. The management of high-grade astrocytoma is more uniform. Radical excision has proven to be superior to partial resection in children as well as in adults. The association with radiation and chemotherapy doubles the 5-year survival. Nevertheless, the prognosis is poor and parallels that observed in the adult population, with disease-free survival at 5 years of 20–40% for anaplastic astrocytoma, and only 5–15% for glioblastoma.

3.2.9.2.1.2 Ependymoma
Ependymomas are mostly paraventricular (in contrast to infratentorial forms) and predominate in boys less than 5 years of age (approximately one-third of all CNS ependymomas). Generally, they present as well-differentiated tumor masses with a variable incidence of malignant
forms. Although for practical purposes, one distinguishes between low-grade (grade II of the WHO classification) and high-grade (grades III and IV) ependymomas, the histological grade is not usually a reliable prognostic factor. Ependymomas are mostly well-demarcated and cystic (about 50%), but these features are not a sign of malignancy; malignant forms tend to be more invasive, to grow significantly inside the ventricular space, and to be highly vascular.

Histologically, ependymomas are characterized by a perivascular cell distribution with rosette or pseudorosette formation; malignant forms show increased cellularity and mitotic activity, and nuclear polymorphism; and necrosis, vascular proliferation, and endothelial hyperplasia are less reliable signs of malignancy. Ependymoblastoma is a poorly differentiated malignant form prevalent occurring in children, and represents the embryonic form of the ependymal tumor (PNET with ependymal differentiation, according to Rorke). The prognosis is invariably poor.

3.2.9.2.1.2.1 Neuroimaging
Ependymomas are either hypo- or isodense on basal CT; calcifications and cysts are very frequent. CE is usually heterogeneous. On MRI ependymomas are hypointense on T1-weighted images, and hyperintense on proton density and T2-weighted images. They are usually well-demarcated from the surrounding brain parenchyma, but with inhomogeneous signal characteristics owing to the presence of calcifications, microhemorrhages, mineralization, and increased vascularity. Also, with MRI, CE is usually inhomogeneous (Fig. 3.2.83b,d).

3.2.9.2.1.2.2 Management
Surgical excision followed by radiotherapy is the mainstay of treatment for these tumors. As tumor recurrence is mainly local (spinal metastases are reported in only 10–13% of cases in most recent series), local irradiation can be a valid alternative to classical whole-brain irradiation. After complete treatment, the overall 5-year survival varies from 44 to 66%, and the 5-year progression-free survival from 23 to 61%. Adjuvant therapy, after total resection of low-grade ependymomas, is not recommended in young patients (who constitute the majority).

Various chemotherapy regimens have been utilized over the years, but the results of currently available protocols remain quite disappointing, due to the lack of chemosensitivity of these tumors.

The most relevant factor for the patient’s outcome is the extent of surgical resection, with 5-year survival of 80% for total resection, 48% for near total, and only 22% for partial. Also, tumor seeding seems influenced by the extent of removal, as no dissemination was found in 83% of totally resected tumors compared with 71% of those subtotally resected. The patient’s age is another important factor as children less than 3 years old show a significantly worse outcome than older children; however, this seems related to their inability to receive optimal treatment.

3.2.9.2.1.3 Oligodendroglioma
Oligodendrogliomas account for 2–3% of supratentorial tumors in children; when considered together with mixed gliomas, which are characterized by a mixture of two or three types of mature cells (oligoastrocytoma, oligoependymoma), their incidence reaches 9–30%. Calcification is usually abundant. Pediatric oligodendrogliomas have a predisposition to spontaneous hemorrhage due to their rich vascular bed. The grading system identifies a benign and an anaplastic form, the latter being more frequent than in the adult population. Furthermore, even benign forms may spread along CSF pathways. Histologically, they present as sheets of monomorphous cells with small round nuclei, surrounded by a clear cytoplasm; anaplastic nuclei and a variable degree of mitoses identify the malignant variants. Clinically, a history of seizures is present in 52–67% of cases.

3.2.9.2.1.3.1 Neuroimaging
Oligodendroglioma is usually hypodense on basal CT, with a variable degree of calcifications (the pattern of gyriform calcifications is pathognomonic) and cysts; CE is inhomogeneous. MRI characteristics are similar.

3.2.9.2.1.3.2 Management
Radical surgery is the most effective therapy. Unfortunately, the infiltrative nature of the tumor, and the presence of calcifications, can prevent radical removal; in such cases, as well as in cases of malignant forms, adjuvant radiotherapy is indicated. The effectiveness of chemotherapy is still under discussion. Five-year survival varies from 75 to 85%, but is significantly lower in anaplastic forms.

3.2.9.2.1.4 Ganglion Cell Tumor
Ganglion cell tumors include ganglioglioma, gangliocytoma, and desmoplastic infantile ganglioglioma (DIG). All these forms are characterized by a mixture of astrocytes and neurons. Together they constitute 1–7.5% of all primary CNS neoplasms. Gangliogliomas are more frequently found in children and young adults, with a peak incidence between 5 and 6 years. More than 80% of the cases involve the mesial aspect of the temporal lobe, the amygdala, and the hippocampus. The predominant (in about 80% of the cases) seizure pattern is that of complex partial seizures; seizures may arise either from irritation of normal brain surrounding the tumor, or from its neuronal component. Neuropsychological tests show mild cognitive impairment in almost all the patients with temporal lesions and longstanding seizures. Verbal and visuo-spatial performance are the most frequently compromised functions for dominant and nondominant tumors respectively.
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Gangliogliomas are staged according to the WHO classification, grades I and II constituting 80–90% of the cases.

Histologically, they consist of a mixture of glial cells and neurons; the former may be made up of mature astrocytes, gemistocytes or oligodendroglial cells; and the neurons are clearly heterotopic or atypical, showing disorientation, bizarre shapes, and nuclear hyperchromatism. Anaplastic gangliogliomas (WHO grade III) and ganglioblastomas (WHO grade IV) constitute less than 10% of all gangliogliomas. The glial component represents the malignant portion of the tumor in the majority of cases. Gangliocytomas are a far less common subgroup characterized by the presence of only abnormal neurons inside the tumor, and their clinical behavior parallels that of traditional gangliogliomas. The DIG is a distinct form of ganglioglioma peculiar to the pediatric age, occurring almost exclusively in children under 18 months of age; they are usually large and cystic and they show diffuse arachnoidal infiltration. Nevertheless, their biological behavior is indolent and the clinical course may be unremarkable for a long time.

### 3.2.9.2.1.4.1 Neuroimaging

The CT appearance of gangliogliomas is usually that of a well-demarcated hypodense area, with absent perilesional edema, rare calcifications, and occasional cysts. In the case of cortical localization, scalloping of the inner skull table can be observed. On MRI they are usually isointense on T1-weighted and hyperintense on proton density and T2-weighted MRI (hyperintense in 30%). CE is usually moderate and homogeneous. Anaplastic variants (WHO grade III) are spontaneously hyperdense on CT and hyperintense on T1-weighted MRI scans. A comparison of PET/MRI studies has revealed heterogeneous metabolic behavior in low-grade tumors, and increased metabolic activity in high-grade gangliogliomas.

### 3.2.9.2.1.4.2 Management

Radical excision, whenever feasible, is the treatment of choice and assures long-term survival or cure. In children with medically intractable epilepsy there is controversy as to whether simple lesionectomy or identification and resection of epileptogenic areas should be considered. Data from the literature suggest that tumor removal is indicated as the primary treatment in children with a short epileptogenic clinical history, reserving intraoperative mapping and more extensive resections for patients with long-standing seizures and multifocal EEG patterns.

The role of adjunctive therapies in the case of incomplete removal remains uncertain. Radiotherapy after partial tumor removal is generally considered of little benefit. The 10-year actuarial survival rate for gangliogliomas of the cerebral hemispheres is more than 90%.

### 3.2.9.2.1.5 Dysembryoplastic Neuroepithelial Tumors

Dysembryoplastic neuroepithelial tumors (DNETs) are rare neoplasms, with a male predominance, and are almost exclusively found in the pediatric age (1–19 years, mean 9 years). Histologically, they resemble mixed tumors. Typical features are cortical location, multinodular architecture (the nodules consisting of areas resembling astrocytoma, oligodendroglioma, cortical dysplasia), the presence of specific neuronal elements disposed perpendicularly to the cortical surface. They are most frequently located in the temporal lobe and associated with long-standing seizure disorder (usually early onset partial seizures); neurological deficits are minimal or absent.

### 3.2.9.2.1.5.1 Neuroimaging

The CT appearance of DNET is usually that of a well-demarcated hypodense area, with focal calcifications, and calvarial erosion (typical “pseudocystic lesion”). On MRI (Fig. 3.2.84) they are hypointense on T1-weighted im-

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**Fig. 3.2.84a,b** Axial a T1-weighted and b T2-weighted images of a dysembryoplastic neuroepithelial tumor (DNET), demonstrating a well-demarcated lesion with low-intensity signal on T1-weighted images that becomes hyperintense on T2-weighted images.
ages and hyperintense on T2-weighted images; they may look like large cortical gyri. CE is usually uniform and marked.

3.2.9.2.1.5.2 Management
Radical excision, whenever feasible, is the treatment of choice, which also results in seizure control. No adjuvant treatment is indicated, even in the case of incomplete removal.

3.2.9.2.1.6 Embryonal Tumors
Embryonal tumors are small cell neoplasms with divergent differentiation; they include primitive neuroectodermal tumors (PNET), medulloepithelioma, neuroblastoma, and ATRT. In particular, PNETs are undifferentiated neoplasms, considered to originate from a common primitive neuroepithelial cell. They are relatively rare in the supratentorial compartment compared with the infratentorial one. PNETs are composed of poorly differentiated neuroepithelial cells with clusters of cells with astrocytic, ependymal, oligodendroglial, or neuronal differentiation. Necrosis, hemorrhage, and cyst formation are very common, and their clinical behavior parallels that of a medulloblastoma. Approximately two-thirds occur in children under 3 years of age.

3.2.9.2.1.6.1 Neuroimaging
The CT appearance of PNET is that of a large isodense or hyperdense lesion that usually enhances homogeneously (but less markedly than medulloblastoma). Necrosis, cyst formation, and hemorrhage are frequent. The MRI appearance is that of an iso-/hyperintense lesion on T1-weighted images and hyperintense on T2-weighted images. CE is homogeneous.

3.2.9.2.1.6.2 Management
Attempted radical surgery is the first step of treatment, as the entity of tumor removal seems to affect positively disease-free survival. Surgery, however, must be integrated with chemotherapy (cisplatin, lomustine, and vincristine) and craniospinal irradiation, as in the case of medulloblastoma. Children less than 3 years of age are treated only with multiagent chemotherapy with the aim of postponing the time until irradiation can be administered. The prognosis is poor irrespective of treatment, with a median survival time of less than 1 year.

3.2.9.2.1.7 Atypical Teratoid/Rhabdoid Tumors
Atypical teratoid/rhabdoid tumors (ATRT) are peculiar to the early pediatric age, three-quarters of them occurring in young children less than 3 years of age. Histologically, they are largely similar to PNET, with a relevant malignant mesenchymal component (almost 30% of the tumor), and epithelial differentiation in a quarter of them. Neuroimaging (Fig. 3.2.85) and treatment parallel those of PNET, with an even poorer prognosis.

3.2.9.2.1.8 Meningiomas
Meningiomas are predominantly observed in adulthood; nevertheless, they can also be found in children, constituting 1–3% of intracranial tumors in this age group, and 1–2% of all meningiomas. No gender predominance is observed in children, in contrast to adults in whom a clear female predominance is well-established. About 40% are associated with neurofibromatosis types 1 and 2 (often multiple in this case). About one-third of childhood meningiomas are purely intraparenchymal or intraventricular; they are mostly supratentorial (>80%) and about 20% intraventricular (see below); and they are frequently cystic. Giant forms are observed in >40%. Up to 40% of pediatric meningiomas disclose malignant features (hemangioepithelioma, papillary meningioma). The peak of incidence in this case is about 3 years (compared with 11 years for classical forms), and they are more frequent in females. Some radiological aspects (hyperostosis, “dural tail”) are quite rare.

Fig. 3.2.85a,b Axial a T2-weighted and b FLAIR coronal images of a huge ATRT. Note the heterogeneous signal characteristics of the lesion.
The treatment of choice is total resection, which is feasible in most cases (>80%); subtotal or partial resection will suffice in tumors involving the skull base. In these cases as well as in malignant forms postoperative radiotherapy is required. Recurrences after total resection are reported in 10–20% of cases, 70–80% after partial removal.

3.2.9.2.1.9 Teratomas
Teratomas are among the most frequently diagnosed hemispheric tumors in neonates and infants, as well as in the prenatal period (about one-third). Over 50% are found in the pineal region, while the remainder are suprasellar or intraventricular. They are usually large when they are first identified by ultrasound (US) or MRI. Histologically, they are composed of multiple tissues deriving from all (in 90%) or two of the three germ layers. The presence of cellular populations with embryonal features distinguishes the immature subtype.

3.2.9.2.1.9.1 Neuroimaging
The US appearance is that of a large cystic mass with heterogeneous echogenic characteristics, owing to the concomitant presence of calcified or cartilaginous components; increased vascularity with low-resistance flow may be demonstrated by color Doppler. Likewise, CT and MRI demonstrate a heterogeneous mass, with different signal characteristics (Fig. 3.2.86).

3.2.9.2.1.9.2 Management
Surgical resection is the treatment of choice and it is curative in the case of mature teratoma; however, particularly in neonates and infants, the huge tumor size, and the already stabilized compromise of the surrounding brain structures, can prevent the feasibility of such radical surgery, not to mention the elevated surgery-related mortality and morbidity. Immature teratomas and teratocarcinomas have a poor prognosis, even though adjuvant therapy is provided.

3.2.9.2.2 Intraventricular Tumors
Tumors located inside the lateral and third ventricles originate both from the anatomical structures located within the ventricles or in their walls. They grow prevalently within the ventricular cavities and often remain silent for a long time until they reach a huge size or cause hydrocephalus. Focal signs are remarkably rare, although seizures may occur; the clinical picture is dominated by symptoms and signs of increased ICP. Tumors arising from intraventricular structures mainly consist of choroid plexus tumors; those originating from the ventricular walls include all the tumors described in the above sections, mainly ependymomas and astrocytomas. Intraventricular ependymomas account for about 20% of supratentorial ependymomas, and share with them the same characteristics and management. A peculiar form is the subependymoma, an exceedingly rare, truly benign tumor (WHO grade I) with a mixed population of ependymal and astrocytic cells. It originates from either the ventricular walls or the septum pellucidum, and appears as a well-circumscribed nodule on the ventricular walls. MRI appearance is that of an isointense lesion on T1-weighted images, and is hyperintense on T2-weighted images.

Another intraventricular tumor with a similar location is the subependymal giant cell astrocytoma (SEGA), a benign lesion that is a manifestation of tuberous sclerosis, which is believed to derive from the neoplastic transformation of one of the subependymal nodules (typical of this neurocutaneous syndrome). Owing to their mostly intraventricular growth, they may remain asymptomatic for a long time, or indefinitely, unless they obstruct CSF flow and cause obstructive hydrocephalus. In this case tumor removal should be the first option rather than CSF shunting.

Neurocytoma, a benign tumor consisting of mature neurons, seemingly originates in the septum pellucidum or ventricular walls, and grows inside the ventricles.

Fig. 3.2.86 a Axial and b sagittal T1-weighted images of a congenital teratoma
Other possible, though rare, intraventricular tumors are the meningioma and the teratoma. Intraventricular meningioma originates from the arachnoid tissue in relation to the choroid plexus. Characteristic of, although not exclusive to, the pediatric age, they may reach a huge size before becoming symptomatic, as with other intraventricular tumors. Hydrocephalus is not frequent, whereas exclusion and consequent dilatation of the temporal horn of the lateral ventricle are possibilities.

3.2.9.2.2.1 Choroid Plexus Papilloma
Choroid plexus papilloma is a rare tumor accounting for less than 1% of brain tumors overall, but for 5% of those occurring in the pediatric age; its incidence is even higher (10%) when only infancy and early childhood are considered. From another point of view, 70–90% of these tumors occur in the first 2 years of life. They look like a lobulated, pink mass, varying in size from a small pedunculated lesion to a large one filling the ventricle completely. They are highly vascular, the arterial supply being contributed by the anterior and posterior choroidal arteries.

Histologically, they consist of mature, benign choroidal cells quite similar to that constitute the normal choroid plexus, albeit with a higher cellularity. Increased cellularity with lack of differentiation, increased mitoses, vascular proliferation, and necrosis identify the malignant form of the choroid plexus tumor (carcinoma).

Papillomas are typically associated with hydrocephalus that has a multiple pathogenesis. In fact, an overproduction of CSF (up to three to four times the normal amount produced by the choroid plexus) has been documented, but there is also the possibility of an obstruction to CSF flow (mainly for tumors located in the third and fourth ventricles), and a resorption defect, possibly related to asymptomatic hemorrhage from the tumor, which in turn may lead to increased CSF protein content and fibrosis of the arachnoid villi. The latter mechanism may account for the persistence of hydrocephalus after tumor removal.

3.2.9.2.2.1.1 Neuroimaging
On CT the tumor appears as a lobulated, hypodense lesion filling the ventricle, which enhances brightly and homogeneously. MRI gives similar information and may document directly the rich vascular supply to the mass (Fig. 3.2.87). This aspect may be further investigated by means of MR angiography.

3.2.9.2.2.1.2 Management
Gross total resection is the mainstay of treatment, which may ensure definitive cure. The concomitant hydrocephalus may be treated before, concomitantly or after craniotomy; in the former instance, ventricular dilatation may facilitate the surgical approach to the lesion.

The main advantage of preoperative shunting is that, while relieving the increased ICP, it allows an increase in the thickness of the cortical mantle, thus reducing the risk of post-craniotomy collapse. A possible complication of CSF shunting in this situation is the occurrence of ascites. This complication, peculiar to this particular tumor, may be explained on the basis of the increased protein content of the CSF (and consequently abdominal fluid), which is responsible for the reduced resorptive ability of the peritoneal membrane.

The most relevant complications in choroid tumor surgery are intraoperative bleeding and brain collapse. Even a discrete hemorrhage can become life-threatening, when considering the limited blood volume of infants

Fig. 3.2.87a–c Axial a T1-weighted and b T2-weighted images, and coronal CE c T2-weighted images of a huge choroid plexus papilloma of the lateral ventricle with associated hydrocephalus. Note the typical signal characteristics of the lesion and the bright enhancement after Gadolinium administration
and young children. To prevent such a complication the arterial supply should be identified and divided prior to proceeding to tumor removal (possibly en bloc). To prevent persistent ventriculo-subarachnoid fistulae and brain collapse, the cortical incision may be obliterated with fibrin glue, after filling the ventricular chamber with saline. Another possibility is a temporary external drainage maintained for 5–7 days after the operation.

Complete surgical resection is curative for papillomas, although local recurrences have been rarely described. Carcinoma is more difficult to resect because of its infiltrative behavior and increased vascularity. Nevertheless, in this case, too, the aim of surgery should be gross total resection. Radiation and chemotherapy are indicated in the case of incomplete removals, with the well-known limitations related to the patient’s age. In the case of prenatal hydrocephalus the prognosis may be poor, in spite of successful surgical removal of the tumor.

### 3.2.9.2.3 Tumors of the Suprasellar Region

Two main tumors, the craniopharyngioma and the optic pathway/hypothalamic glioma, encompass the field of suprasellar region neoplasms diagnosed in the pediatric age. Their peculiar location accounts for the clinical symptomatology that translates into damage to the optic pathway and the hypothalamic–pituitary axis. Compression of the third ventricle and of the foramina of Monro justifies the associated obstructive hydrocephalus that frequently accompanies these lesions.

#### 3.2.9.2.3.1 Craniopharyngioma

Craniopharyngioma is dealt with in Sect. 3.2.5.5; however, some of the characteristics peculiar to the pediatric age must be underlined. First of all, as many as 30–40% of craniopharyngiomas occur in children or adolescents less than 18 years of age, and consequently a large number of these tumors are treated in a pediatric neurosurgical environment. Pediatric craniopharyngiomas are usually of large or huge size, with abundant calcification (90%) (Fig. 3.2.88a). Of the two histological variants, the adamantinous is prevalent in children, whereas the papillary is practically non-existent. Concerning the traditional surgical classification, the retrochiasmatic variant is more frequent, and accordingly hydrocephalus is much more frequently observed than in the adult population. Clinical manifestations include increased intracranial pressure in more than 50% of cases, related to both the huge tumor size and the concomitant hydrocephalus. Likewise, endocrine dysfunction is very frequently observed, short stature and growth retardation being the most common complaints. Ocular signs are less common (also considering the difficulty in demonstrating such dysfunction in young patients).

#### 3.2.9.2.3.1.1 Management

Traditionally, radical surgery is the preferred treatment for this benign tumor, with the goal of curing the patient and avoiding tumor recurrence. However, the close relationship of the tumor with vital surrounding structures makes this goal only partially achievable.

In many cases, operative morbidity, especially concerning the endocrinological function, is high following an aggressive surgical approach. Indeed, while long-term follow-up is good in terms of survival, the endocrinological sequelae, as well as postoperative neurological and behavioral changes relating to hypothalamic insult, can limit significantly the quality of life of these long-term survivors of radical (“successful”) craniopharyngioma surgery. Nevertheless, in most surgical series the judgment of a successful surgery is expressed only in terms of percentage of radical resection and recurrence rate. This evaluation may be very limited when dealing with children, as the life-long necessity of hormone replacement, pathologic obesity, and the detrimental effect on the intellect are major limiting factors for acceptable quality of life. Furthermore, total resection is not devoid of the risk of tumor recurrence. Recurrence is treated mainly by repeated surgery and with radiotherapy. Intracavitary radiotherapeutic agents, bleomycin, and more recently, in-

![Fig. 3.2.88](image-url) a Sagittal T1-weighted image of a huge craniopharyngioma and b sagittal T1-weighted CE image of a midline pilocytic astrocytoma
terferon alpha, seem to assure a definitive cure or tumor stabilization in purely cystic forms.

In order to avoid the hypothalamic compromise, an increasing number of pediatric neurosurgeons are presently in favor of a less invasive surgical attitude for those craniopharyngiomas that, on preoperative MRI, clearly involve the hypothalamic structures; this means renouncing detaching the tumor capsule from the hypothalamus, and relying on radiotherapy for the treatment of possible regrowth.

3.2.9.2.3.2 Optic Pathway/Hypothalamic Gliomas

Optic pathway/hypothalamic gliomas are considered together because of the peculiar anatomy of the chiasmatic region and the consequent reciprocal involvement of the two structures in tumors in this area. They are the most frequent suprasellar tumors in the pediatric age. In most pediatric series they make up approximately 10% of supratentorial tumors. Age distribution is peculiar, as 80–90% of these neoplasms are diagnosed in the pediatric age, with a peak incidence at 2–4 years for hypothalamic tumors, and slightly higher for optic nerve involvement.

Histologically, they are mainly pilocytic astrocytomas, although fibrillary astrocytomas are observed on some occasions (Fig. 3.2.88b). A peculiar aspect of these astrocytomas is their variable biological behavior. In fact, they can remain static and stable for years; they can shrink and eventually disappear, spontaneously or after biopsy; or they can behave as aggressive tumors with rapid increases in size and metastatic seeding, despite their histological benignity. Optic pathway gliomas may be a manifestation of neurofibromatosis type 1 (NF-1) in 15–20% of cases. The presence of NF-1 seems to confer a protective effect with regard to tumor progression.

Clinical manifestations include visual acuity and visual field defects. A peculiar manifestation of the hypothalamic involvement, observed only in infants or children less than 3 years of age, is the so-called hypothalamic cachexia (Russell’s syndrome), which can be present in up to 25% of cases. It is characterized by marked emaciation and loss of the subcutaneous fat, contrasting with normal height and almost normal muscle mass.

3.2.9.2.3.2.1 Management

Therapeutic options vary according to tumor location. Optic nerve gliomas involving only one nerve and with limited impairment of visual function are monitored by means of serial ophthalmologic evaluations and MRI. In the case of loss of visual acuity or growing intraorbital tumors (especially when responsible for marked exophthal- mos), surgical excision is indicated, with the aim of preventing tumor spread to the opposite optic nerve and for cosmetic purposes. In the case of tumors located in the chiasm or hypothalamus, surgical debulking of the exophytic portion and removal of the cystic components are indicated to reduce the mass effect (more radical removal in the case of severely impaired vision or amaurosis). Radiation therapy is more and more rarely utilized as an adjuvant treatment. On the contrary, single or multiagent chemotherapy (carboplatin and vincristine) represents a promising approach in the treatment of these tumors; although no definitive remission is obtained, the reduced growth rate may be considered a useful result. Nowadays, chemotherapy is regarded as the first-line treatment for these tumors.

Selected Reading


3.2.9.3 Congenital and Infantile Brain Tumors

GIANPIERO TAMBURRINI, CONCEZIO DI ROCCO

3.2.9.3.1 Definition

There is no definite agreement on the definition of congenital and infantile brain tumors. Solitare and Krigman [5] considered three distinct categories:

• “Definite congenital tumors,” presenting or producing symptoms at birth
• “Probable congenital tumors,” presenting or producing symptoms within the first week of life
• “Possible congenital tumors,” presenting or producing symptoms during the first months of life.

Advances in prenatal and neonatal diagnosis have led to an extension of this original classification. Jellinger and Sunder Plassman [4] consider as “definite congenital tumors” those producing symptoms within the first 2 weeks of life, tumors first seen within the first year of life as “probably congenital,” and tumors seen in infants beyond
1 year of age as “possibly congenital.” Some authors, however, still refer to the Collins law stating that all intracranial tumors diagnosed up to the 9th month of life should be included in the category of congenital brain tumors, while other authors have put this cut-off age at 18 months [1]. A further problem lies in the different biological behavior of some tumors. For example, medulloblastomas, teratomas, hamartomas, and craniopharyngiomas are known to be of congenital origin, but rarely manifest at an early age, suggesting that some pediatric neoplasms might be congenital in origin despite clinical manifestations occurring later than in infancy [2, 3].

3.2.9.3.2 Epidemiology
The incidence of infantile brain neoplastic lesions has significantly changed in the last 15 years thanks to advances in neuroimaging techniques. Their overall occurrence rate is actually reported to be up to 3.6 per 100,000 newborns, accounting for 0.04 to 0.18% of deaths in children under 1 year of age [4]. In the Cooperative survey study of the International Society for Pediatric Neurosurgery in 1991 [1] it was confirmed that 15% of all pediatric brain tumors are diagnosed in infants. No significant differences were found among different geographic areas. The sex incidence was nearly equal, with a slight male predominance (males 54.2%; females 45.8%), and again, there were no significant differences among the different geographic areas. Two peaks of age were recorded, one under 1 month of age (13.9%) and the second toward the end of the first year.

3.2.9.3.3 Etiological and Molecular Biology Considerations
The regional prevalence of some histological types reported in different retrospective studies has led to racial and/or environmental effects to be considered in the pathogenesis of intracranial tumors in infants. A higher incidence of brain tumors in infancy has also been described among family members and siblings with cerebral neoplasms or other diseases of the nervous system, various associated congenital anomalies, birth defects, genetic factors and malformative factors (in 15% of cases), maternal exposure to ionizing radiation and toxic substances, and other kinds of cancer, have been reported in many series [4]. However, epidemiological investigations on large series have not always led to conclusive remarks. Since the early 1990s, a number of genes alterations have been individuated, most of which concern malignant tumors in which a more stable representation of genetic alterations has been reported (Table 3.2.16).

Data available for benign tumors are more uncertain; the most relevant are summarized in Table 3.2.17.

Similar to brain tumors of older children and adults most of the actual basic research on intracranial tumors of infancy has been directed toward the differentiation of tumor stem cells from their lineage-differentiated forms.

<table>
<thead>
<tr>
<th>Genetic and/or protein alterations</th>
<th>Detected rate</th>
<th>Clinical association</th>
</tr>
</thead>
<tbody>
<tr>
<td>TrkC</td>
<td>48% of MB cases</td>
<td>Low expression → unfavorable outcome</td>
</tr>
<tr>
<td>erbB-2 (HER2)</td>
<td>84% of MB cases</td>
<td>High expression → unfavorable outcome</td>
</tr>
<tr>
<td>MYCC</td>
<td>42% of MB/PNET cases</td>
<td>Mutation → development of sporadic and nonsporadic desmoplastic MB</td>
</tr>
<tr>
<td>PTCH</td>
<td>8–10% of MB cases</td>
<td>Deletion → unknown significance; putative tumor suppressor gene locus</td>
</tr>
<tr>
<td>17p</td>
<td>35–50% of MB cases</td>
<td>Expression of trilateral retinoblastoma</td>
</tr>
<tr>
<td>Beta-tubulin class III expression</td>
<td>15–20% of MB cases</td>
<td>MB differentiation in neuronal cells: indicator of lower aggressiveness</td>
</tr>
<tr>
<td>13q14 deletion</td>
<td>93% of pinealoblastoma</td>
<td>Altered expression of SWI/SNF protein (oncosuppressor protein)</td>
</tr>
<tr>
<td>22q11 deletion (hSNF5/INI1 gene); 22 monosomy</td>
<td>85% of AT/RTs</td>
<td>Putative tumor suppressor gene locus</td>
</tr>
<tr>
<td>9p deletion</td>
<td>40% of malignant gliomas</td>
<td>Hyperdiploid state indicative of tumor aggressiveness</td>
</tr>
<tr>
<td>17q deletion</td>
<td>60% of PNETs</td>
<td>Hyperdiploid state indicative of tumor aggressiveness</td>
</tr>
<tr>
<td>+7, +12, and +20 (hyperdiploid chromosomes)</td>
<td>30–40% of choroid plexus carcinomas</td>
<td>Hyperdiploid state indicative of tumor aggressiveness</td>
</tr>
</tbody>
</table>
3.2.9.3.4 Anatomical Distribution

In contrast to what occurs in older children, congenital and infantile brain tumors have a significant predilection for the supratentorial compartment compared with the infratentorial space. In the Cooperative survey of the ISPN, published in 1991, supratentorial tumors accounted for 65.4% of the 840 collected cases and infratentorial tumors for 29.6% [1]. This kind of anatomical distribution has been confirmed by subsequent series. In the 20-year review of series of pediatric CNS tumors, Rickert et al. reported a supratentorial/infratentorial ratio varying from 1.5 to 9.0, with the exception of two series in which an almost equal distribution between the supratentorial and the infratentorial compartment was found [4]. A predominance for midline and ventricular/periventricular tumors has been reported in most series; among hemispheric locations the frontal lobe appears to be more frequently affected. No definitive explanation of the prevalent location of congenital and infantile brain tumors along midline and ventricular structures has been found. One of the possibilities that has been claimed is their proximity to secondary germinal areas, where substantial cell proliferation occurs in the first 6 months of extrauterine life; the neoplastic transformation interestingly proliferating primitive cell populations Physiologically would also explain the frequent finding of mixed populations and immature/aggressive tumors in this subset of patients. Another feature of brain tumors in infants, if compared with those occurring in older children, is their higher tendency to occupy more than one intracranial compartment. Their frequent origin from multiple cell lineages and the big tumor size often present at diagnosis may help to explain this finding.

3.2.9.3.5 Clinical Presentation

Advances in prenatal neuroimaging techniques (ultrasonography, MRI) have led to a significant improvement in the prenatal diagnosis of congenital intracranial tumors. Maternal and fetal signs that are considered important in this context are large-for-gestational-age uterus, polyhydramnios, rapidly evolving hydrocephalus, and hydrops [3]. A typical clinical presentation in neonates is stillbirth. In his review of perinatal brain tumors, Isaacs [4] reported that 21 of the 250 cases (21%) were stillborn. In infants clinical manifestations may be delayed; indeed the head enlargement and the plasticity of the developing brain often allow tumor growth without producing significant neurological changes [3, 4]. In the Cooperative Survey of the International Society for Pediatric Neurosurgery [1], the most common clinical findings that first lead to diagnosis of an intracranial tumor in the first year of life were signs of intracranial hypertension (41%) and seizures (12%).

Macrocrania (64–82%) and vomiting (39.2–56%) were the most frequent symptoms found by Rickert et al. [4] in their review of the literature up to 1997. Associated congenital anomalies are most often located in the head, with cleft, lip or palate being most frequently involved [3, 4]. A review of neonatal brain tumors by Wakai et al. [5] revealed that of 230 cases, 23 (11.5%) had associated congenital malformations. As in older patients more malignant tumors usually have a shorter duration of symptoms and might be more frequently associated with an acute clinical onset. In this context the incidence of hemorrhages from malignant tumors at diagnosis has been reported to be as high as 14–18%, which is much higher than the rate otherwise seen in children and adults [2, 4]. The rapid tumor growth has been claimed to contribute to this rate, as has the presence of isoforms of vascular endothelial growth factors.
3.2.9.3.6 Histological Types

Histological types of congenital and infantile brain tumors are significantly different from those found in the older child and adolescent. A further distinction should be made between tumors presenting at birth or in the first weeks of life and those diagnosed between the first month and the first year of age. Teratomas constitute between one-third and one-half of tumors diagnosed prenatally or in the first month of life. Their incidence progressively decreases when considering older patients [2, 3]. In the series by Wakai et al. [5] teratomas represented 54.4% of tumors diagnosed at birth or in the first week of life, but only 28.8% of all the tumors diagnosed between 1 month and 1 year of age (Fig. 3.2.89). The second most common perinatal brain tumors are neuroepithelial tumors, which have been reported to have an incidence between 37.4% and 42.5%, most of them being astrocytomas (13–16%) and medulloblastomas (7–8%) [2, 3]. Choroid plexus papillomas (6–7%) and craniopharyngiomas (5–6%) are relatively frequent, while mesenchymal tumors are rare, the whole group constituting about 5% of all intracranial tumors in this age group [2, 3]. On the other hand, when dealing with brain tumors diagnosed between 1 month and 1 year of age the most common histological types are neuroepithelial tumors. In the Cooperative Survey of the International Society for Pediatric Neurosurgery [1], astrocytomas (28.6%), ependymomas (11.4%; Fig. 3.2.90), medulloblastomas (11.5%), and choroid plexus papillomas (10.6%) (Fig. 3.2.91) were by far the most common oncologic types. Teratomas represented 5% and primitive neuroectodermal tumors 6.2%. Craniopharyngiomas

Fig. 3.2.89  a Sagittal, b axial, and c coronal T1 MRI sequences after gadolinium injection of a 20-day-old baby with an immature intracranial teratoma. Anatomical structures of the anterior cranial fossa are almost completely replaced by the tumor; thus, the exact site of initial tumor growth cannot be determined

Fig. 3.2.90  a Sagittal, b axial, and c coronal T1-weighted MRI sequences after gadolinium injection of a 3-month-old baby with an anaplastic ependymoma. The tumor has a multicystic appearance and extensive intraventricular growth
were extremely rare (0.4%). Similar results have been reported by other authors in more recent related papers, the whole group of neuroepithelial tumors rating between 63 and 80% of the reported cases [3, 4].

3.2.9.3.7 Treatment
Surgery is the main step in the treatment of neonatal and infantile brain tumors. The extent of tumor removal is directly related to the patient’s outcome. However, radical resections are conditioned by a frequently undefined and/or eloquent area tumor location and by their frequent multicompartmental extension [2–4]. This is particularly true for teratomas: anatomic landmarks cannot be determined in up to one-half of the cases and sites like the hypothalamus, the pineal or the suprasellar region are often involved [2, 3]. The difficulty in achieving a radical tumor resection is confirmed by data from the literature. Of the 886 cases of the International Society for Pediatric Neurosurgery survey [1] only 389 (43.9%) underwent total tumor removal. In 290 cases (32.7%) partial tumor removal could be achieved, while in 85 cases (9.5%) only a biopsy was carried out. Similar results have been reported by other authors quoting overall rates of total tumor resection between 27 and 58%, subtotal/partial resection between 17 and 46%, and biopsy between 5 and 20% [4, 5].

Radiotherapy is not advised at this early age, because of its long-term cognitive and endocrinological sequelae. Cognitive decline is progressive over at least a decade. The most common radiation-induced endocrinopathies are hypothyroidism and growth hormone deficiency. Treatment effects on growth are multifactorial and include growth hormone deficiency, spinal shortening, precocious puberty, undetected hypothyroidism, and poor nutrition. Fifty to 80% of children treated with craniospinal radiation for brain tumors will experience growth failure.

On the contrary, preoperative and/or postoperative conventional chemotherapy has been used in adjunct to surgery in most series, particularly those dealing with more aggressive histologies or infiltrating lesions; in specific histological subtypes (i.e., medulloblastomas and ependymomas) its role is considered particularly important in delaying radiotherapy, although the influence of conventional chemotherapy on patients’ outcome has still not been completely clarified and improvement in survival rates has been reported. Chemotherapy has also been suggested as preoperative treatment in infants whose general condition is too grave for a major surgical procedure. A reduction of up to one-third of the tumor’s original size has been reported. Operative findings suggest that the main action of chemotherapeutic agents in this context may be on tumor vascularization, with the induction of fibrotic changes.

3.2.9.3.8 Prognosis
The patient-dependent factors that appear to be mostly related to survival rates are:
- Age at diagnosis
- General condition at diagnosis
- Histological type of the tumor

The role of patient age and general conditions at diagnosis has been underlined by Wakai et al. [5]; in this paper the overall survival rate among 200 infants reviewed from the literature was 7% if the tumor was diagnosed at birth, and 25.6% if the tumor was diagnosed between the first
week and the first 2 months of life. Histology also resulted in an important clue.

Table 3.2.18 summarizes the mean survival rates of congenital and infantile brain tumors compared with the most frequent histological types.

Some comments should be added in order to better understand the results cited above:

- The fair prognosis of infantile intracranial teratomas can be attributed to the presence in the majority of these patients of advanced disease at the time of diagnosis with multicompartmental tumor location and involvement of eloquent areas [2, 3].
- The wide range of survival rates reported for infants with medulloblastoma is influenced by patients’ selection criteria in the different series and time of patients’ data collection. In fact, advances in surgical techniques have led to a significant improvement in the extent of tumor removal in recent years, a factor that has been related to an improvement in survival rates; new chemotherapeutic regimens have also been claimed to contribute to more favorable results.
- The restriction for radiotherapy before the third year of life contributes to the fair results obtained in infants with neoplastic lesions who are unresponsive to chemotherapeutic agents like ependymomas and malignant astrocytomas.

Concerning the quality of life, many authors have pointed out the high “price of survival” observed in infants with intracranial tumors; endocrinopathies have been reported in up to 70% of cases, and cognitive deficits have been described in 40–100% of long-term survivors. Again, the younger age and a more malignant histological type are significantly related to a worse outcome [2, 3]. Long-term in utero development of associated hydrocephalus contributes to a poor outcome independently of the histological type of the tumor.

Selected Reading


### 3.2.10.2 Mechanism of Action

Radiotherapy is the treatment of disease using ionising radiation. It is normally directed at malignant disease, but some benign conditions (e.g. pituitary macroadenomas) are also treated. Most radiotherapy for brain tumours is delivered using postoperative, external beam X-rays. A variety of other techniques is possible including intraoperative radiotherapy, particle radiotherapy and brachytherapy. The value of radiotherapy depends largely on the intrinsic radiosensitivity of the tumour. It may be curative (e.g. in medulloblastomas, germ cell tumours), or prolong survival (e.g. in gliomas). The ambition is to deliver a maximal or curative dose to the entire tumour, whilst minimising the normal tissue damage [1].

### Table 3.2.18 Mean survival rates in most frequent congenital and infantile brain tumors

<table>
<thead>
<tr>
<th>Histology</th>
<th>Mean survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratoma</td>
<td>7.2–12%</td>
</tr>
<tr>
<td>Benign astrocytoma</td>
<td>34–44.4%</td>
</tr>
<tr>
<td>Anaplastic astrocytoma and glioblastoma</td>
<td>2–14%</td>
</tr>
<tr>
<td>Primitive neuroectodermal tumors</td>
<td>5–12%</td>
</tr>
<tr>
<td>Choroid plexus papillomas</td>
<td>50–73%</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>8.8–23.5%</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>7–42.1%</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>3–9%</td>
</tr>
<tr>
<td>Ependymoblastoma</td>
<td>0–1%</td>
</tr>
<tr>
<td>Meningeal tumors</td>
<td>14–36%</td>
</tr>
</tbody>
</table>
response to radiation, the total dose is divided into smaller doses or “fractions”. In general, the more fractions delivered, the greater the differential one can achieve. Hence, radical treatments are given in 30 or more fractions, whilst palliative treatments comprise far fewer.

### 3.2.10.3 Standard Basic Equipment

Central nervous system (CNS) irradiation should be performed on a linear accelerator of energy 4–6 MV. It should have the capability for beam conformation and intensity modulated radiotherapy (IMRT). There should be access to modern radiotherapy planning facilities based on CT, with image fusion and a simulator for palliative work and beam verification.

Most radiotherapy is given at a rate of one fraction of 1.8–2.0 Gy per day, 5 days a week. For rapidly growing tumours there is a theoretical advantage to giving more than one fraction per day (accelerated radiotherapy). Also, by giving radiotherapy at low doses per fraction, a higher total dose can be given to normal tissue (hyperfractionated radiotherapy) with a better effect on the tumour. This may be effective in some paediatric tumours. In adult tumours neither accelerated nor hyperfractionated radiotherapy has been shown to be of greater benefit [4, 5].

### 3.2.10.4 Recent Developments

#### 3.2.10.4.1 Conformal Radiotherapy

Conformal radiotherapy means shaping each of the treatment beams to fit the tumour outline. This can be achieved using a (micro) multi-leaf collimator or cast lead blocks [6, 7].

#### 3.2.10.4.2 Beam Intensity Modulated Radiotherapy

Conventionally, the radiation dose intensity across any treatment beam is uniform. By using multiple beams with non-uniform (intensity modulated) profiles it is possible to create uniform doses in highly complex (even concave) volumes. This has advantages when working close to sensitive or vital structures [8–10] or when non-uniform dose distributions are desired, so-called dose painting [11].

#### 3.2.10.4.3 Stereotactic Radiosurgery/Radiotherapy

Stereotaxy in radiotherapy means localising a lesion with respect to an external co-ordinate system. With adequate patient fixation, stereotactic radiation can be delivered with an accuracy of better than 1 mm. Using this system to eliminate vital structures from the beam, ablative doses of radiation can be given at a single application. Stereotactic Radiosurgery (SRS). Stereotactic Radiotherapy (SRT) uses the same method of localisation applied to conventionally fractionated radiotherapy [7, 12].

#### 3.2.10.4.4 Radiation Sensitisers

A variety of agents, which theoretically should sensitise tumour tissue to radiation, have been tried in the CNS. These include sensitisers at a subcellular level such as IUdR and hypoxic cell sensitisers such as misonidazole. None has been effective [13].

### 3.2.10.5 Standard Approaches to Radiotherapy

#### 3.2.10.5.1 High-Grade Glioma

Radiotherapy prolongs survival for patients with newly diagnosed high-grade glioma (HGG), e.g. [14]. Prognostic factors, including age, performance status, precise histology and to a lesser extent tumour size and resectability, operate in these patients, allowing their treatment to be optimised [15]. Patients who are most likely to benefit should be selected for maximal treatment, whilst those with a poor outlook can be given short courses of radiotherapy or none at all.

Treatment should be delivered promptly after surgery. High-dose radiation is localised to the enhancing region or the resection rim plus approximately 2 cm. Irradiating large volumes of brain unnecessarily, and whole brain radiotherapy, is no longer acceptable. Tumour resection may improve tolerance to radiation and reduce the need for steroids, which are frequently given during radiotherapy.

The maximal standard treatment is 56–66 Gy in 5–7 weeks. There is no evidence that increasing the intensity of treatment by using interstitial radiotherapy (iodine seeds) or stereotactic radiosurgery, or by using alternative fractionation schemes improves outcome [4].

Patients with poorer prognosis may be offered short course radiation (e.g. 30 Gy in six fractions)

It has been established that temozolomide given during and after radiation, improves survival in patients with glioblastoma [16]. In that study the 2-year survival was improved from 10 to 26% with improved “time to progression” and no detriment to quality of life. Patients with good performance status who had undergone tumour resection benefited most. This concomitant/adjuvant regime is now accepted as the standard of care for patients with glioblastoma in many countries.

#### 3.2.10.5.2 Low-Grade Astrocytoma

It is a matter of common experience that radiotherapy can induce regression of low-grade gliomas and improve symptoms. However, the role of radiation is less clear than
in HGG. Large-scale trials of the EORTC and RTOG have established that radiotherapy, given at the time of the first diagnosis, does not improve survival, but does delay the time to tumour progression [17]. Intermediate dose treatment (45Gy) is as effective as higher doses (60 Gy) [18, 19]. Furthermore, risk factors have been shown to predict those patients who might benefit from early treatment [20].

Patients with good prognostic indicators (age < 50, tumours < 6 cm, not involving the midline, with a good performance status) may be kept under surveillance following initial diagnosis. When radiation is required, the irradiated volume should include the entire T2-weighted abnormality plus a 1- to 2-cm margin. Image fusion should be used to optimise target identification and CT planned, non-coplanar conformed fields should be used to optimise tumour coverage. The total radiation dose should be no more than 54 Gy (typically 50 Gy) with no more than 1.8 Gy per fraction [17].

3.2.10.5.3 Tumours Associated with Widespread Metastatic Potential

Some tumours tend to spread via the CSF (e.g. PNETs, some germ cell tumours). For these, radiation to the whole neuraxis may be required. A uniform radiation dose must be delivered to the entire meningeal surface and its contents with boost doses to the sites of original primary disease and to any bulky metastatic deposits.

Patients should be planned using CT with compensators and customised shielding to reduce the risk of damage to vital structures and long-term complications. Typically, a parallel pair of fields irradiates the brain and upper cord with a matched single posterior field to the spine. In standard medulloblastoma treatment without chemotherapy the whole neuraxis receives 30–35 Gy and the tumour is boosted to 55 Gy. Doses may be lowered when combined with chemotherapy. Refinements of treatment are the subjects of contemporary trials [21–23].

3.2.10.5.4 Radiotherapy for Benign Tumours

Some benign tumours benefit from radiotherapy (meningioma, pituitary adenoma, cranioopharyngioma). Long-term survival prospects are good so particular care must be taken with localisation and delivery using stereotaxy, conformality, IMRT and non-coplanar planning where appropriate. The minimum effective dose is delivered in fraction sizes less than 2 Gy. SRS may also be used in some situations.

3.2.10.5.5 Metastases

Radiation is established in the management of brain metastases from systemic cancer, but is probably overused. Patient selection should be based on an accepted classification scheme [24]. Patients with multiple metastases and poor performance status (RPA 3) probably gain no benefit from treatment. Younger patients with better PS (RPA 2) should receive short-course radiation (20 Gy in five fractions in 1 week).

Patients with solitary (or few) brain metastases, particularly if they have controlled systemic disease (RPA 1) should be considered for a radical approach to their intracranial disease. Surgery and stereotactic radiosurgery (SRS) to the index lesion appear to produce the same level of control for small tumours. The addition of whole brain radiotherapy reduces relapse within the brain [25] and may be beneficial [26–28].

3.2.10.6 The Late Consequences of Radiation Therapy to the Brain

Healthy brain adjacent to a tumour that is unavoidably irradiated is at risk of damage. The most important changes occur late after the delivery of radiation (6 months to 10 years) and comprise white matter change, vascular damage, neuronal fallout, gliosis and calcification. Clinical manifestation may vary from minor cognitive deterioration to gross neurological deficit. The risks following carefully delivered and scheduled radiation have probably been overstated. In patients with low-grade glioma the late consequences may be modest in patients with no pre-irradiation deficit [29]. In patients with abnormal baseline cognitive function there may be improvement following radiation therapy [30].

3.2.10.7 Clinical and Research Developments

3.2.10.7.1 Protons

Protons travelling in a medium deposit a large amount of energy in the final few millimetres of their path, known as the Bragg peak. This property can be used to deliver highly localised 3-D conformed dose distributions to tumours requiring high doses that lie immediately adjacent to vital structures. The most common applications in the CNS are chordomas of the clivus, and other skull base tumours. High-energy proton beams are expensive and the technique is available in very few centres [31].

3.2.10.7.2 Brachytherapy

Brachytherapy, usually using temporary, high activity $^{125}$I seed implants, has been used to treat high-grade gliomas at relapse or as a boost at first presentation. Mature results have not confirmed the value of brachytherapy [32–34]. Implants have also been used to treat low-grade gliomas and iridium wire afterloading has been used for palliation in glioblastoma.
3.2.10.7.3 Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT) relies on the capture interaction of very low-energy (thermal) or low-energy (epithermal) neutrons with the stable isotope Boron-10 ($^{10}$B). Capture causes the $^{10}$B to split, releasing α and lithium particles.

$$N + ^{10}B \rightarrow ^{4}\text{He} + ^{7}\text{Li}$$

Successful BNCT requires selective accumulation of $^{10}$B into brain tumours using boron labelled compounds such as $^{10}$B-BSA. Irradiation with low-energy neutrons releases short-range, high linear energy transfer (LET) particles in the vicinity of the tumour. The technique is under study in a few centres world-wide [35, 36].

3.2.10.8 The Future of Radiation Therapy in the CNS

Radiation therapy is a major treatment modality in the management of many intrinsic, particularly malignant, brain tumours. This will remain true for the foreseeable future. However, we are approaching a limit beyond which technical improvement in the delivery of radiation will have little additional benefit. Future improvement will result from our increasing understanding of the mechanisms of cell cycle control and its response to radiation insult.

Selected Reading

3.2.11 Chemotherapy for Brain Tumors

### General Guidelines

- Before treatment, hematological, renal, and hepatic function must be checked.
- Do not give chemotherapy in the presence of infection.
- For females: preclude pregnancy if of fertile age; for both males and females: advice on contraception. Consider semen preservation.
- The patient should be seen by a specialist with expertise on chemotherapy.
- For scoring of toxicities see the Common Terminology Criteria for Adverse Events, [http://ctep.cancer.gov/forms/CTCAEv3.pdf](http://ctep.cancer.gov/forms/CTCAEv3.pdf); Table 3.2.19 displays hematological toxicities.
- The dosage is determined using the body surface area (BSA). In patients with a calculated body surface area $> 2.1$, the BSA should be taken as 2.1.

#### Temozolomide

3.2.11.2.1 Treatment Schedule of Radiotherapy with Concomitant and Adjuvant Temozolomide for High-Grade Glioma (EORTC 26981 Schedule)

Treatment consists of two phases: concomitant radiotherapy and temozolomide chemotherapy, followed by six cycles of the classic regime of temozolomide chemotherapy days 1–5 every 4 weeks.

<table>
<thead>
<tr>
<th>Adverse event, unit</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>&lt;LLN-6.2</td>
<td>6.2–4.9</td>
<td>4.9–4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Leukocytes, $10^9$/L</td>
<td>&lt;LLN-3.0</td>
<td>3.0–2.0</td>
<td>2.0–1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>ANC, $10^9$/L</td>
<td>&lt;LLN-1.5</td>
<td>1.5–1.0</td>
<td>1.0–0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Lymphocytes, $10^9$/L</td>
<td>&lt;LLN-0.8</td>
<td>0.8–0.5</td>
<td>0.5–0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>CD4 count, /mm$^3$</td>
<td>&lt;LLN-500</td>
<td>500–200</td>
<td>200–50</td>
<td>50</td>
</tr>
<tr>
<td>Platelets, $10^9$/L</td>
<td>&lt;LLN-75</td>
<td>75–50</td>
<td>50–25</td>
<td>25</td>
</tr>
</tbody>
</table>

LLN: lower limit of normal
3.2 Brain Tumors

3.2.11.2.1 Temozolomide in the Concomitant Phase

Radiotherapy (RT) 60 Gy (30×2 Gy) combined with temozolomide (daily 75 mg/m²). Expected duration: 6 weeks; concomitant temozolomide should not exceed 7 weeks

- Administer temozolomide 1 h before each session of RT on weekdays. At weekends etc. without RT temozolomide is to be continued and to be taken in the morning.
- One hour before the first and second dose of temozolomide, anti-emetic prophylaxis with a 5-HT₃-antagonist (e.g., 8 mg ondansetron, 1 mg granisetron) is recommended. During the concomitant radiochemotherapy with low-dose daily TMZ, continuation of anti-emetic prophylaxis beyond the first 2 days is only occasionally necessary.
- Pneumocystis jiroveci pneumonia (PCP) prophylaxis (960 mg cotrimoxazole three times a week or pentamidine inhalations) is indicated especially in patients using steroids, either during the entire concomitant phase or if CD4 counts are <200/mm³. Prophylaxis should continue until patients have fully recovered from any lymphocytopenia (CTC grade ≤1).
- During the radiotherapy patients should be monitored for toxicity once a week.
  - Weekly: complete blood count (Hb, Ht, WBC, ANC, platelets, CD4 counts if used for decision on PCP prophylaxis)
  - At the end of week four and prior to the start of adjuvant treatment: serum chemistries (renal, hepatic function, serum electrolytes, glucose)
- Temozolomide delay and stopping rules in the concomitant phase (Table 3.2.20).

3.2.11.2.2 Temozolomide in the Adjuvant Phase for Newly Diagnosed Glioma

The start of the first cycle will be scheduled 28±3 days after the last day of radiotherapy. See the standard schedule of temozolomide on days 1–5 every 4 weeks for the dosing specifications.

3.2.11.2.3 Standard Temozolomide Chemotherapy for Recurrent Disease or Adjuvant Treatment

- Treatment is given according to the standard schedule of administration on days 1–5 every 4 weeks:
  - The starting dose for the first adjuvant cycle is 150 mg/m²/day on days 1–5, with a single dose escalation to 200 mg/m²/day on days 1–5 in subsequent cycles in the event of no significant toxicity in the first cycle (all CTC non-hematological toxicity Grade ≤2 (except for alopecia, nausea, and vomiting) and with platelets ≥100×10⁹/L and ANC ≥1.5×10⁹/L).
  - For treatment of recurrent disease:
    - In patients at the beginning of the next cycle who have undergone previous chemotherapy the starting dose for the first cycle will be 150 mg/m²/day on days 1–5, with a single dose escalation to 200 mg/m²/day in subsequent cycles in the event of no significant toxicity (see above).
    - Chemo-naive patients start on 200 mg/m²/day on temozolomide on days 1–5.
  - Three dose levels are used: 200 mg/m², 150 mg/m², and 100 mg/m² daily on temozolomide.
- Duration of treatment:
  - In newly diagnosed glioma after concomitant chemo-irradiation a maximum of six cycles of adjuvant treatment.
  - For recurrent disease until progression or 12 cycles.
- During standard days 1–5 temozolomide treatment anti-emetic prophylaxis with a 5-HT₃-antagonist is recommended as nausea and vomiting may be severe, especially on days 1 and 2. Because 5-HT₃-antagonist may induce constipation it is advised to give ondansetron (8 mg) or granisetron (1 mg) once or twice daily.

### Table 3.2.20 Temozolomide (TMZ) delay and stopping rules in the concomitant phase

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Value</th>
<th>CTCAE grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC</td>
<td>≥0.5 and &lt; 1.5×10⁹/L</td>
<td>2, 3</td>
<td>Delay TMZ until normalization</td>
</tr>
<tr>
<td>Platelets count</td>
<td>≥25 and &lt; 100×10⁹/L</td>
<td>1, 2, 3</td>
<td>Stop concomitant TMZ</td>
</tr>
<tr>
<td>CTC non-hematological toxicity (except for alopecia, nausea, and vomiting)</td>
<td>&lt; 0.5×10⁹/L</td>
<td>4</td>
<td>Stop concomitant TMZ</td>
</tr>
<tr>
<td>ANC</td>
<td>&lt; 0.5×10⁹/L</td>
<td>4</td>
<td>Stop concomitant TMZ</td>
</tr>
<tr>
<td>Platelets count</td>
<td>&lt; 25×10⁹/L</td>
<td>4</td>
<td>Stop concomitant TMZ</td>
</tr>
<tr>
<td>CTC non-hematological toxicity (except for nausea, vomiting)</td>
<td>&lt; 0.5×10⁹/L</td>
<td>3, 4</td>
<td>Stop concomitant TMZ</td>
</tr>
</tbody>
</table>
Lymphopenia is a side effect of all dose-dense regimens except for alopecia) have resolved to CTC grade ≤ 1.5 × 10^9/L and/or platelet count ≥ 100 × 10^9/L on day 29 (100 × 10^9/L on day 21 in the first cycle or after dose increase.

3.2.11.2.3 Alternative Temozolomide Chemotherapy Dosing Regimen

- Several other temozolomide regimens have been used that allow a more dose-dense temozolomide administration, by giving temozolomide on more days every 4 weeks. The most frequently used are:
  - One week on, 1 week off: alternately 1 week of daily temozolomide and 1 week of rest
    - Dose levels used: 100 mg/m² daily, 125 mg/m² daily, 150 mg/m² daily
    - Three weeks on, 1 week off: alternately 3 weeks of daily temozolomide followed by 1 week of rest
      - Dose levels used: 75 mg/m² daily, 100 mg/m² daily
- Nausea and vomiting is often less troublesome than with the standard dosing regimen, lower dosages of anti-emetics can be tried; preferably 5HT_3_ antagonists (domperidone or metoclopramide, if necessary ondansetron or a similar agent)
- Stop treatment in the case of grade 3 cardiototoxicity, grade 4 hematological toxicity or grade 3 non-hematological toxicity at the dosage of 100 mg/m² daily (500 mg/m² per cycle), or any non-hematological toxicity CTC grade 4 (except for alopecia) have resolved to CTC grade ≤ 1:
  - If not, delay the next cycle until resolved
  - If not resolved by 3 weeks, discontinue treatment

- Recommended duration of treatment in recurrent disease: up to 1 year

3.2.11.3 PCV Chemotherapy

- Each course of standard PCV chemotherapy consists of:
  - CCNU (lomustine), 110 mg/m² orally on day 1 with anti-emetics (domperidone or metoclopramide, if necessary ondansetron or a similar agent)
  - Procarbazine (Natulan), 60 mg/m² orally for 14 days on each cycle, on days 8–21
  - Vincristine, 1.4 mg/m² i.v. on days 8 and 29 of each cycle (maximum 2 mg)
- A full course of therapy will be repeated every 6 weeks (42 days), for a maximum of six cycles.
- The efficacy of vincristine has been questioned, and is left out of the schedule by many physicians.
- Toxicity consists mainly of cumulative myelosuppression, nausea, alopecia, fatigue, loss of appetite, liver disturbances, and polyneuropathy (vincristine).
  - Procarbazine may cause an allergic skin reaction.
  - The ingestion of tyramine-containing foods such as red wine, ripe cheese, and bananas during treatment with procarbazine may induce a hypertensive crisis (mono-amine oxidase effect), and patients should be warned not to use these products. Patients should also be warned for a disulfiram-like effect after the ingestion of alcohol (headache, flushes, and sweating).
- The nausea and vomiting caused by the PCV scheme is usually manageable with conventional anti-emetic treatment, i.e., domperidone or metoclopramide.
- Follow-up schedule:
  - Hematological parameters on days 1, 8, and 43 (= day 1 of the next cycles)
  - Serum chemistry before the start of each cycle
- Dosage modifications:
  - If the regimen is used after previous combined chemo-irradiation with temozolomide: decrease the dosage of CCNU and procarbazine by 25%
  - In the case of white blood cell count < 3.010^9/L or thrombocytes < 100 × 10^9/L at day 1:
    - CCNU will be delayed 1 week. In the case of persistent leukopenia < 3.0 × 10^9 or thrombocytopenia < 100 × 10^9 treatment will be delayed another week. If leukopenia or thrombocytopenia persist thereafter, discontinue chemotherapy.
  - In the case of a cycle having to be delayed for 2 weeks for toxicity, reduce the dosage of CCNU and procarbazine by 25%.
  - Reduce the dosage of CCNU and procarbazine by 25% in the case of grade III/IV leuko- or granulocytopenia, or in the case of grade III/IV thrombocytopenia.
3.2 Brain Tumors

– In the case of WBC < 3.0 \times 10^9/L or thrombocytes < 100 \times 10^9/L at day 8:
  - Both vincristine and procarbazine will be delayed for 1 week. In the case of persistent leukopenia < 3.0 \times 10^9 or thrombocytopenia < 100 \times 10^9 treatment will be delayed another week. If hematological abnormalities persist the patient comes off the treatment.
– Reduce the dosage of CCNU and procarbazine by 25% in the case of CTCAE (Common Toxicity Criteria for Adverse Events) vs 3 grade 2 or 3 non-hematological toxicity.
– Stop treatment in the case of:
  - CTCAE grade 3 cardiotoxicity
  - Grade 4 hematological toxicity or a CTCAE vs. 3 grade 3 non-hematological toxicity, despite dose reductions
  - Or any non-hematological toxicity CTCAE vs. 3 grade 4 (except for nausea and vomiting)
– In the case of an allergic skin reaction, procarbazine must be discontinued.
– Vincristine will be stopped in the case of a grade II neurotoxicity.
– Because of the cumulative myelosuppression of CCNU, continuation of treatment in the presence of marginal hematological abnormalities will result in more severe toxicity in subsequent cycles.
– As a rule, hepatic abnormalities improve slowly.

3.2.11.4 BCNU (Carmustine)

Sixty mg/m² on days 1–3 every 8 weeks:
– The most common regimen for BCNU (carmustine) is 130–200 mg/m² every 6 weeks, but an 8-week regimen at the dosage of 80 mg/m² given days 1–3 proved to be feasible in a phase II study including 40 patients with high-grade glioma. A study on GBM patients pretreated with temozolomide (combined chemo-irradiation) observed significant hematological toxicity at this dose level and reduced the dosage to 60 mg/m² on days 1–3 in 8-week cycles.
– Major side effects are hematological toxicity, long-lasting liver toxicity, nausea, and pulmonary toxicity.
– BCNU is administered intravenously on days 1 to 3 at the dosage of 60 mg/m²/day (dose per cycle 180 mg/m²) every 8 weeks. Prescribe anti-emetics (metoclopramide, domperidone).
– Contra-indications: a history of pulmonary disease that may affect pulmonary function, the patient should have their respiratory function evaluated by carbon monoxide diffusion capacity (DLCO), which must be more than 60% of the predicted value.
– Follow-up schedule:

3.2.12 Advantages and Limits of Adjuvant Treatments in Pediatric Brain Tumors

VITA RIDOLA, JACQUES GRILL

3.2.12.1 Epidemiology

Malignant brain tumors are the leading cause of cancer death among children and the second most common type of pediatric cancer after leukemia, comprising 20–25% of all childhood cancers.

Astrocytomas account for 52% of childhood brain tumors, medulloblastoma/embryonal tumors account for 21%, ependymomas for 10%, and other gliomas for 15%.
3.2.12 Advantages and Limits of Adjuvant Treatments in Pediatric Brain Tumors

3.2.12.2 Background

Gross total surgical removal alone is curative for low-grade tumors and it is the optimal condition required to obtain a cure in the case of high-grade tumors. Nevertheless, surgery alone is rarely curative in patients with histologically malignant lesions. Adjuvant treatments such as chemotherapy and/or radiotherapy are needed to improve disease control for medulloblastomas and ependymomas, high-grade gliomas, tumors in deep-seated midline structures, and for recurrent or metastatic disease. Despite advances in neurosurgery, oncology, and radiotherapy, pediatric brain tumors still pose considerable therapeutic challenges:

- Intrinsic tumor resistance to adjuvant therapies, including chemotherapy and radiotherapy.
- Inadequate drug delivery, given the presence of the blood–brain barrier.
- Considerable heterogeneity both between different histologies and within one tumor type (i.e., there are at least four different types of medulloblastoma).
- The benefit of potentially curative radiotherapy is offset by the significant and unacceptable long-term sequelae.

3.2.12.3 Adjuvant Treatment Options

3.2.12.3.1 Radiotherapy

For many childhood CNS tumors, radiotherapy plays an essential role. Frequently, these tumors cannot be completely cured with surgery because of their location or because of microscopic or macroscopic spread. Therefore, radiation therapy is frequently employed alone or as part of a multimodal treatment approach in combination with surgery and/or chemotherapy. Nonetheless, conventional radiotherapy is associated with worrying long-term side effects:

- Late neurocognitive sequelae and intellectual impairment
- Hearing loss
- Endocrinological deficits of hypothalamic–pituitary axis (i.e., growth hormone deficiency)
- Potential development of second malignancies

Potentially long-term intellectual sequelae are a major concern for patients treated with CNS irradiation. The main risk factors for cognitive damage in irradiated children are:

- Cranio-spinal irradiation (CSI): in cross-sectional comparative studies, less severe deficits in IQ have been shown in ependymoma patients irradiated on the posterior fossa alone than in medulloblastoma patients treated with cranio-spinal irradiation.
- Age: younger ages at the time of treatment are at a higher risk of IQ deficits with particularly devastating effects under the age of 3 years.
- Decline in IQ is progressive over time without reaching a "plateau," in longitudinal studies.
- Dose of cranio-spinal irradiation: IQ is significantly lower in children irradiated at a standard CSI dose of 35 Gy than in those irradiated at a reduced dose of 24 Gy.

In order to decrease the late effects of radiotherapy, conformal radiation therapy techniques have been developed to deliver the high radiation dose to the tumor target with very little dose to the adjacent normal tissue. Included in such techniques are three-dimensional conformal radiotherapy, radiosurgery, intensity-modulated radiotherapy, and proton irradiation.

3.2.12.3.2 Chemotherapy

In the last few decades chemotherapy has been introduced into the treatment of pediatric brain tumors with the aim of:

- Improving the prognosis
- Postponing or avoiding radiotherapy in very young children
- Decreasing the dose of cranio-spinal irradiation in MB/PNETs

The most effective drugs are: platinum compounds, nitro-surea, cyclophosphamide, topoisomerase inhibitors such as CPT-11 or etoposide, busulfan, thiotepe, and other alkylating agents such as temozolomide.

For chemosensitive tumors such as medulloblastoma and germ cell tumors, high-dose chemotherapy followed by autologous stem cell rescue has been used to achieve better survival rates in high-risk or relapsed patients, as well as to supplant CSI in very young children. High-dose chemotherapy regimens are frequently based on a combination of two or three drugs (thiotepa, melphalan, busulfan, carboplatin, etoposide, and cyclophosphamide). The use of a high systemic dose allows high concentration within the tumor, but leads to more severe toxicities. Myelosuppression is transient and is overcome by the use of stem cell rescue; however, other dose-limiting toxicities can occur, including those to the liver, lung, kidney, CNS, and cardiovascular system. Toxic deaths range from 5 to 10%, mainly due to infections, veno-occlusive disease, and multi-organ failure.

Although standard chemotherapy kills most dividing cells in a tumor, it is not effective against cancer stem cells that are naturally resistant through their quiescence, capacity for DNA repair, and resistance to apoptosis. Consequently, at least some of the tumor stem cells can survive chemotherapy and result in regrowth of the tumor.
Interactions can occur between antineoplastic agents and other drugs and can also be affected by the patient’s genetic polymorphism in metabolizing enzymes. Drugs interactions can modify the pharmacokinetics of chemotherapy agents and may significantly alter its efficacy or toxicity. For example, antiepileptic drugs and chemotherapeutics share common metabolic pathways via the hepatic cytochrome P450 isoenzymes (CYP). Phenytoin, carbamazepine, and phenobarbital are potent inducers of CYP that can cause a decrease in the serum concentration of chemotherapeutics, potentially compromising antitumor activity. Other agents, such as valproic acid, are enzyme inhibitors that can potentially increase the serum concentrations of anticancer drugs (e.g., cisplatin, nitrosourea). New antiepileptic drugs, such as gabapentin or levetiracetam, are not metabolized by CYP and do not interact with chemotherapy. Steroids may alter the blood–brain barrier and limit drug penetration, and some compounds, such as dexamethasone, can induce CYP and alter the pharmacokinetics of chemotherapy.

Significant limitations are associated with the use of standard radiographic measurements as indicators of response in chemotherapy trials on brain tumors. There is a need to standardize the methodology to assess and simplify objective tumor response to treatment. Actually, the response rates can be derived from 1D (greatest length; RECIST criteria), 2D (two-dimensional: product of the two longest perpendicular diameters; WHO criteria), or 3D (three-dimensional: product of the longest perpendicular diameters in one plane and the longest orthogonal diameter to that plane). More recently, several new classes of anticancer drugs have been explored in clinical trials. These new drugs often act through different molecular pathways and they do not induce massive cell kill like standard chemotherapeutics; evaluating their therapeutic effect should also take into consideration endpoints such as duration of response, 6-month progression-free survival (PFS), and quality of life.

### 3.2.12.4 Malignant Gliomas

High-grade gliomas (HGG; WHO grade III–IV) account for 15% of pediatric brain tumors, excluding brain stem tumors. They are characterized by histological features of glial origin, namely glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), and oligodendroglioma, with high malignancy and a generally poor prognosis, despite multimodal treatment. Overall survival at 5 years is at the best 40% in published series.

- The current therapeutic management includes maximal tumor resection, whenever possible, followed by radiation therapy. Because chemotherapy has shown some benefit, inclusion in chemotherapy trials is advised, especially in patients who could not be completely resected.
- Different from adult patients, gross total resection is of major importance for prognosis: PFS at 5 years is 35% in patients who undergo a complete resection (26% for GBM and 44% for AA) compared with 17% in patients with incomplete resection (4% for GBM and 22% for AA).
- Radiation therapy is recommended in children with HGG and who are over 3 years of age. The total dose of radiation to the tumor bed is up to 54–59.5 Gy with a 2-cm margin with conventional fractionation. Craniospinal radiation therapy is performed only for the rare patients with disseminated disease at diagnosis.
- Chemotherapy has shown a very limited benefit in the treatment of high-grade gliomas. In a randomized CCG study radiotherapy plus adjuvant CCNU/vincristine/prednisone results in a PFS at 5 years of 46% versus 18% in children treated with radiotherapy alone. High-dose chemotherapy, despite high acute toxicity, does not seem to improve the overall survival, with some exceptions for children with a minimal tumor burden at the time of treatment.
- Children younger than 3 years of age have been enrolled in prolonged chemotherapy regimens (Baby-POG; BabySFOP) with delayed radiotherapy. Five-year PFS and OS are 31–43% and 50–54% respectively. Cases of long-term survivors who did not receive radiotherapy are reported and overall survival is around 50% despite the avoidance of RT (no studies yet).
- Temozolomide has shown to be a promising agent against adult high-grade gliomas. Its low toxicity profile and good bioavailability after oral administration make it an interesting drug even if, at the moment, the results of pediatric studies are less encouraging than in adults.

#### 3.2.12.5 Low-Grade Gliomas

Low-grade gliomas (LGG; WHO grade I–II; Fig. 3.2.92) are a heterogeneous group of tumors in which most have prolonged indolent phases, whereas some tumors progress quickly, and others are associated with neurofibromatosis type 1 (NF1) and rarely progress after the first decade of life.

Primary surgery with gross total resection is the treatment of choice whenever possible (i.e., hemispheric, cerebellar, exophytic brain stem and spinal tumors). The extent of resection correlates with clinical evolution and PFS. In the case of recurrence, repeated attempts at total surgical removal can be performed before considering adjuvant therapy.

Non-surgical treatment is not indicated for tumors that have been completely removed.
For unresectable LGG (i.e., optic pathways; hypothalamus; thalamus; brain stem) chemotherapy and radiotherapy have to be considered, especially in cases of symptomatic, clinically or radiologically progressive lesions.

In the case of stable disease at the moment of diagnosis, for unresectable tumors, such as optic pathway gliomas occasionally ascertained in the initial staging of NF1, a “wait and see” policy with close follow-up is currently adopted.

In the setting of diffuse chiasmatic/hypothalamic tumors radiotherapy is effective for tumor control, with overall survival at 5 years reaching 90%. Doses allowing favorable outcomes are in the range of 45–56 Gy. Because of long-term radiation-induced side effects such as endocrinopathy, developmental abnormalities, neurocognitive impairment, and vasculopathy (there is a higher risk of “moya-moya” syndrome in NF1 patients who undergo RT), chemotherapy has been proposed to postpone or avoid radiotherapy, especially in young children. Actually, in patients less than 8 years of age first-line treatment is deemed to be chemotherapy, based on the “Packer regimen” with carboplatin/vincristine association for at least 1 year. Median radiotherapy-free intervals obtained by chemotherapy are between 22 and 35 months according to the different protocols. In a French study, 5-year radiotherapy-free survival was 61% employing a multidrug regimen. Progression-free survival at 5 years is in the range of 34–40% in different chemotherapy protocols. For children older than 8 years of age, radiotherapy at 50–54 Gy can be considered the first-line treatment, but chemotherapy may still be proposed when the radiation field is too large.

In NF1 patients leukemogenic chemotherapy (i.e., etoposide) and radiotherapy should be avoided as they have an accrued risk of leukemia and cerebral vasculopathy.

Leptomeningeal spread has been observed in 5 and 12% of cases at diagnosis or at progression respectively. It is an indication for treatment with chemotherapy or radiotherapy depending on the age of the patient. Multicentric disease can be more often associated with the pilomyxoid astrocytoma and the evolution of disease is extremely variable, with the potential for prolonged disease stabilization. Patients often require multiple lines of chemotherapy, possibly associated with repeated surgery.

### 3.2.12.6 Medulloblastoma/sPNETs

Medulloblastoma (WHO grade IV; Fig. 3.2.93) is a malignant, invasive primitive neuroectodermal tumor (PNET) arising in the cerebellum and it accounts for 16% of primary CNS tumors in childhood, with a peak incidence at 5 years of age. Most (80%) arise in the median part of the cerebellum and the remaining 20% in the cerebellar hemispheres. Leptomeningeal dissemination is present in one-third to one-half of patients at diagnosis.

At histopathology four main variants are recognized: classic MB; anaplastic/large cells MB, desmoplastic MB, and MB with extensive nodularity.

Correct staging for children with MB includes:
- Preoperative brain and spine MRI
- Early postoperative brain CT or MRI with and without contrast (in the first 72 h after surgery)
- CSF cytology through lumbar puncture at 15 days after surgery

![Diagram](image-url) 

**Fig. 3.2.92** Management of childhood low-grade gliomas (LGG)
Regarding risk stratification, patients are currently classified as:

- **Standard risk**: no metastases on cranio-spinal MRI + negative CSF cytology + absence of postsurgical residual disease on early postoperative CT/MRI and on surgical report. All these conditions are needed to be assigned to the standard risk group.
- **High risk**: postsurgical residual disease and/or metastatic disease on cranio-spinal MRI and/or CSF cytology.

Treatment protocols start with maximal surgical resection followed by adjuvant radiation and chemotherapy given the high radio- and chemo-sensitivity of MB and the ineluctable poor prognosis of children treated with neurosurgical resection alone.

Standard radiation therapy for MB is based on cranio-spinal irradiation (CSI) at 35 Gy with a boost to the posterior fossa, assuring a total dose to this area of 50–55 Gy and allowing a survival rate of about 50%. Randomized clinical trials have demonstrated an improved event-free survival (EFS) in patients with non-metastatic MB when chemotherapy is administered before radiotherapy compared with radiotherapy alone (EFS at 5 years: 74 vs 60% respectively).

In order to reduce the long-term neurocognitive sequelae associated with this amount of CSI, trials have been conducted to decrease the dose of CSI. Efforts to reduce CSI, without impairment of overall survival, have succeeded in standard risk patients only when a reduced dose of CSI has been coupled with adjuvant chemotherapy. The highest EFS ever published in standard risk MB patients has been reported by Packer et al. using vincristine during postoperative radiotherapy, with reduced CSI of 23.4 Gy, and the combination of vincristine, cisplatin, and CCNU for eight 6-week cycles after completion of radiotherapy (EFS at 5 years: 79%).

For high-risk patients, radiation treatment remains the essential component of therapy. Adjuvant chemotherapy adds a significant benefit in overall survival compared with radiotherapy alone. Nevertheless, in this setting of patients, the use of standard dose chemotherapy is not sufficient to allow the reduction of the cranio-spinal dosage under 35 Gy. Five-year EFS in metastatic patients ranges between 40 and 67% when full-dose cranio-spinal radiotherapy is administered with adjuvant chemotherapy. Treatment approaches currently under investigation in this poor prognosis subset of patients include the use of:

- Radiosensitizing agents such as carboplatin
- High-dose chemotherapy with peripheral blood stem cell rescue
- Hyperfractionated accelerated radiation therapy

Supratentorial PNETs (sPNETs) account for 3–5% of childhood brain tumors and behave much more aggressively than their infratentorial counterparts. Outcome seems to be improved in recent studies adopting multi-modality treatments after total resection. They are considered as high-risk PNETs and generally treated according to the same protocols of metastatic medulloblastomas. Non-metastatic PNETs of the pineal region seem to have a better prognosis than non-pineal sPNETs.

Treatment of very young children under 3–5 years of age with MB is still the greatest challenge for pediatric neuro-oncologists. Concerns about neurocognitive outcome, growth delay, and endocrinological deficits due to irradiation of the developing brain and cranio-spinal axis have led to the designing of treatment protocols based on chemotherapy in order to either delay or even avoid radiotherapy. The most common strategies have adopted:

- Conventional chemotherapy
- High-dose chemotherapy

---

**Fig. 3.2.93** Management of childhood medulloblastoma
The EFS of infants in these studies delaying or avoiding irradiation are inferior to those obtained in older children, especially in cases of incomplete resection or metastatic tumor. Nevertheless, 30–50% of the patients with a completely resected local tumor can be cured without irradiation. The overall survival rates in standard-risk MB could reach those observed in older children, despite the omission or reduction of radiotherapy.

Future prospective trials will evaluate histopathological characteristics and molecular markers (i.e., β-catenin, Trk-C, ErbB2, p53, c-Myc, OTIP-2) in order to allow better disease risk stratification and the identification of patients curable with less intensive therapy (such as desmoplastic MB) or, in contrast, with more aggressive treatment (such as anaplastic/large cells MB).

### 3.2.12.7 Ependymoma

Ependymomas (Fig. 3.2.94) occur in two thirds of cases in posterior fossa and one third of cases at the supratentorial level. Tumor grading is an important prognostic factor in some studies and is based on the distinction, according to the WHO classification, between differentiated (grade I–II WHO) ependymomas and anaplastic (grade III) ependymomas. To date, however, few groups use grading to stratify patient’s treatment. Seven per cent of children have leptomeningeal dissemination at diagnosis. In most cases tumor relapse occurs as a result of local failure.

The most effective treatment for localized ependymoma is gross total resection followed by focal radiation therapy (53–59.4 Gy). In children over 3 years of age this treatment strategy results in 50–65% PFS at 5 years. Cranio-spinal irradiation (36 Gy) is employed in patients with metastatic disease.

Chemotherapy at standard or high doses has not shown any increase in overall survival.

Phase II studies of single or combination drugs show the poor response of ependymomas to chemotherapy. In spite of this, chemotherapy has often been used in an adjuvant setting, especially:

- In infants < 3–5 years with the aim of avoiding or delaying radiotherapy. With prolonged adjuvant chemotherapy (French study: BBSFOP protocol), 40% of patients are alive and radiotherapy-free at 2 years and 23% at 4 years; OS at 4 years is 74% in patients with complete resection and 35% after incomplete resection. RT can be safely deferred in children with radiological gross total resection until the time of progression.
- A brief course of chemotherapy is given in patients with residual tumor after initial surgery in order to let children recover and plan the second surgery to achieve gross total resection.

A few retrospective institutional studies report sporadic cases of long-term survivors, cured by surgery alone without any adjuvant treatment. These data need to be confirmed in large prospective series. Observation could be proposed, inside a treatment protocol, for patients with supratentorial, low-grade ependymomas after microscopically complete resection.

There is a clear need for new markers defining relevant prognostic groups.
3.2 Brain Tumors

3.2.13 Novel Therapies

JAN JAKOB A. MOOIJ, MANFRED WESTPHAL

Disappointment with the failure of so-called standard therapies for glioblastoma multiforme (GBM) – including chemotherapy – has led to a series of new concepts that form the basis of new ways to attack brain tumours in general and the GBM in particular. These “novel therapies” share two main concepts: specific targeting and dedicated delivery [33]. Failure of surgery is primarily due to a lack of boundaries to brain tumours [8]; failure of radiation and drug therapy is due to the variable stages of genetic aberrations in the tumour cells [13], their heterogeneity [27] and the impossibility of adequate delivery of drugs thanks to the blood–brain barrier (BBB) and the inconsistency of tissue resistance to diffusion, enhanced by the primarily lipophilic basis of the brain structure.

3.2.13.1 Targeting and Delivery

The concept of targeting comprises a wide variation of therapeutic concepts based on specific properties of brain tumour cells that make them different from the surrounding tissue and also centred around the idea that drugs may be administered directly into the tumour, the resection cavity or the brain. Targeted therapy includes gene therapy- and gene technology-based approaches; therapies based on immunological properties and the immunological system in general; drug targeting using specific and tumour-unique membrane receptors, including the use of naturally occurring as well as artificial ligands and ligand-connected drugs; intracellular pathway interference, in particular, various membrane receptor-linked tyrosine–kinase pathways; interference with tumour-related angiogenesis; interference with the migration properties of tumour cells into the surrounding matrix, which are essential for their survival and proliferation [5, 11, 21].

Targeted delivery includes specific methods intended to overcome the problems of the classical oral, intravenous or intra-arterial drug delivery that is hampered by the BBB and other forms of resistance mentioned above. Techniques that have evolved and have been developed into clinically applicable use are local delivery by direct intraparenchymal injections of viruses at the time of surgery [14], vector-producing cells [25], or slow-release polymers with chemotherapeutic agents [20]. Also, polymer wafers with sustained slow-release properties for BCNU have been used for intracavitary placement [34]. Intracavitary delivery via a catheter connected to a subgaleal reservoir is another option used for radioimmuno-

therapy [9]. Most recently, direct interstitial application of a drug via slow infusion with catheters, which is called convection enhanced delivery (CED), is finding its way into clinical trials [17]. In the next few paragraphs examples will be given of novel therapies based on this specific targeting, the advanced delivery methods and often the combination of both technologies.

3.2.13.1.1 Gene Therapy- and Gene Technology-Based Therapies

In the context of brain tumours the concept of gene therapy is mostly based on strategies for transferring into tumour cells the so-called suicide genes – genes that force the cell to produce certain enzymes that could convert prodrugs into locally (intracellularly) killing substances. The most frequently explored approach has been the herpes simplex tyrosine kinase (HSTK) ganciclovir system. For transfection, retrovirus and adenovirus have been used. With the retrovirus system, worldwide multicentre trials (phases II and III) have been performed, but with unsatisfactory results [24]. Inefficient gene delivery leading to an insufficient transduction rate, with a technique of multiple depositions of vector-producing cells in the surrounding of the tumour cells, seems to have been the major cause of failure. Adenoviral vector transfection seems to be more efficient, but also more risky, and will be explored next [14].

Another method of gene therapy is the restoration of one or more of the genes that are deleted in the process of tumourigenesis. The most challenging candidate may be the TP53 gene, involved in several aspects of cell cycle control, and deleted in a significant percentage of GBM tumours. With the use of adenoviral vector-based TP53 gene transfer, successful tumour killing has been achieved in the laboratory [15], and clinically for, e.g., colorectal cancer. Clinical studies in GBM patients have been started, the results of which are yet to come.

A third field in which gene technology plays a role is that of enhancing (natural) immune responses towards the tumour cells. This can be achieved for example by the elimination of immunosuppressors. Techniques consist of silencing the genes for the formation of insulin-like growth factor I (IGF I), transforming growth factor beta (TGFbeta) [19] and others. See also Sect. 3.2.13.1.2.

In the same way as has been done concerning the modulation of immunological factors by interference with relevant genes, manipulation of the genes pertinent for angiogenesis can be interfered with [4]. The high-grade gliomas have a high angiogenic activity, which is necessary for their growth and survival. The main factors involved in neo-angiogenesis belong to the VEGF family. Antisense techniques with retroviral or adenoviral vectors to silence the genes involved are almost at a
3.2.13 Novel Therapies

3.2.13.1 Novel Therapies

3.2.13.1.2 Immunotherapy and Related Techniques

The limited immunogenicity of intrinsic brain tumours is not only due to the BBB, but also to immunosuppression by factors that hamper such immunogenicity. In particular, IGF and TGFbeta-2 are the factors involved. As already stated in Sect. 3.2.13.1.1, elimination or minimalisation of their effect by downregulation of their production seems to raise immune responses, also to GBM. For example, local (intratumoural) application of a TGFbeta 2 antisense oligonucleotide (AP 12009) has now been tried in a clinical setting using microperfusion for several months, with an interesting response [30].

Various other techniques exist and work in the laboratory environment, and some have already reached the clinical stage (reviewed in [31]). Among them are the transduction of IL2 and IL7 into tumour cells, in order to raise T cell responsiveness; the ex vivo activation of APCs and dendritic cells (passive and active immunisation, with risks of autoimmune reactions in the non-tumorous CNS), and various forms of autologous tumour cell immunisation. The latter method has been tried in a clinical multicentre study in which tumour cells are transfected ex vivo with IFN-γ and then used for repeated vaccination.

Developments in the field of antigen targeting with specific (monoclonal) antibodies are dealt with in the next section.

3.2.13.1.3 Membrane Receptor Targets and Their Applications

As in many other tumours, high-grade brain tumours like GBM express specific receptors on their cell membrane, or have a specific amplification of such receptors. Among the most common receptors found on the surface of gliomas are EGF-R, PDGF-R, FGF-R, VEGF-R, transferrin, and the receptors for cytokines such as TGF-β, IL-13 or IL-4. By coupling specific antibodies against these receptors with certain drugs or toxins, so-called immuno-toxins (conjugates) are formed. Several of these products have been subjected to clinical trials to date. The most important are:

- Transferrin with diphteria toxin (TransMID) [17]
- TGF (a ligand for EGF-R) with *Pseudomonas* exotoxin (TP-38) [29]
- IL-4 ligand with *Pseudomonas* exotoxin (NBI-3001) [23]
- IL-13 with *Pseudomonas* exotoxin (PRECISE) [22]

Other receptors that have already been "targeted" are the PDGF-R and the VEGF-R, although these are mostly targeted by smaller molecules, the tyrosine kinase inhibitors [28]. It is noteworthy that the tumour cells overexpress all these receptors as well as their ligands, leading to autocrine loops that stimulate and support cell proliferation. A special group of ligands and receptors to be mentioned are the TNF-related apoptosis-inducing ligands (TRAIL) and the TRAIL receptors. Many tumours, including GBM, express TRAIL and TRAIL receptors. TRAIL can be given as a single drug, but can also be targeted by conjugation to a specific antibody, and thus become a specific targeting apoptotic drug too [18].

3.2.13.1.4 Membrane Receptor-Related Intracellular Pathways as a Target

Most of the ligands and receptors mentioned are related with their intracellular domain to tyrosine kinase (TK) pathways. Activation results in cascades of intracellular processes, many of them leading to further cell proliferation and/or migration. Direct interference with these TK pathways can interrupt such events and subsequently lead to apoptotic cell death. Many (small) molecules have been developed, ATP mimetics, which have such an action, and are now tested in many cancer types, including GBM. Examples are erlotinib (Tarceva), which interferes with the EGF-R-related TK; gefitinib (Iressa, same pathway); imatinib (Glivec), which interferes with the PDGF-R-related TK.

3.2.13.1.5 Anti-Angiogenesis and Antimigration Therapy

Malignant tumours, and very markedly GBM too, induce neo-angiogenesis. Neovascularisation is necessary for further growth, and inhibition of angiogenesis may prevent that. Therefore, anti-angiogenesis seems to have become a strategy with high expectations for cancer therapy. The target cells in anti-angiogenic therapy may be the tumour cells that produce angiogenic factors, like VEGF and its corresponding VEGF-R, but also the endothelial cells themselves, which are more readily accessible, being outside the BBB.
3.2 Brain Tumors

Closely connected to angiogenic activity of tumour cells is their migratory potential [16]. In order to proliferate, cells must invade the surrounding matrix, for which they produce matrix metalloproteinases (MMPs) [26]. Inhibition of MMPs prevents tumour cells from migrating, and indirectly from proliferating, bringing tumour growth to a halt. The close biochemical relationship between angiogenic factors and MMPs results in a double action of anti-angiogenic drugs against angiogenesis as well as migration. Since these drugs do not kill the tumour cells but only prevent further growth, they are often called cytostatic drugs.

Examples of anti-angiogenic drugs that have been tested already in clinical studies are: thalidomide, angiostatin, endostatin, ZK222584/PTK787 and COX-2 inhibitors like celecoxib and cilengitide [3]. The most promising results are those of studies in which these drugs are combined with radiation therapy and/or cytotoxic chemotherapy.

### 3.2.13.2 Delivery

In order to overcome the main obstacles to adequate delivery of therapeutic drugs or cells into the brain, various methods have been developed over recent years.

#### 3.2.13.2.1 Local Injections

In the design for retroviral vector transfection it was necessary to use producer cells. These cells could only be placed in or around residual tumour or cavities by direct injections into the parenchyma. It has been shown in a variety of studies that this method of delivery did not do any harm to the patients in most cases, and produced only minimal changes on MRI. However, the efficiency of delivery, even with some 50 injections, was poor.

Injection of cells or drugs by means of an Ommaya reservoir and an indwelling catheter results in a pooling of the injected material around the tip of the catheter. Drugs may dissolve into the tissue, by diffusion, but it is a prerequisite that they be lipophilic and of low molecular weight.

#### 3.2.13.2.2 Slow-Release Systems

More promising seems the concept of slow-release systems, although with these, too, diffusion is the driving force of drug delivery, with the aforementioned limitations, especially when in brain oedema the interstitial pressure is high. Most experience has been obtained with biodegradable wafers containing (and releasing) BCNU, the Gliadel wafer [34]. This has had a significant but modest effect on survival, and is important, especially as a benchmark in comparison with other novel therapies. Other slow-release systems, tested in the laboratory, and some already in patients, are liposomes, alginate spheres [2], and polymeric nanoparticles. Chip technology may also have a place in controlled local drug delivery, and has been tested on a limited scale.

#### 3.2.13.2.3 Convection-Enhanced Delivery

In contrast to diffusion, where a concentration gradient is the driving force behind the dispersion of molecules/drugs, convection is based on a pressure gradient. This makes it possible to deliver even large molecules over a longer distance [12]. This technique is especially feasible when immunotoxins are considered, which are indeed large molecules. The technique is rather consistent in smaller animals, whereas in humans it appears that the variation in brain tissue resistance and in that of the (residual) tumour tissue hampers a predictive distribution of solvents and drugs. Nevertheless, after a lot of lessons learned over the last few years, the feasibility of CED has now been proven in several of the afore-mentioned studies using this technique (e.g. TP 38, PRECISE). With a maximum of four catheters placed in the brain one can cover quite a large part of one hemisphere for the delivery of large molecules. All studies with drugs of large molecular weight are now using this CED technique.

It has to be proven whether the combination of immunotoxins applied by the CED technique does indeed combine an ideal targeting drug with an optimal delivery technique.

#### 3.2.13.3 Future Developments

- In the near future another way of targeting may reach the clinical stage: neural stem cells and progenitor cells seem to have a tropism towards brain tumour cells. In the laboratory situation these cells, after having been loaded with a killing mechanism (transfection with specific genes) have been shown to be able to chase and kill brain tumour cells even far away from the injection site.

- Surgical refinements may lead to a real and significant reduction of tumour load: intraoperative imaging, by intraoperative MRI, or by visualisation of residual tumour cells through vital staining (the ALA experience), may help to reach that goal.

**Selected Reading**


3.3 Vascular Diseases

3.3.1 Aneurysms

3.3.1.1 Pathogenesis

KEN LINDSAY

Cerebral aneurysms arise at the bifurcation of blood vessels. They are primarily saccular in shape, but may have additional lobules or “nipples”. Far less commonly, fusiform dilatation or ectasia of intracranial vessels occurs and in some cases may be associated with connective tissue or atherosclerotic disease. Most saccular aneurysms occur in relation to the anterior cerebral artery (35%), followed by the internal carotid artery (30%), and the middle cerebral artery (25%). About 10% arise from the posterior circulation.

The formation of cerebral aneurysms was originally attributed to the presence of developmental defects in the tunica media, but defects in this layer occur as frequently in extracranial vessels where saccular aneurysms are rare. Furthermore, cerebral aneurysms are rarely seen in children.

Most now believe that the pathogenesis of intracranial aneurysm formation is multi-factorial and that acquired factors may combine with an underlying genetic susceptibility. Disruption of the internal elastic lamina appears to be most relevant. Those factors that contribute to atherosclerotic damage of blood vessel walls – hypertension and smoking – may produce local thickening in elastic regions within the intimal layer, i.e. “intimal pads”, leading to increased strain on the adjacent parts of the vessel wall. Degenerative change occurs predominantly at sites of haemodynamic stress – at vessel bifurcations – but particularly where developmental anomalies alter flow patterns. For example, with a hypoplastic anterior cerebral artery on one side, aneurysms tend to form on the wall that faces the brunt of the incoming flow from the dominant A1 vessel on the opposite side. Inflammatory processes similar to those seen in atherosclerotic plaques (not in themselves necessary for aneurysm formation) are found in the vessel wall and release matrix metalloproteinases (MMPs) and other proteolytic enzymes, and may play a role. The extracellular matrix provides strength and elasticity to intracranial arteries and is composed of collagen and elastin fibres embedded in glycoproteins and proteoglycans. A balance normally exists between degradation by proteases (e.g. MMPs and elastase) and synthesis by protease inhibitors (e.g. MMP inhibitors, anti-trypsin), growth factors and cytokines. Over- or under-expression of such proteins may disturb this balance and result in remodelling of the extracellular matrix. Four genome-wide linkage studies have identified genetic loci for intracranial aneurysms, of which three include functional candidate genes coding for structural proteins of the extracellular matrix, including elastin and collagen type 1A2. This may in part explain how genetic factors could increase the tendency towards aneurysm formation.

In a few patients, aneurysm formation has been associated with hereditary disorders of connective tissue such as polycystic kidney disease, Ehlers-Danlos disease type IV, fibromuscular dysplasia and Marfan’s syndrome.

3.3.1.2 Epidemiology

The prevalence of cerebral aneurysms depends on the method used for detection, how carefully this is applied and on the age of the patients undergoing investigation. Retrospective autopsy studies report an incidence of 0.4%, but this increases to 3.6% when aneurysms are sought prospectively. Angiographic studies detect cerebral aneurysms incidentally in 3.7–6% of patients, but this patient group may harbour a higher incidence of risk factors. For adults without risk factors, the prevalence lies between 2 and 3%. Cerebral aneurysms are rarely formed in patients under 20 years of age and numbers peak between 60 and 80 years. Female gender increases the likelihood of an incidental aneurysm (relative risk of 1.3) as does the presence of atherosclerosis. A family history of two or more affected first-degree relatives or a history of polycystic kidney disease increases the relative risk by a factor of 4. Those patients who have undergone repair of a ruptured aneurysm have an increased tendency to form other aneurysms.

3.3.1.2.1 Subarachnoid Haemorrhage

At least 75% of haemorrhage into the subarachnoid space results from a ruptured aneurysm. In about 20% of patients there is no identifiable cause; the remainder have
3.3 Vascular Diseases

Various causes, including arteriovenous malformation, vasculitis and arterial dissection.

The incidence of subarachnoid haemorrhage (SAH) varies from study to study and from country to country. In most western countries SAH occurs in about 8 patients per 100,000 per year, but this falls to 5.6 for SAH confirmed by CT. In Finland and Japan the figure increases to over 20 per 100,000 per year. Women have a 1.6-times greater risk of subarachnoid haemorrhage than men. In first-degree relatives the risk of SAH is increased 3–7 times. Other risk factors include excess alcohol intake (>2 units per day), smoking, hypertension and the presence of inherited connective tissue disorders.

3.3.1.2.2 Incidental Aneurysms – Risk of Haemorrhage

Data from the International Study of Unruptured Intracranial Aneurysms (ISUIA), by far the largest study published on incidental aneurysms, has shown that for aneurysms < 7 mm in diameter the risk of haemorrhage is extremely small. This risk increases with increasing size (Table 3.3.1) and for those situated in the posterior circulation. Incidental aneurysms in patients with a previous history of SAH from a separate aneurysm are also at higher risk of rupture. The risk of treatment of incidental aneurysms (whether endovascular or surgical) must be weighed against the risk of rupture over the patient’s expected lifespan. Treatment risks increase with increasing age, with the location (highest risk in the posterior circulation) and with the size of the aneurysm.

3.3.1.3 Symptomatology – Subarachnoid Haemorrhage

Most cerebral aneurysms present acutely with SAH. A few present with symptoms and signs from pressure of the aneurysm sac on adjacent structures, either alone or in association with a subarachnoid haemorrhage. A third nerve palsy is the most commonly encountered pressure effect — usually from a posterior communicating artery aneurysm, but occasionally from a superior cerebellar artery aneurysm. Carotid aneurysms within the cavernous sinus may compress the third, fourth, fifth and sixth cranial nerves. Rarely, visual field defects occur from pressure on the optic nerve or chiasm. More and more aneurysms are now discovered incidentally by the use of increasingly sensitive imaging techniques for investigation of unrelated symptoms.

The classic description of SAH includes severe headache of instantaneous onset, often described as like a “blow to the back of the head” and accompanied by vomiting, neck stiffness and photophobia. About 50% of patients lose consciousness at the onset, in some due to a seizure. Coma may persist from an associated haematoma mass, acute hydrocephalus or global cerebral ischaemia. Reduced cerebral perfusion can occur from a sudden acute rise in intracranial pressure at the time of the bleed and should be differentiated from “delayed cerebral ischaemia” related to vasospasm, usually occurring 7–10 days after the haemorrhage. About one third of patients develop focal signs (dysphasia and/or hemiparesis), often only lasting a few hours.

In some patients the diagnosis is more difficult to establish from the clinical history since the headache is less pronounced and the onset more gradual. Neck stiffness may take hours to develop and does not always appear. On occasions, the patient fails to seek medical help. Many authors describe the occurrence of headache preceding SAH as a “sentinel bleed” or a “warning leak”. Such terms are misleading and although in some cases pain may result from expansion of the vessel wall, most probably represent a missed haemorrhage.

Of those patients who present with sudden headache, only 1 in 4 will have had an SAH. Other causes include thunderclap headache, migraine and headache related to sexual activity and exertion. Only 1 in 10 of patients presenting with sudden headache alone are shown to have had a haemorrhage.

<table>
<thead>
<tr>
<th>Aneurysm location</th>
<th>&lt;7 mm (No previous SAH (%))</th>
<th>&lt;7 mm (Previous SAH (%))</th>
<th>7–12 mm (%)</th>
<th>13–24 mm (%)</th>
<th>&gt;24 mm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior circulation (excluding posterior communicating artery)</td>
<td>0</td>
<td>1.5</td>
<td>2.6</td>
<td>14.5</td>
<td>40</td>
</tr>
<tr>
<td>Posterior circulation (including posterior communicating artery)</td>
<td>2.5</td>
<td>3.4</td>
<td>14.5</td>
<td>18.4</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 3.3.1 Data from the International Study of Unruptured Intracranial Aneurysms (ISUIA) showing the 5-year cumulative risk of bleeding according to aneurysm location. SAH subarachnoid haemorrhage
3.3.1.4 Diagnostic Procedures

None of the clinical features alone is sufficiently reliable to establish the diagnosis. When SAH is suspected, the inconvenience and cost of further investigations is offset by the importance of failing to establish the diagnosis of aneurysm rupture. An unenhanced axial CT scan will confirm the presence of SAH in 98% of patients if performed within 12 h of the bleed, but this high detection rate falls off over time to 94% at 24 h, 50% on day 7 and 20% on day 9 from the bleed. Hyperdense blood is usually most evident within the basal cisterns, in the interhemispheric and Sylvian fissures, in the cortical sulci and within the ventricles (Fig. 3.3.1). Changes are often subtle depending on the time of the scan and severity of the haemorrhage, e.g. the normal hypodense fissure may be absent or an isodense fluid level may lie within the occipital horn of the lateral ventricle. The pattern of blood on the axial CT can provide a guide to the site of the ruptured aneurysm, which is important for determining the source of the bleed when multiple aneurysms are found.

In contrast, a “peri-mesencephalic” pattern of blood (Fig. 3.3.1) indicates the likelihood of negative angiography, although it is still essential to exclude the possibility of an aneurysm around the distal basilar artery.

The greater the amount of blood on the initial CT, the higher the risk of delayed cerebral ischaemia and the worse the outcome.

In patients presenting with an impaired level of consciousness, a CT is essential, not only to establish the diagnosis, but to exclude the presence of hydrocephalus or a haematoma mass, either of which may require treatment in their own right.

3.3.1.4.1 Lumbar Puncture

Patients with a suspected SAH and normal CT require a lumbar puncture, but only after a delay of at least 6 h and preferably 12 h from the bleed to allow time for the red blood cells to break down and produce xanthochromic staining of the cerebrospinal fluid (CSF). The CSF should be centrifuged and the supernatant examined by spectro-

**Figure 1** CT appearances - SAH

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Fig. 3.3.1 Computed tomography appearance – subarachnoid haemorrhage
photometry for oxyhaemoglobin and bilirubin (the cause of the xanthochromia). The naked eye is insufficient to detect small amounts of pigment change. Red cells lyse in the CSF to produce oxyhaemoglobin either in vitro or in vivo, but conversion of oxyhaemoglobin to bilirubin requires the enzyme haemoxigenase, which is only present in macrophages, the arachnoid membrane and the choroid plexus. Thus, any delay in centrifuging RBCs from the CSF can lead to an erroneously high level of oxyhaemoglobin, but the presence of bilirubin (in the absence of jaundice) establishes a diagnosis of SAH and excludes a traumatic tap as a cause of the blood staining. Xanthochromia should persist for at least 2 weeks after the bleed, but thereafter a negative result does not exclude SAH.

3.3.1.4.2 Further Investigation of SAH

Computed tomographic angiography will detect all but the smallest of aneurysms; 3D reconstruction allows detailed assessment of the neck and helps guide further treatment (see Sect. 3.3.1.5). If a negative and an “aneurysmal” pattern of blood exist within the Sylvian or the interhemispheric fissure, digital angiography is still required to ensure that a small aneurysm is not missed. Until now digital angiography has been assumed to be the gold standard for aneurysm detection, but some now claim that CT angiography may replace this, particularly when blood within the fissure guides the neuroradiologist to the likely source of the bleed. The latest digital angiography equipment also allows three-dimensional rotation of the image to improve aneurysm detection and to help evaluate the aneurysm neck. This technique can detect even the smallest aneurysmal “bleb”. In patients with a peri-mesencephalic pattern of blood on CT, CT angiography is sufficient to exclude a posterior circulation aneurysm, but digital angiography may still be necessary to exclude a small arteriovenous malformation or fistula.

3.3.1.4.3 Subarachnoid Haemorrhage with Negative Digital Angiography

In about 20% of patients investigation fails to detect the cause of the SAH. A degree of vasospasm occurs in up to 50% of patients and may hinder aneurysm detection, particularly if severe. Patients with an “aneurysmal” pattern of blood on CT with negative angiography should undergo a repeat examination after 1 or 2 weeks, or when the vasospasm has subsided. For those patients with a “peri-mesencephalic” pattern of blood and a negative angiogram, no further investigation is required and the outlook is excellent.

3.3.1.4.4 Transcranial Doppler

High-flow velocities in intracranial vessels (>120 cm/s) suggest the presence of vasospasm. A sudden increase in flow velocity may precede the development of clinical signs of cerebral ischaemia and provide an opportunity to initiate early prophylactic measures.

3.3.1.4.5 Screening for Incidental Aneurysms

Screening (CT angiography) is considered in individuals aged between 25 and 70 years with a family history of two or more first-degree relatives with SAH or with polycystic kidney disease. The clinician must inform the patient that a negative investigation does not exclude subsequent aneurysm development and rupture in future years and that the discovery of a small aneurysm left untreated may raise additional problems of anxiety or limitation of life insurance. The management of larger aneurysms requires careful discussion to ensure that the patient can compare the risk of treatment against the risk of conservative management. Any patient with a positive family history, whether or not they opt for investigation and/or treatment, should be advised to give up smoking and to undergo regular blood pressure checks.

3.3.1.4.6 Perioperative Management of Subarachnoid Haemorrhage

3.3.1.4.6.1 Clinical Assessment

The clinical condition of the patient, along with age and amount of blood seen on the CT, is an important guide to eventual outcome. The Glasgow Coma Score on admission, combined with the presence or absence of focal signs, makes up the WFNS grading scale (Table 3.3.2).

The WFNS scale correlates strongly with outcome (Table 3.3.3). An impaired conscious level indicates the need for an urgent CT scan to exclude concomitant hydrocephalus or a haematoma mass, either of which may require urgent treatment.

3.3.1.4.6.2 Re-Bleeding

About 40% of patients with an aneurysmal SAH will re-bleed in the first 3 weeks if left untreated. This risk is the highest in the first 24 h after the ictus. After 6 months the risk falls to 3.5% per year and this risk persists for at least 10 years. Only aneurysm repair prevents re-bleeding. Antifibrinolytic medication is of no benefit since the reduced risk of re-bleeding is offset by an increased risk of cerebral ischaemia.

3.3.1.4.6.3 Delayed Cerebral Ischaemia

The development of focal signs with or without deterioration in the level of consciousness occurs in about 25%
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3.3.1 Aneurysms

The time course of blood vessel constriction on angiography ("vasospasm") matches this and is the prime cause, but a fall in plasma volume occurs in association with a negative sodium balance in one third of patients after SAH, and this may also contribute to ischaemic damage.

The calcium antagonist nimodipine (60 mg 4-hourly) reduces the incidence of delayed cerebral ischaemia by about one third and improves outcome. All patients should receive this from the outset.

To prevent hypovolaemia, give patients 3 l per day of normal saline.

If hyponatraemia develops, do not restrict fluid as this can compound the fall in plasma volume. Treat with hypertonic saline or fludrocortisone.

Avoid antihypertensive medication unless the patient is already on this therapy.

If clinical signs of delayed cerebral ischaemia develop, the standard practice is to treat with hypervolaemia, haemodilution and induced hypertension (triple H therapy), but there is no evidence of benefit from randomised controlled trials. Initially, give plasma volume expanders, e.g. Gelofusine. If ischaemic signs persist, induce hypertension with inotropes (but only if the aneurysm has been repaired, otherwise there is a high risk of re-bleeding).

• If triple H therapy fails to reverse the neurological deficits, balloon angioplasty with or without infusion of papaverine may improve cerebral perfusion, but again no controlled trials have been published to confirm a beneficial effect.

• Other treatments include the use of magnesium sulphate. Initial studies noted a possible benefit, but full evaluation is awaited.

### Table 3.3.2 World Federation of Neurological Surgeons (WFNS) grading system for SAH

<table>
<thead>
<tr>
<th>WFNS grade</th>
<th>Glasgow Coma Scale</th>
<th>Motor deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>Absent</td>
</tr>
<tr>
<td>II</td>
<td>13–14</td>
<td>Absent</td>
</tr>
<tr>
<td>III</td>
<td>13–14</td>
<td>Present</td>
</tr>
<tr>
<td>IV</td>
<td>7–12</td>
<td>Absent or present</td>
</tr>
<tr>
<td>V</td>
<td>3–6</td>
<td>Absent or present</td>
</tr>
</tbody>
</table>

### Table 3.3.3 Data from the UK National Study of SAH, showing the relationship of WFNS grade to outcome

<table>
<thead>
<tr>
<th>WFNS grade on admission</th>
<th>Number of patients</th>
<th>Percentage with unfavourable outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1,214</td>
<td>24.7</td>
</tr>
<tr>
<td>II</td>
<td>378</td>
<td>37.6</td>
</tr>
<tr>
<td>III</td>
<td>88</td>
<td>48.9</td>
</tr>
<tr>
<td>IV</td>
<td>164</td>
<td>64.0</td>
</tr>
<tr>
<td>V</td>
<td>118</td>
<td>71.2</td>
</tr>
<tr>
<td>Total</td>
<td>1,962</td>
<td>34.4</td>
</tr>
</tbody>
</table>

3.3.1.4.7 Outcome

Outcome from the repair of incidental aneurysms, whether endovascular or surgical, depends on age, aneurysm site and size. Overall mortality, as reported in the International Study of Unruptured Intracranial Aneurysms, lies in the region of 1–2% with a morbidity of around 10%.

After SAH, 10–15% of patients die before reaching hospital and a further 15% die within the first 24 h. Of those patients reaching a neurosurgical unit, the outcome relates to age, clinical grade (Table 3.3.3), the amount of blood on the CT scan, the site and size of the aneurysm and the presence of associated medical conditions.

### 3.3.1.5 Surgical Therapy

KEN LINDSAY

3.3.1.5.1 Preoperative Considerations

Prior to operation the surgeon must assess the available imaging to determine:

• The width of the aneurysm neck and the configuration of the surrounding vessels
• The optimal side and route of approach
• The ease of obtaining proximal control
• The potential need for by-pass

Rotation of a 3D digital or CT angiographic image provides the ideal method of preoperative assessment of the aneurysm neck. Try to envisage how the clip will be applied – preferably in the plane of the distal vessels to minimise kinking, and decide on the optimal route to achieve this. Aneurysms of the anterior communicating complex can be approached from either side or occasionally from an anterior inter-hemispheric approach. For such aneurysms points to consider include not only the configuration of the vessels, but also the side of the predominant filling (to aid proximal control) and whether or not a haematoma has already damaged the gyrus rectus on one side (if so, the preferred side of approach). Aneurysms arising at the origin of the ophthalmic artery often
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point medially and an approach from the contra-lateral side may provide an unobstructed route to the aneurysm neck.

3.3.1.5.2 General Techniques of Operative Repair

3.3.1.5.2.1 Dissection
Dissection, if possible, should initially expose the proximal vessel, and then work towards the aneurysm neck. Use only sharp dissection for any resistant tissue in the vicinity of the aneurysm.

3.3.1.5.2.2 Direct Clipping
Direct clipping should aim to obliterate the aneurysm sac. Where possible, puncture the fundus to ensure complete occlusion of the aneurysm neck. Postoperative angiography shows that a residual neck remnant remains outside the clip in 2–10% of patients.

3.3.1.5.2.3 Wrapping
Wrapping the aneurysm fundus with muslin provides some protection, but fails to eliminate the risk of re-bleeding. Only use this technique if direct clipping and endovascular repair methods have failed.

3.3.1.5.2.4 Trapping/Extracranial–Intracranial Bypass
Trapping of the aneurysm, combined where necessary with extracranial–intracranial bypass, minimises the risk of ischaemic complications when size or shape (e.g. fusiform) prevents application of a clip or endovascular occlusion.

3.3.1.5.2.5 Temporary Clipping
Temporary clipping of the proximal vessel may facilitate dissection of the aneurysm neck and occlusion of the sac. If used, vessels should be occluded for no longer than 3–5 min and a similar duration allowed for re-perfusion before re-applying the temporary clip. When the proximal vessel is difficult to access (e.g. low basilar bifurcation or supraclinoid aneurysm), temporary occlusion can be provided with an endovascular balloon.

3.3.1.5.2.6 Doppler Microprobe
A Doppler microprobe applied to the distal vessels can provide some reassurance that flow persists.

3.3.1.5.2.7 CSF Drainage
After subarachnoid haemorrhage, about 50% of patients develop some obstruction to CSF flow. Of these, about half require CSF drainage either via an external ventricular drain, or where the blood clot does not obstruct the third or the fourth ventricles, by a lumbar drain. Lumbar drainage during any operative procedure helps improve access and minimises the effect of any brain retraction. Opening the lamina terminalis may reduce the need for a permanent CSF shunt.

3.3.1.5.3 Anterior Circulation Aneurysms – Operative Techniques – the Pterional Approach
The pterional route remains the standard approach for most anterior circulation aneurysms. The patient is positioned with the head slightly up, with the malar bone at the highest point and the head rotated to about 45° (more or less depending upon the intended direction of approach). Figure 3.3.2a shows the line of the scalp flap (dotted line). Reflection must permit access to the angle between the zygoma and the frontal bone. The shaded area shows the extent of bone removal. A supra-orbital incision combined with a 2- × 3.5-cm “keyhole” bone flap (Fig. 3.3.2b) can provide access to most aneurysms approached through the standard pterional route, but the small flap limits the angle of approach and it is not clear whether any cosmetic benefit produced by such a small flap justifies the restricted access. The supra-orbital line

Fig. 3.3.2 a Pterional approach – skin flap (dotted line) and area of bone removal. b Supraorbital approach – area of bone removal
of approach gives good access to the Circle of Willis and I would always advise extending the pterional bone flap in this direction rather than limiting the craniotomy to the fronto-zygomatic angle. The outer sphenoid wing is removed with either rongeurs or a drill until flush with the floor of the anterior fossa. For supra-clinoid aneurysms, some prefer to drill the anterior clinoid process extradurally to permit access to the carotid cave, while others prefer to remove this intradurally. When the surgeon requires access from a low trajectory, removal of the zygomatic arch with or without removal of the superior orbital rim can improve access and minimise brain retraction (Fig. 3.3.3), although these techniques are rarely necessary.

3.3.1.5.3.1 Carotid Artery Aneurysms
For aneurysms arising at the origin of the posterior communicating artery, the direction of the fundus should determine the head position. When the aneurysm projects posteriorly, position the head almost laterally. When the aneurysm projects laterally, position the head about 45°. Open the arachnoid over the carotid artery without retracting the temporal lobe; retraction may cause rupture if the fundus of a laterally projecting aneurysm is adherent. Removal of the anterior clinoid may aid access to low-lying aneurysms. Try to identify both the posterior communicating and the anterior choroidal arteries before clipping. Occlusion or compromise of the posterior communicating artery, although best avoided, should not cause harm provided the posterior cerebral artery on that side fills from the posterior circulation, but occlusion of the anterior choroidal artery will cause a capsular infarct. For anterior choroidal and carotid bifurcation aneurysms, it is essential to ensure that no perforating vessels are compromised during clipping.

Paraclinoid aneurysms (comprising ophthalmic, superior hypophyseal and posterior paraclinoid aneurysms) require extensive removal of the anterior clinoid process to provide access to the carotid cave and allow proximal control. The transcranial approach described by Dolenc provides excellent access to the intracavernous carotid artery. Alternatively, the carotid artery can be exposed in the neck.

3.3.1.5.3.2 Anterior Cerebral/Communicating Artery Aneurysms
Identify the carotid bifurcation and follow the anterior cerebral vessel anteriorly. Take care retracting the frontal lobe – an anterior communicating artery aneurysm pointing forwards and downwards could be adherent to the skull base. Removal of the gyrus rectus medial to the olfactory nerve on that side will improve access to the anterior communicating artery complex, particularly for aneurysms pointing posteriorly and superiorly between the distal vessels. Ensure that no damage occurs to the recurrent artery of Heubner; otherwise, a capsular infarct will result. Identify the proximal and distal vessels on each side before clipping and beware incorporating hypothalamic perforators within the clip. Opening the lamina terminalis may avoid the need for a shunt at a later stage. For some aneurysms of the anterior communicating artery complex, the surgeon may opt for an anterior interhemispheric approach, but this route tends to expose the fundus before gaining proximal control. Aneurysms arising at the origin of the pericallosal artery always require an interhemispheric approach.

3.3.1.5.3.3 Middle Cerebral Artery Aneurysm
For difficult aneurysms or for the less experienced surgeon, it is always wise to begin dissection at the proximal (medial) end of the fissure before working more distally. Take care not to damage the lenticulo-striate perforators on the superior surface of the middle cerebral artery. Alternatively, start by opening the fissure more laterally, either by direct dissection or by injecting saline through a small opening. Occasionally, the fissure does not split and it is necessary to enter the superior temporal gyrus to gain access to the middle cerebral vessels.
3.3.1.5.4 Posterior Circulation Aneurysms – Operative Technique

The approach to posterior circulation aneurysms depends on where the aneurysm lies on the arterial tree (Fig. 3.3.4).

3.3.1.5.4.1 Upper Basilar/Superior Cerebellar/Posterior Cerebral Arteries

3.3.1.5.4.1.1 Basilar Bifurcation Aneurysms

The hazards of operative repair at this site lie primarily with the risk of damage to perforators supplying the midbrain and thalamus. These arise from P1, a few millimetres from the bifurcation, but some may arise directly from the basilar artery and adhere to the posterior surface of the fundus. The subtemporal approach is particularly suited for posteriorly projecting or low-lying basilar bifurcation aneurysms (Fig. 3.3.5). A linear or curvilinear incision extends from the junction of the zygoma with the temporal bone. This provides a surface landmark for the basilar bifurcation. CSF drainage and mannitol aid retraction of the temporal lobe, but care is required to avoid damaging bridging veins, in particular, the vein of Labbé. Stitching back the edge of the tentorium (avoiding the 4th nerve) before opening the arachnoid layers over the interpeduncular fossa, improves the exposure. It is important to try to identify the left posterior cerebral artery before clipping and to separate any perforators from the posterior surface of the neck and fundus. Anteriorly projecting aneurysms tend to lie free from perforators and carry least risk during clipping. Superiorly and posteriorly projecting aneurysms usually require a fenestrated clip to encircle the right posterior cerebral artery and occasionally the III nerve. The clip length should only extend to the distal edge of the neck; otherwise, this may occlude perforators arising from the left P1.

The transsylvian pterional approach was first described by Yasargil. The Sylvian fissure is widely opened and the frontal lobe, internal carotid artery and middle cerebral vessels retracted medially and the temporal lobe laterally. Following the posterior communicating artery posteriorly, the basilar artery and bifurcation are approached from an antero/lateral direction (Fig. 3.3.2, 3.3.5). Dissection continues either lateral to the posterior communicating artery or medially between the branches of its perforators.
tors. Dividing the posterior communicating artery between liga clips may improve access; this carries little risk provided that this vessel is not the dominant source of filling of the right posterior cerebral artery.

The transsyllvian pterional approach provides good exposure of both posterior cerebral vessels, but has the disadvantage of preventing direct visualisation of the perforators behind the aneurysm fundus. This approach requires less temporal lobe retraction than the subtemporal route, but access may still be difficult for aneurysms >10 mm above the posterior clinoids. Such patients may benefit from a zygomatic or orbito-zygomatic approach (Fig. 3.3.3), as these permit a higher trajectory with less retraction. Aneurysms lying below the level of the posterior clinoids preclude a transsyllvian pterional approach, unless this is combined with the trans-cavernous route described by Dolenc.

The temporo-polar approach (Fig. 3.3.5) provides a combination of both routes. By changing the direction of temporal lobe retraction, the surgeon can approach from a more anterior or lateral direction as required. Posteriorly projecting aneurysms carry a greater risk of operative complications because of the direct relationship with the perforating vessels; for these aneurysms a subtemporal approach aids identification of these perforators and should provide the safest approach.

Basilar bifurcation aneurysms lying >10 mm below the posterior clinoids require one of the approaches detailed in the next section.

### 3.3.1.5.4.1.2 Superior Cerebellar Artery Aneurysms

The subtemporal route demands an approach from the same side as the aneurysm, whereas the pterional route permits clipping of aneurysms on either side. With these aneurysms, perforators are less likely to involve the neck or the fundus, but the III nerve is often closely adherent and must be dissected off the neck before clipping.

### 3.3.1.5.4.1.3 Posterior Cerebral Artery Aneurysms

Aneurysms arising anterior to the midbrain (on either P1 or P2) can be approached via the subtemporal, the trans-sylvian pterional or the temporo-polar route. Those lying in the ambient cistern arising from the P2 segment require a subtemporal approach. Those in the most distal P3 segment may require an occipital interhemispheric approach. Occlusion of the distal posterior cerebral artery beyond the origin of the midbrain perforators or of the posterior choroidal artery seldom causes a permanent visual defect.

### 3.3.1.5.4.2 Basilar Trunk/Vertebro-Basilar Junction/Low-Lying Basilar Bifurcation

The subtemporal transtentorial approach permits access to aneurysms extending down to 18 mm below the floor of the sella turcica (i.e. to the level of the internal auditory meatus) – in some as low as the vertebro-basilar junction. The temporal craniotomy is sited more posteriorly, centred above the mastoid. Considerable caution is required during retraction to avoid damaging the vein of Labbé. The tentorium is incised from just behind the entry point of the IV nerve, and extended back to the transverse sinus. By stitching back the tentorial edge, the surgeon looks down the medial wall of the petrous bone. Aneurysms can be approached either medial or lateral to the trigeminal nerve (Fig. 3.3.6, black and grey arrows), as required. Kawase et al. described an extradural transpetrosal approach where the petrous edge is drilled off between the internal auditory meatus inferiorly, the cochlea posteriorly and the trigeminal ganglion anteriorly; however, the operative field is restricted by the narrow bony opening (Fig. 3.3.6, white arrow). The same technique can be adopted during an intradural transtentorial approach if a more anterior approach is required.

Alternatively, aneurysms at the vertebro-basilar junction and on the basilar trunk can be approached from below. The standard lateral suboccipital route seldom affords sufficient exposure, but this approach can be improved by a variety of methods. Extending the area of bone removal to include a limited mastoidectomy exposes the sigmoid sinus. Opening the dura behind the sinus and either retracting the sinus anteriorly (retrosigmoid approach) or even dividing and reflecting the sinus anteriorly (transsigmoid approach; Fig. 3.3.6) improve exposure of both the prepontine and cerebello-pontine angle cisterns from a more anterior direction and reduce the distance to the midline. Alternatively, a combined supra- and infratentorial approach provides a wide view of the basilar trunk and vertebro-basilar junction. Al-Mefty et al. described this petrosal approach, in which in addition to a large temporo-occipital bone flap, a mastoidectomy provides a presigmoid retrosphenoidal route to the posterior fossa (Fig. 3.3.6). Dividing the superior petrosal sinus and tentorium and retracting the transverse and sigmoid sinus medially gain extensive exposure, provide the shortest route to the aneurysm and minimise retraction of the pons and cerebellum. For the above-mentioned infratentorial approaches, the VII–XII cranial nerves lie between the surgeon and the vessels, and all are at risk of damage. The transclival approach (Fig. 3.3.6), through either a transfacial route or a transoral route avoids brain stem and cranial nerve retraction. Such techniques present significant hazards – the operative corridor is long and narrow and the lateral exposure usually extends only 5 mm from the midline. Anteriorly pointing aneurysms could rupture when opening the dura and the problems of postoperative CSF leaks persist, despite the availability of modern tissue glues.
3.3.1.5.4.3 Vertebral Artery

Most vertebral aneurysms arise at the origin of the PICA, but the height of this origin is variable, ranging from the level of the foramen magnum to the vertebro-basilar junction. Rarely, aneurysms lie extracranially – arising at the level of the anterior spinal artery or from a very low PICA origin. The standard lateral suboccipital approach usually provides sufficient access for most of these aneurysms. The craniectomy extends from the midline to the edge of the transverse/sigmoid sinus and includes a rim of foramen magnum. For low-lying aneurysms, to gain proximal control, the vertebral artery can be exposed extracranially in the sulcus arteriosis as it crosses the arch of C1 before penetrating the dura. The far lateral transcondylar approach, removing up to a third or even half of the occipital condyle, aids direct access to the hypoglossal and jugular region and provides a more caudal to rostral trajectory and a shorter route to the midline (Fig. 3.3.7). In general, the larger the aneurysm and the nearer to the midline, the greater the need to extend bone removal in a lateral direction. With both the above approaches, it is often necessary to work between the branches of the lower cranial nerves to reach the aneurysm neck; this requires extreme care to avoid permanent nerve damage.
3.3.6 Endovascular Therapy

3.3.6.1 Techniques
Attempts at occluding the aneurysm sac with detachable balloons in the 1980s carried high risks and failed to prevent re-bleeding. The introduction of the Guglielmi detachable coil (GDC) in 1990 proved to be a far safer and more effective alternative (Fig. 3.3.8). Helical platinum coils are inserted through a tracker catheter into the aneurysm fundus and detached electrolytically when a satisfactory position is achieved. "Dense packing" of the aneurysm sac with multiple coils on screening (Fig. 3.3.9) equates to the platinum occupying less than one-third of the actual volume, but this is sufficient to disrupt flow and prevent re-bleeding in most patients. In about one-third of cases, the radiologists intentionally leave a remnant of the aneurysm neck, rather than risk obstructing a distal vessel. In this instance, the risk of re-bleeding is higher. Approximately 5% of attempted coil procedures fail.

Aneurysms suitable for coil embolisation require a fundus: neck width of more than 2:1. The radiologists can select coils of different diameter and 3D shape. Usually, four to five coils are necessary, but the number required varies from a single coil for a 3-mm aneurysm to over 20 coils for a giant aneurysm.

3.3.6.1.1 Balloon Remodelling
This technique, developed by Moret, permits coil embolisation in wide neck aneurysms. Periodically inflating a balloon on a separate catheter within the feeding vessel during coil insertion prevents the coils from falling back into the vessel lumen (Fig. 3.3.10). On completing the procedure, the coils adjacent to the vessel lumen retain the shape of the inflated balloon. Some centres use this technique in 30–40% of endovascular cases.

Fig. 3.3.9 a Digital angiogram showing anterior communicating artery aneurysm. b Final stage of coil embolisation showing fundus packed with coils.
3.3.1.6.1.2 Bio-Absorbable Polymer
More recent developments include the use of a bio-absorbable polymer coated around the coil (Matrix) or within the coil (Cerecyte). Experimental work in animals has shown that these polymers stimulate cell regeneration and repair, promote organisation of the thrombus within the aneurysm and encourage neo-intima formation. Whether these coils improve overall results remains uncertain and we await information from further trials.

3.3.1.6.1.3 Hydrogel and Fibre Coils
Hydrogel coils coated with a hydrophilic polymer expand on contact with blood to help fill adjacent space within the aneurysm lumen. Similarly, detachable fibre coils of Dacron or Nylon produce a more thrombogenic reaction than platinum; however, all these new technologies await full evaluation.

3.3.1.6.1.4 Intracranial Stents
The introduction of stents of suitable size and of sufficient flexibility to manoeuvre through intracranial vessels has provided another alternative for wide necked, giant or even fusiform aneurysms, particularly those arising from the internal carotid artery or basilar bifurcation. After placement of the stent, a microcatheter is manoeuvred through the mesh into the fundus to permit coil deposition without fear of occluding the vessel lumen (Fig. 3.3.11). Distal thrombi may complicate stent usage and life-long anti-platelet therapy is essential in such patients.

3.3.1.6.1.5 Onyx
Onyx, a liquid polymer that solidifies on contact with blood, can be injected into an aneurysm sac with the neck protected by either an inflatable balloon or a stent. Although this technique sounds theoretically attractive, an initial series reported a high complication rate and prevented more widespread use.

3.3.1.6.1.6 Endovascular follow-up
All these interventional techniques require check angiography, usually 6 months after treatment. Re-canalisation due to compaction or movement of the coils requires re-treatment in about 10%.

3.3.1.6.2 Treatment Selection
In the 1990s, endovascular treatment was initially reserved for inoperable aneurysms. As techniques and results improved, coil treatment was increasingly used for aneurysms that were difficult to treat surgically, in particular those of the posterior circulation, despite any conclusive evidence of benefit. The International Subarachnoid Aneurysm Trial (ISAT) of clipping versus coiling began in 1994. The Data Monitoring Committee stopped data collection in 2001 after centres had entered 2,143 patients. At 1 year follow-up endovascular coiling showed an absolute reduction in the risk of death or dependency of 7% (a relative risk reduction of 23%) compared with patients undergoing clipping. Significantly more re-bleeds and deaths from re-bleeding occurred within the first year in
the coiled group, but despite this, analysis still favoured this treatment. Despite the absence of long-term follow-up and the fact that trial patients were a selected group of almost exclusively good grade patients with small anterior circulation aneurysms, an immediate shift in practice towards coil embolisation occurred in the UK, with the proportion of patients undergoing coil treatment increasing from 37 to 54%. In many units this figure now exceeds 80%. Subsequent follow-up of the ISAT patients for up to 7 years has shown that the survival benefit is maintained for that period, despite a higher risk of late re-bleeding in the coiled group.

Aneurysm treatment requires a neurovascular team composed of interventional radiologists and neurosurgeons. Even if there were no difference in outcome between the two treatments, most patients would opt for the least invasive approach. The ISAT results support the use of coil embolisation as the first-line approach. However, not all aneurysms are suitable for endovascular treatment. The following factors make coil embolisation more difficult or impossible:

- Aneurysm in the middle cerebral artery territory
- Aneurysms with a wide neck and a fundus/neck width ratio of less than 2:1
- Aneurysms < 3 mm in size
- Large or giant aneurysms, particularly if partially filled with thrombus

Unfortunately, those aneurysms that are difficult to coil are often difficult to clip. The future vascular neurosurgeon (if not directly involved in endovascular techniques) will be required not only to deal with technically demanding aneurysms, but also aneurysms partially packed with coils in which re-embolisation has failed. The most complex aneurysms may require a joint approach combining endovascular occlusion with high- or low-flow bypass. Finally, those patients who deteriorate from a haematoma mass with an underlying aneurysm will require an operative approach to evacuate the haematoma and simultaneously repair the aneurysm.

### 3.3.1.6.3 Treatment Timing

Approximately 30% of re-bleeds occur within the first month, but the highest risk of re-bleeding occurs within the first 24 h. Operative mortality falls the longer operation is delayed after the ictus, but the longer the delay, the greater the possibility of death from re-bleeding.

Although there is no convincing evidence to support early operation a meta-analysis of non-randomised studies does suggest that there might be some benefit when the operation is performed within the first 3 days of the ictus. Most surgeons follow a policy of early “operation, at least for Grade 1 to 3 patients”. Once the aneurysm is repaired, aggressive methods of treating cerebral ischaemia can be applied. Coil embolisation avoids the potentially harmful effects of brain retraction and vessel dissection, and some studies suggest that early coiling carries no additional risk. Whichever technique is planned, it makes sense to employ this whenever manpower and facilities permit – even within the first 12–24 h, if possible, to avoid the period of highest risk of re-bleeding.

### Selected Reading

3.3 Vascular Diseases

3.3.2 Arteriovenous Malformation

3.3.2.1 Pathogenesis

HANS-JAKOB STEIGER, DANIEL HÄNGGI, R. SCHMID-ELSAESSER

Arteriovenous malformations (AVM) of the brain are a complex tangle of abnormal blood vessels. They have three morphologic components:

- The dysplastic vascular core (nidus) in which arterial blood flows directly into draining veins without the normal capillary beds interposed
- The feeding arteries
- The draining veins

In most cases, the nidus appears well circumscribed with little intervening parenchyma and is considered to be the source of haemorrhage. The vessels within the nidus usually have markedly attenuated walls due to a deficient muscularis. They are exposed to an increased intravascular pressure because of the absence of normal, high-resistance arteriolar and capillary beds. Feeding arteries and draining veins are not exclusively devoted to the AVM. Therefore, the haemodynamic characteristics of the AVM may lead to physiologic changes in the normal vasculature adjacent to the malformation with dilatation of the feeding arteries and draining veins. AVM tend to enlarge with age and often progress from a low-flow lesion at birth to high-flow lesions in adulthood.

Although the possibility exists that a pial AVM may develop as an acquired lesion, AVM are generally regarded as congenital lesions representing inborn errors of embryonic vascular morphogenesis caused by malfunction of the embryonic capillary maturation process. The lesions are thought to represent a perpetuation of a primitive arteriovenous communication, a shunt that normally would be replaced by an intervening capillary network. Capillary penetration of the cerebral hemisphere is a relatively late event in the development of the brain's vascular system. This begins during the seventh week and continues almost until the end of the first trimester. It is generally believed that congenital vascular anomalies originate during the embryonic stage of vessel formation or at the foetal stage. However, there is some evidence that cerebral AVM may develop postnatally. The course of AVM cannot be easily predicted: they may remain static, grow, or even regress and recur.

Little is known of the molecular mechanisms mediating the genesis and subsequent biological behaviour of CNS vascular malformations. Unlike cavernous malformations of the brain, it is unknown whether or not genetic mechanisms contribute to the pathogenesis and phenotype of cerebral AVM. Possible germline mutations affecting distinct angiogenetic pathways have been proposed to be the underlying cause of a variety of vascular malformations, including AVM. Familial clustering of AVM suggests the involvement of genetic factors. On the other hand, this could be coincidental considering the low incidence of a familial occurrence when specific congenital diseases, such as the Sturge–Weber syndrome (encephalotrigeminal angiomatosis), Rendu–Osler–Weber syndrome (hereditary haemorrhagic telangiectasia), Louis–Barr syndrome (ataxia telangiectasia), or Wyburn–Mason syndrome (encephaloretinofacial angiomatosis), which are associated with vascular malformations, are ruled out. Hereditary haemorrhagic telangiectasia (HHT), or Rendu–Osler–Weber disease, is an autosomal dominant disorder of localised angiodysplasia. The vascular lesions that develop consist of direct arteriovenous connections without an intervening capillary bed. Germ-line mutations in one of two different genes, endoglin or ALK-1, can cause HHT. Both are members of the transforming growth factor (TGF)-beta receptor family of...
proteins, and are expressed primarily on the surface of endothelial cells.

Considering factors of the surrounding parenchyma, ischaemia must be seen as a primary one. A number of case reports on the association between AVM and moyamoya disease are found in the literature.

### 3.3.2.2 Epidemiology

The incidence of intracranial vascular malformations is not known with certainty. The prevalence data of cerebral AVM reported in the literature range between 0.02% and 0.5% and are probably influenced by geographical and racial factors. In Europe and the United States up to 0.1% of the population may have an AVM.

There seems to be a modest male predominance among patients with an AVM, with a male/female ratio of about 1.4:1, and the majority of AVM become symptomatic before the age of 40.

### 3.3.2.3 Symptomatology

#### 3.3.2.3.1 Haemorrhage

Intracranial haemorrhage is the most common clinical presentation with a reported frequency ranging from 30 to 80%. It is not unusual for old haemorrhagic areas and haemosiderin deposits to be detected on MR images, during open surgery or in autopsy series in patients in whom these events have not been recognised before. The reported risk of haemorrhage as the initial symptom is 2–4% per year.

Ondra and collaborators followed 166 unoperated symptomatic patients with cerebral AVM (mean follow-up period 23.7 years). The rate of major re-bleeding was 4.0% per year. There was no difference in the incidence of re-bleeding regardless of presentation with or without evidence of haemorrhage. In contrast, many other studies showed that patients initially presenting with haemorrhage are at higher risk of subsequent bleeding than those presenting with other symptoms. The Arteriovenous Malformation Study Group reported that on average the annual rate of re-haemorrhage was 18% among patients who had had haemorrhage at initial presentation, compared with a rate of 2% among those with no history of bleeding. The risk of re-bleeding appears to be higher in men than in women. Rates of repeated bleeding have been reported to be higher in the first year after initial haemorrhage and to decline rapidly thereafter.

The mortality rate associated with the first haemorrhage has been estimated to be about 10–15%, and the overall morbidity about 50%.

Nevertheless, since haemorrhage is the most common initial presentation and associated with a significant risk of death or permanent morbidity, it would be helpful to identify other risk factors that predispose to haemorrhage. Several factors may increase the risk of haemorrhage:
- High intranidal pressure due to high pressure in the feeding arteries or restrictions in venous outflow
- Presence of an intranidal or feeder-related aneurysm
- Deep location
- Small size

In earlier investigations the incidence of aneurysm with AVM was reported to be around 10%. With the advent of superselective angiography and higher resolutions aneurysms are detected in up to 50% of patients with AVM. A uniform system is emerging in which it is proposed that aneurysms related to AVM can be divided into four groups: unrelated dysplastic or incidental, flow-related on proximal feeding vessels, flow-related on distal small feeding vessels, and intranidal. Flow-related distal feeder aneurysms appear to be the source of haemorrhage in up to 50% of the posterior fossa AVM, while intranidal aneurysms appear to be more important in supratentorial AVM.

The relationship between the size of an AVM and its propensity to haemorrhage is unclear and a matter of continuing discussion. Some studies reported that small AVM present more often with haemorrhage than do large AVM. On the other hand it is conceivable that the impression that small AVM carry an increased bleeding risk is a misinterpretation, because small AVM are less likely to cause any other symptom and are therefore less likely to be diagnosed unless they bleed.

#### 3.3.2.3.2 Seizures

Seizures are the second most common presenting symptom and may also be a clinical manifestation of haemorrhage. Seizures that are not caused by haemorrhage are reported as the initial symptom in 20–70% of patients. As expected, seizures are usually associated with AVM that involve the motor/sensory cortex or the temporal lobe.

The natural history of AVM presenting with seizures is less well known. Some studies have postulated a relationship between seizures and a history of haemorrhage. However, it is unclear whether AVM that present with a seizure without a history of haemorrhage are more likely to bleed than AVM that do not cause seizures. Anticonvulsant medication provides satisfactory control of the seizures, and further improvement is usually seen after treatment of the AVM.

#### 3.3.2.3.3 Focal Neurological Deficits

Less common but more dramatic is the syndrome of progressive neurological deterioration. This syndrome is usually associated with large AVM and has been presumed to be caused by the vascular steal phenomenon, in which cerebral arterial hypotension leads to ischaemia in brain ar-
eas adjacent to the lesion. This concept is supported by the fact that occlusion of the feeding arteries can ameliorate symptoms. Progressive neurological deficits have been reported in 1–40% of patients, and the wide range reflects the diversity of definitions of such deficits. Although it appears that steal is a logical haemodynamic consequence of AVM and may well be responsible for progressive neurological deficits, this concept has recently been challenged. Other non-haemorrhagic mechanisms that may explain the progression of deficits are venous hypertension due to arterialisation of the venous system, mass effect, perifocal oedema, and obstructive hydrocephalus from ventricular compression by dilated deep veins.

3.3.2.3.4 Other Manifestations
After haemorrhage and seizures, recurrent headaches are probably the next most common presenting symptom reported in 7–50% of patients, with no distinctive features such as frequency, duration, or severity. Not infrequently, imaging studies are performed because of severe headache and lead to the diagnosis of unruptured AVM.

Several reports suggest a relationship between AVM in the occipital lobe and migraine-like symptoms with visual phenomena and headaches. Also, symptoms clinically indistinguishable from classic migraine were reported to immediately resolve after removal of the AVM. There is no doubt that headache is a symptom that can be related to AVM and may possibly be cured after treatment of the lesion. In particular, patients with new-onset headaches, headaches with a progressive course, headaches with a significant change in pattern, headaches that never alternate sides, and headaches associated with any neurological findings or seizures are substantially more likely to have a secondary cause, such as a tumour or AVM.

Neuropsychiatric disturbances and progressive intellectual deterioration may also be caused by AVM. Interestingly, learning disorders have been documented in most adults with AVM. These patients were significantly more likely to report at least one skill difficulty during their school years than patients with a tumour or aneurysm despite the absence of other neurological symptoms of diseases not diagnosed for another 20 years.

3.3.2.4 Diagnostic Procedures

3.3.2.4.1 Haemorrhagic Presentation
Standard diagnostic work-up in the case of intracranial haemorrhage includes CT and/or MRI and selective angiography. Angiography is not indicated in a patient with a typical hypertensive-type haemorrhage located in the basal ganglia, who has a known history of arterial hypertension and is of advanced age.

These basic examinations are sufficient for emergency management. If initial conservative management is planned for a small haematoma, additional functional diagnostics can be added after the acute phase. On the other hand, in the case of an acute mass haemorrhage with deteriorating neurological condition evacuation of the haematoma should be considered prior to selective angiography. Major vascular malformations can be identified on a CT angiography sequence, which can be added to the plain CT within a short time.

3.3.2.4.2 Epilepsy
Magnetic resonance imaging is the first step in the work-up of epilepsy. This examination can reliably identify intraparenchymal AVM. Selective angiography can subsequently define the angio-architecture. If surgical therapy is considered, functional MRI has become more and more accepted for eloquent locations.

3.3.2.4.3 Other Manifestations
In the case of unspecific neurological deficits, the primary imaging parallels the procedure with epilepsy. If steal phenomena are suspected perfusion studies with SPECT, MRI etc. may be useful, although the impact on therapeutic strategy remains ill-defined.

3.3.2.5 Surgical Therapy

Although there are various kinds of modern treatment modalities for cerebral AVM, surgery is the best-known form of curative treatment, and should be the first choice whenever possible. Since the development of microsurgical techniques, both the operability and the success rates of complete excision have improved remarkably.

Decision-making with cerebral AVM is one of the most difficult aspects of neurosurgical practice. The decision whether to recommend surgery should be based on an objective comparison of the long-term risks presented by the untreated AVM with the more immediate risk of operative treatment. In young patients, especially in the presence of neurological symptoms, attempts at surgical removal are justifiable since the surgical risk, albeit high, is still less than that of the natural history. In middle-aged and older patients with minimal symptoms, a conservative approach seems more reasonable as the risk of therapy may not be less than that of the natural history.

The most popular system for estimating the risk of surgery is the five-point grading score developed by Spetzler and Martin. It incorporates three variables:
- The size of the AVM
- The pattern of venous drainage
- Neurological eloquence of the brain regions adjacent to the AVM
Grade I malformations are small, superficial and located in the non-eloquent cortex, whereas Grade V lesions are large, deep and situated in neurologically critical areas. The size and pattern of venous drainage of an AVM as surgical risk factors are relatively easy to assess, but it is more difficult to assess the eloquence of brain regions. Alterations in gyral contour and translocation of function due to cortical reorganisation in patients with AVM can make it difficult to identify critical areas adjacent to the lesion. Preoperatively, functional MR imaging or positron emission tomography activation studies are helpful in determining eloquent areas of surrounding brain and in providing information on the location of speech, motor, sensory, and visual cortex for treatment-planning decisions. Intraoperatively, identification and preservation of eloquent brain tissue can be facilitated by electrophysiological monitoring, cortical mapping and neuronavigational systems.

In general, small and medium-sized lesions of the convexity that do not involve critical areas should be surgically excised. Compared with radiosurgery or observation alone, surgical excision is highly cost-effective and very efficacious in prolonging quality of life expectancy. In our experience about one-third of AVM can be managed by surgery alone and in two-thirds of the cases embolisation and/or radiosurgery are required before, after or instead of surgery.

Large AVM in critical areas with subcortical wedge-shaped extensions reaching the ventricular wall pose complex management problems. The deep portion usually recruits the choroidal arteries or small vessels that normally supply the basal ganglia, the internal capsule and the thalamus. Bleeding from these vessels during surgery may result in haematocephalus. Furthermore, difficulties in controlling deep feeding vessels, such as the lenticulostriate arterial supply, with the use of a cortical approach or via the ventricle, increases the risk of surgical complications. In these cases it is helpful when the deep arterial supply is obliterated by endovascular embolisation before surgery.

Large high-flow AVM usually require preoperative staged embolisation and some authors recommend multiple-stage resections (Fig. 3.3.12). The stepwise throttling of large AVM seems to minimise the risks of normal perfusion pressure breakthrough, which is hyperperfusion and haemorrhage of the surrounding brain after removal of the AVM.

### 3.3.2.6 Endovascular Therapy

**J. MARC C. VAN DIJK**

An alternative to surgical resection of an AVM is endovascular embolisation. The principle of embolisation is to permanently occlude the nidus of the AVM with either particles or with a liquid substance that quickly solidifies when deposited in a blood vessel. Since particles have failed to result in durable occlusion, nowadays embolics as NBCA (“glue”) and ONYX® are regularly used. Both agents have been demonstrated to be durable after long-term follow-up.

The embolisation procedure is usually performed under general anaesthesia. Through a puncture of the femoral artery, using the Seldinger technique, a catheter is introduced and proceeds to the carotid artery. With a micro-catheter, superselective catheterisation of the feeding pedicle(s) of the AVM is performed, leading to a precise depiction of the nidus and its possible risk factors, e.g. intranidal aneurysms. Since most arterial pedicles not only feed the nidus, but also feed normal brain tissue (so-called “en-passage feeding” of the nidus), it is then attempted to put the tip of the micro-catheter in a position from where only the nidus is fed. In this ideal position the embolic agent is released and pushed forward into the nidus. As a rule, multiple sessions are necessary to achieve a favourable result.

Although the technique of endovascular embolisation is elegant and is appealing to the patient because it obviates a craniotomy, the downside is that a cure is only obtained in about 15% of the cases and that the multiple embolisation sessions lead to cumulative complication rates. From this perspective, embolisation is mostly applied as a part of combination therapy with surgery or radiosurgery of Spetzler 3 or higher AVMs. Embolisation then serves, for example, as a tool to make the nidus smaller and therefore more amenable to radiosurgery, or to occlude deep feeders that are difficult to deal with in a surgical approach.

In conclusion, endovascular embolisation is a well-established modality in the treatment of AVMs. Its associated significant risks must be weighed against its potential benefits in each patient. Therefore, it has earned its place mostly in a multimodal treatment setting.

### 3.3.2.7 Stereotactic Radiosurgery for Cerebral Arteriovenous Malformations

**ANDRAS KEMENY**

#### 3.3.2.7.1 Definition

Single-fraction, highly focused and stereotactically guided radiation to a small volume within the intracranial compartment.

#### 3.3.2.7.2 Synonyms

Radiosurgery, SRS, STRS, and Gamma knife surgery.
Fig. 3.3.12  a,b Example of a large right parietal arteriovenous malformation supplied by the middle, c,d anterior and e posterior cerebral arteries as well as by f the external carotid artery. This 63-year old man presented with haemorrhage. Venous drainage takes place via the superior sagittal sinus. Treatment consisted of combined embolisation with microsurgery
3.3.2.7.3 Historical Notes
- 1951: the concept was introduced by Lars Leksell (1907–1986)
- The first treatments were carried out in the 1950s with an X-ray tube attached to a stereotactic arc
- 1954: cross-fired proton beam treatments were developed at the Lawrence and Berkeley laboratory
- 1968: the first Gamma knife (GK) treatment was carried out
- 1985: the modified linear accelerator was developed by Colombo
- 2000: the automatic positioning system (APS) was developed for the GK

3.3.2.7.4 Principles of Radiosurgery
The treatment is usually carried out under local anaesthetic, as a day-patient, from children or claustrophobic individuals. The principle steps are:
- Stereotactic imaging
- Dose planning
- Dose delivery

3.3.2.7.4.1 Stereotactic Imaging
First, a set of standard reference points, or a “fiducial system”, is established around the head using a stereotactic frame.

The lesion is demonstrated by digital subtraction angiography (DSA), aided by an MRI and/or CT to provide axial information. In selected rare cases axial images alone may be sufficient. The contours of the target are delineated.

3.3.2.7.4.2 Dose Planning
The aim is to match the radiation treatment to the contour of the lesion with high conformity. Inclusion of adjacent normal tissue would lead to side effects and complications whereas omission of part of the lesion reduces efficacy. In addition to matching the shape, care is taken to avoid passing the radiation beams through eloquent structures adjacent to the lesion or even at a distance (e.g. the lens of the eye). This is achieved by plugging some of the radiation sources in the Gamma knife or choosing the entry of the beams in linear accelerator (LINAC) techniques (see below).

3.3.2.7.4.3 Dose Delivery
The two basic technologies for dose delivery are the Gamma knife and LINAC. In terms of the number of patients and publications, the field is dominated by the Gamma knife and thus it is considered the “gold standard”.

3.3.2.7.4.3.1 Gamma Knife
A concentric array of 201 Co\textsuperscript{60} sources provides the output of gamma rays, highly focused to the target by a precision engineered shield (Fig. 3.3.13). The combination of fixed sources and collimators results in 0.1-mm targeting precision.

3.3.2.7.4.3.2 LINAC
There are several LINAC techniques. Modified radiotherapy LINACs with a secondary collimator system or dedicated radiosurgery LINACs can be used. A single-focus multiple non-coplanar arc and conformal block techniques are the most widely applied. The former means that the radiation source is moved along several arcs, while the latter involves manufacturing an irregularly shaped portal for each beam. The so-called micro-multileaf collimator consists of a series of individually motorised tungsten leaves that can be positioned automatically to create any desired beam shape. In the intensity modulation technique (IMRT) the dose is delivered in different intensities across the lesion. The collimator leaves dynamically open and close under computer control to selectively expose or shield portions of the target. This technique is in its early stages of development and is still under clinical evaluation.

3.3.2.7.5 AVM Treatment
The target is the nidus of the AVM. The nidus is defined as a network of poorly differentiated and immature vessels to which feeding arteries converge and from which engorged veins drain.

Fig. 3.3.13 The Leksell Gamma knife
Mechanisms of action:
- Predominant factor: endothelial proliferation and hyalinisation in the vessel wall.
- Secondary factor: myofibroblast development in the adventitia.

### 3.3.2.7.6 Patient Selection Criteria

Management of AVM is multidisciplinary. For selection criteria see Table 3.3.4.

### 3.3.2.7.7 Suitable Targets

Most AVMs are suitable. The ideal lesion is small (<3 cm), compact, and in a deep and eloquent position. Features of unsuitable AVMs include:
- Pure fistula (endovascular treatment is usually successful)
- Diffuse nidus (often untreatable by any method)
- Wrapped around an eloquent structure (e.g. the optic nerve in Wyburn–Mason syndrome)
- Most dural AVMs (large flat volume or no true nidus)
- Maximum diameter > 4 cm, unless very compact

### 3.3.2.7.8 Results

Outcome is dependent on lesion size and peripheral dose. In small (< 2 cm) AVMs 85–95% obliteration rates are reported (Figs. 3.3.14, 3.3.15).

### 3.3.2.7.9 Complications

- Swelling on MRI: mean onset at 11 months, occurs in 2.5% of patients
- Symptomatic focal neurological deficit (paresis, visual field, worsening seizures) or raised ICP, in 2–8% of patients
- Risk factors: eloquent position (e.g. brain stem, thalamus), size > 3.5 cm, peripheral dose > 25 Gy, non-conformal dose plan is too simple

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#### Table 3.3.4 Selection criteria for AVM treatment

<table>
<thead>
<tr>
<th>Radiological factors</th>
<th>Patient factors</th>
<th>Departmental factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Surgical” (Spetzler–Martin)</td>
<td>Clinical state (after haemorrhage)</td>
<td>Skills available (surgery, endovascular, radiosurgery)</td>
</tr>
<tr>
<td>Size</td>
<td>Presentation</td>
<td></td>
</tr>
<tr>
<td>Site (eloquence)</td>
<td>Bleed? Epilepsy? Steal phenomenon?</td>
<td></td>
</tr>
<tr>
<td>Draining veins (deep or superficial)</td>
<td>Age (lifetime risk)</td>
<td></td>
</tr>
<tr>
<td>Radiosurgical</td>
<td>Expectation and wishes</td>
<td></td>
</tr>
<tr>
<td>Diffuseness of the nidus</td>
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<tr>
<td>Shape of the nidus</td>
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<tr>
<td>Interventional radiology</td>
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<tr>
<td>Angio-architecture, nidal aneurysm</td>
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</tbody>
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**Fig. 3.3.14** Arteriovenous malformation at radiosurgery

**Fig. 3.3.15** Two-year follow-up angiography showing complete obliteration with radiosurgery
3.3.2.7.10 Options for Large AVMs

- Expectant policy
- Stereotactic radiosurgery
  - Lower dose – less effective
  - Partial volume – aiming at the fistulous point(s)
  - Staging (radiosurgery performed on different parts with some months between treatments)
- Volume reduction
  - Surgery
  - Embolisation

3.3.3 Cavernoma

3.3.3.1 Characteristics

- A well-defined mulberry-like vascular hamartoma usually consisting of a network of vessels with a single endothelial layer without intermingled brain parenchyma.
- Cavernoma may develop de novo and have the potential to grow and cause hemorrhage.
- Treatment can be surgical or conservative

3.3.3.2 Pathogenesis

The biological behavior of cavernomas is not yet completely understood. They are thought to arise during the early stages of embryogenesis and grow according to malformative mechanisms. Blood flow changes may be the cause of the formation of dilated blood vessels. Cavernomas have been considered as static and non-growing lesions for decades; however, growth of these lesions has been frequently reported. Furthermore, de novo formation of cavernomas with and without prior radiotherapeutic induction has also been described. Consequently, the question arises whether these lesions are of a developmental or acquired nature and whether these lesions bear a proliferating or neo-angiogenetic capacity, or both. Immunohistochemical studies showed the expression of both proliferative and neo-angiogenetic factors. Therefore, cavernomas should not be considered as static, but rather as active lesions. Neo-angiogenesis seems to be more prominent in superficial cavernomas than in deep lesions and is not associated with prior hemorrhages.

Cavernomas most often occur sporadically, but may also be inherited dominantly with incomplete penetrance. Patients may have single or multiple malformations. Autosomal dominantly inherited familial CCM has been estimated to occur with a frequency of 1:2,000–1:10,000. It is generally associated with the occurrence of multiple CCMs. In addition to a heterozygous germline mutation in one of three genes, CCM1, CCM2 or CCM3, a second somatic mutation appears to be required for lesion genesis. In familial cases, mutations in the gene CCM1 account for nearly all Hispanic and approximately 40% of non-Hispanic familial CCM cases. With very few exceptions, mutations in CCM genes are truncating or the result of large genomic rearrangements. which facilitates medical genetic counselling.

Selected Reading

### 3.3.3.3 Epidemiology

Studies based on large necropsy series estimated the incidence of cerebrovascular malformations in general to vary between 0.1 and 4%. Incidences of 0.02–0.9% of cavernous malformations were reported, showing a considerable range.

Large studies show agreement that there is no difference in the sex incidence of cavernomas. The range in age varies between neonates and the ninth decade, with a median of 34 years. The highest incidence seems to occur between the third and the fifth decade. The incidence of pediatric cases accounts for approximately one-fourth of the total cases.

A major proportion of the lesions are located supratentorially. In a large series of cases, 67% of the lesions were located supratentorially, 26% were located infratentorially, and 6% of the lesions were found in the spinal cord respectively.

### 3.3.3.4 Symptomatology

Due to the heterogeneity in size, location and propensity of bleeding, cavernous angiomas may cause a wide spectrum of clinical symptoms with frequent changes over time such as repeated exacerbation of complaints and alternating periods of remission. In some instances cavernomas may simulate multiple sclerosis due to the fluctuating progressive neurological deficits. Classically, the clinical syndromes have been divided into the broad categories of seizures, focal neurological deficits and hemorrhages. Neurological disorders may occur at any site of the lesion, usually produced by intralobular or perilesional hemorrhage (see Table 3.3.5). Neurological deficits may be transient, progressive, recurrent or fixed.

Concerning the indication for surgery to treat epileptic seizures caused by cavernomas, it is generally agreed that the excision of the lesion improves seizure control most patients.

### 3.3.3.5 Diagnostics

Today, digital subtraction angiography (DSA) is considered rather an unnecessary diagnostic tool. The most sensitive and therefore the most important imaging study is magnetic resonance imaging (MRI), with particularly high sensitivity of gradient-echo sequences (Fig. 3.3.18). However, since cavernomas are often associated with developmental venous anomalies (DVA), in rare instances (for example, for planning surgical approach) the angiography may complete a preoperative diagnostic work-up for a patient suffering from a cavernoma.

<table>
<thead>
<tr>
<th>Table 3.3.5 Symptomatology of cavernoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hemorrhage (rate per year: 0.4–10.6%)</td>
</tr>
<tr>
<td>• Deep-seated (brain stem, thalamus, basal ganglia) and lesion with prior history of hemorrhage bear a higher risk compared with superficial cavernomas</td>
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<tr>
<td>• Severe headache caused by hemorrhage</td>
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<tr>
<td>• Often causes epilepsy (temporal) or</td>
</tr>
<tr>
<td>• Cranial nerve palsies (brain stem)</td>
</tr>
</tbody>
</table>

In daily clinical practice, T1- and T2-weighted triplanar MRI studies constitute the most important diagnostic tool, not only to establish the diagnosis of cavernoma, but also to define the exact size, location and extent of the lesion, as well as other features such as multiplicity and associated hydrocephalus, or to estimate the condition of the adjacent brain parenchyma and the presence of an intra- or extralesional bleeding. Moreover, postoperative follow-up MRI is indicated in all surgical cases in order to confirm the completeness of cavernoma resection, and later, to assess a possible de novo formation (see Figs. 3.3.16, 3.3.17).

### 3.3.3.6 Therapy

#### 3.3.3.6.1 Stereotactic Radiosurgery

The use of radiosurgical treatment for cavernomas is controversial. Considering the high surgical risk in patients with deep-seated cavernomas, radiosurgery has been introduced in analogy with the successful radiosurgical treatment of arteriovenous malformations. The main goal of radiosurgical treatment must be a significant reduction in the risk of bleeding, especially after a latency period of 2 years. This time delay derives from the experiences with radiosurgical treatment of AVMs, 2 years being the time period over which radiosurgery exerts its effects on these high-flow malformations. Whether the same effect can also be achieved in low-flow malformations such as cavernomas is not yet proven. Different from AVMs, however, MRI or angiography cannot be used to follow the risk of bleeding and there is no obvious end point in evaluating the treatment results.

In particular, Gamma knife treatment may result in a high incidence of neurological sequelae caused either by radiation necrosis or by post-treatment hemorrhage, and even fatal cases have been reported. In contrast to the optimistic view of few studies claiming that the stereotactic radiosurgery of small, deeply situated cavernomas may be superior to the results of microsurgical resection, recent publications have clearly shown that stereotactic radiosurgery appears to be an inappropriate treatment for the prevention of bleeding from a cavernoma.
Preoperative Considerations, Indication for Surgery

The division of cavernous malformations into supratentorial (and cerebellar) and brain stem lesions is helpful in daily clinical practice as there are significant differences in the clinical presentation and management of these subgroups.

Surgery for supratentorial (and cerebellar) cavernomas in young patients with mild or non-disabling symptoms might be questionable. However, in view of the cumulative risk of hemorrhage or neurological disability over time, an elective surgical resection might be indicated for some of these individuals. More problematic are the lesions located either within cortical or subcortical eloquent areas and within other functionally important regions such as basal ganglia and thalamus or those located within the third ventricle, the corpus callosum and cingulate gyrus, the paraventricular and paratrigonal region as well as the deep temporal area. However, recent publications have demonstrated that lesions within all such locations can also be removed safely and with acceptable morbidity.

Brain stem cavernomas account for 9–35% of all cavernomas. This subgroup of lesions constitutes a special entity. The hemorrhage rate of these cavernomas is up to 30 times greater than that of other locations. Due to their anatomy hemorrhage is more likely to cause severe neurological deficits. Brain stem cavernomas represent a formidable treatment challenge because of their location within a parenchyma responsible for critical neurological function, rendering them much more difficult to remove than those in other locations.

Timing of Surgery, Goals of Surgery

For the timing of surgery, the following factors play an important role: the presence or absence of hemorrhage, the presence or absence of intractable seizures, the acuteness and the mass effect of hemorrhage, the patient's
Vascular Diseases

Precise preoperative planning of the surgical approach based on neuroimaging, and technical adjuncts such as image-guided localization and electrophysiological methods (see also below). Precise planning, intraoperative orientation, localization of anatomical landmarks, and avoidance of vital structures are important issues in surgery for cerebral cavernous malformations. With features like route planning, structure identification, and facilitation of anatomical understanding, navigation systems have the potential to aid the resection of cerebral cavernomas. Neuronavigation contributes to the definition of ideal vectors for the approach, an optimized positioning of craniotomy sites, subsequently a minimized cortical trauma, and it aids anatomical understanding, resulting in enhanced confidence and increased safety of surgery (see Fig. 3.3.17).

The goals of surgery are summarized in Table 3.3.6.

### 3.3.3.6.4 Planning, Neuronavigation

The surgical technique includes precise preoperative planning of the surgical approach based on neuroimaging, and technical adjuncts such as image-guided localization and electrophysiological methods (see also below). Precise planning, intraoperative orientation, localization of anatomical landmarks, and avoidance of vital structures are important issues in surgery for cerebral cavernous malformations. With features like route planning, structure identification, and facilitation of anatomical understanding, navigation systems have the potential to aid the resection of cerebral cavernomas. Neuronavigation contributes to the definition of ideal vectors for the approach, an optimized positioning of craniotomy sites, subsequently a minimized cortical trauma, and it aids anatomical understanding, resulting in enhanced confidence and increased safety of surgery (see Fig. 3.3.17).

### Table 3.3.6 Goals of surgery

1. To prevent re-bleeding, which implies total removal of the lesion
2. To minimize damage to the surrounding normal parenchyma, which implies designing a special and individually tailored approach in each patient
3. To preserve an associated venous anomaly (that is often associated and can be diagnosed by MRI and angiography, see above)
Image-guided surgery provides genuinely useful feedback to the surgeon in preoperative the anatomical orientation, planning and simulation of the surgical approach, intraoperative navigation, avoidance of vital neurovascular structures and assessing the extent of possible resection. It provides warning of the proximity of important anatomical structures and identifies the possible location of the residual parts of any lesion.

Current image guidance is dependent on preoperative digital images and the impact of brain shift on image guidance has been recognized. As it is well known that deep structures are remarkable for a small magnitude of post-imaging brain distortion, intraoperative image updating might not be required for the surgical treatment of centrally located lesions. Intraoperative ultrasound can serve as an alternative or an addition to the standard neuronavigation based on preoperatively derived images. As well as intraoperative CT or MRI it is one of the modalities for image-updating that is currently in use. Features of sonography are its flexibility and its simple and independent application. However, intraoperative ultrasound images typically have a low signal-to-noise ratio (see Fig. 3.3.18). Its application, especially when integrated into a neuronavigation system, may be particularly help-

![Fig. 3.3.18 Neurosonography and its integration into neuronavigation. Upper left: male patient (aged 32) with a high frequency of pharmaco-resistant epileptic seizures, axial gradient-echo MRI displays the left frontal subcortical cavernoma. Lower left: intraoperative ultrasound image showing both the sulcal anatomy and the hyperechogenic cavernoma. Rest of the images (same patient): intraoperative screen shot of a neuronavigation system with integrated image-guided ultrasound showing the tip of the pointer at the sulcus where the access was planned (Left row: axial, coronal, and sagittal view). Note the black arrow indicating the planned sulcal approach. The right side of the screen shot illustrates (lower part) the ultrasound image with nice visualization of the sulcus. Furthermore, a MRI image corresponding to the same plane as seen in the ultrasound image is shown (center). The upper part of the right side of the screenshot displays the fusion of both previously described images. In order to better understand the fused images, the ultrasound part of this composed image is transcribed into green, enabling the surgeon to gain a better understanding of which part of the information derives from which imaging modality (MRI or ultrasound). Note the white arrow within this image parallel to the sulcal approach to the cavernoma. Furthermore, this screenshot demonstrates the effect of brain shift, since the cavernoma is not seen in the MRI slice (center part of right side of the screen shot) as expected, which is an effect of the shift that was caused by CSF loss after opening of the dura in this case. Consequently, intraoperative ultrasound may help to overcome the problems of shifting after CSF release.](image-url)
ful for both the sulcal approach planning after craniotomy and the deep cortical incision (see Fig. 3.3.18). However, even with sophisticated equipment and high resolution, the spatial resolution is not superior to that of MRI.

### 3.3.3.6.5 Surgical Approach

A surgical approach that adequately exposes a cavernoma is essential for the success of the procedure. The majority of authors selected the surgical approach according to the relationship between the cavernoma and the pial or ependymal surface of the brain. For most supratentorial cavernomas, simple hemispheric craniotomies centered on the sulcus as the point of intended access offer sufficient visualization for microsurgical manipulation. For deep-seated lesions, standard approaches such as the pterional, suboccipital midline, retromastoid or subtemporal approaches may not be sufficient in many instances. Specially designed access routes and procedures may offer several advantages, particularly for complex and deep-seated cavernomas. For example, a median suboccipital approach exposing the rhomboid fossa is one of the most frequently used routes for accessing brain stem cavernomas. Although an intertensillar approach preserving the cerebellar vermis anatomically is advocated by the majority of neurosurgeons, some still split the vermis in order to expose the floor of the fourth ventricle. However, transection of the posterior inferior vermis may badly impair tandem gait. It is therefore advisable to use the intertensillar approach, which yields sufficient exposure of the floor of the fourth ventricle in all cases. For ventrolaterally located lesions within the pons or the midbrain, a posterior, subtemporal, transtentorial approach with preservation of the trochlear nerve is often required for adequate exposure.

### 3.3.3.6.6 Intraoperative Electrophysiological Monitoring

Particularly for deep-seated cavernomas such as brain stem and basal ganglia lesions, intraoperative neuromonitoring has gained increasing importance.

In these cases, monitoring of motor-evoked potentials (MEP) by high voltage vault stimulation, the continuous monitoring of somatosensory-evoked potentials (SSEP) as well as brain stem auditory-evoked potentials (BAEP) are used routinely in many centers. Critical SEP changes were defined as more than 50% amplitude reduction or latency delays of more than 10%, or an increase in the central conduction time of more than 1.0 ms. Likewise, BAEP amplitude reductions in waves III, IV or V of more than 50% and/or increases in the latencies of the fifth peak of the interpeak latency difference (P5–P1) of more than 1 ms were considered critical.

Furthermore, the technique of phase reversal recording may be used to identify the central sulcus during surgery for primary cortical cavernomas localized within the pre- or post-central gyrus.

### 3.3.3.6.7 Dissection Techniques

Apart from the exact localization and the optimal cortical incision, the dissection technique may significantly influence the outcome after surgery for removal of cavernomas. The identification of a hemosiderin-colored brain surface may guide the surgeon to the correct cortical incision; however, in subcortical or deep-seated lesions the brain surface might not be altered. In these cases, we use the image guidance techniques as well as intraoperative ultrasound image updates (in combination with the functional data from the electrophysiology) to make the decision where to incise the brain surface or where to open a sulcus in order to gain the closest access to a lesion in relation to the brain surface.

Once the cavernoma is identified, it is mandatory to stay within the correct cleavage between the lesion and the healthy parenchyma. A cottonoid should be placed between the separated portions of the malformation and the parenchyma. Bipolar coagulation disconnecting tiny feeders and draining vessels with microscissors is necessary. A high-power magnification and the use of fine bipolar coagulation forceps with low power to limit the spread of current into the adjacent tissue should be used, particularly for deep-seated cavernomas. Associated developmental venous anomalies should be maintained.

Piecemeal removal is required when the parenchymal opening is smaller than the lesion; however, small lesions may usually be shrunk into their cavity and removed in one piece. Once, the cavernoma is removed, it is mandatory to inspect the entire resection cavity in order to exclude any residual part of the lesion. The use of lasers for brain stem cavernoma surgery, as described more than a decade ago, has not gained general acceptance.

Table 3.3.7 shows three aspects that have gained general acceptance in cavernoma surgery.

### 3.3.3.6.8 Postoperative Outcome, Complications, Morbidity and Mortality

Defining the outcome of surgery for cavernoma is a difficult matter. In spite of the clear goals of surgery mentioned above, there is no ultimate method to demonstrate the cure from a cavernous malformation that may even

**Table 3.3.7 Recommendations for surgery**

1. Complete removal of the lesion
2. Avoid injury to an associated venous malformation
3. Leave the surrounding hemosiderin-loaded gliotic parenchyma intact in case of brain stem cavernomas and remove this layer in subcortical epilepsy cases
show de novo appearance after apparently complete removal. Even high-resolution MRI techniques may not furnish 100% evidence of total resection of the lesion and thus elimination of the bleeding risk (see Fig. 3.3.17). Moreover, the surgical procedure itself may cause various side effects that may persist or gradually disappear. Postoperatively, patients may be in the same condition as preoperatively, they may be improved or neurologically deteriorated.

Some patients treated in the 1980s (when surgeons worldwide had little experience with cavernomas) suffered from severe complications, but with increasing surgical experience the outcome results have dramatically improved. Recently, the outcome of even deep-seated lesions (brain stem or basal ganglia) has usually been excellent, with minimal or virtually no surgical morbidity. In the few cases with deterioration, the operative morbidity is usually caused by an edema of critical (brain stem) parenchyma, and includes various degrees of internuclear ophthalmoplegia, worsening of hemiparesis, facial or abducens paresis, gaze palsy, facial, truncal and/or extremity numbness, dysphagia, dysarthria, gait ataxia, etc. In most of the cases the neurological dysfunction resolves completely within the first 6 months of surgery.

### 3.3.3.7 Conservative Treatment

Patients with an established diagnosis of cerebral cavernous malformation who present without gross hemorrhage, seizures or other specific symptoms are candidates for clinical observation and repeated imaging. Non-operative management may be the best modality in patients with purely incidental lesions as well, particularly when the malformation is located deeply within functional areas of the brain, or in individuals harboring multiple lesions, even when accessible malformations have already been resected. Pharmacological treatment is indicated in patients suffering from epileptic seizures. We do not recommend the medication of aspirin for patients suffering from cavernoma.

### 3.3.4 Cranial Dural Arteriovenous Fistulas

#### J. Marc C. van Dijk

### 3.3.4.1 Introduction

Dural arteriovenous fistulas (DAVFs) are a unique neurovascular entity, representing 10–15% of all intracranial arteriovenous lesions. They consist of one or more true fistulas, direct arteriovenous connections without an intervening capillary bed, localized within the leaflets of the dura mater. This anatomical location clearly discerns DAVFs from the pial arteriovenous malformations (AVMs). Furthermore, it is generally accepted that DAVFs are acquired, as opposed to the pial AVMs, which are thought to be congenital. For this reason, although in the literature in many instances DAVFs have also been referred to as “malformations,” in this chapter the term “fistulas” is preferred to avoid confusion.

Dural arteriovenous fistulas were rarely identified before 1960; however, since then have emerged as a distinct entity owing to the advances in angiography, such as magnification and subtraction techniques and selective arterial catheterization. Although case reports had already appeared in the 1930s, the first concept of spontaneous DAVF was introduced in 1951 by Fincher. At first, the dural lesions were regarded as benign in comparison to pial AVMs. In the early 1970s, pioneers such as Aminoff, Newton, and Djindjian broadened the anatomical and clinical knowledge of DAVFs. In 1972, the concept arose that the pattern of venous drainage might relate to the clinical signs and symptoms; however, it was not until 1975 that the risks of particularly the cortical venous drainage (CVR) were recognized. Djindjian et al. made the first classification based on this concept, stating that DAVFs with a free outflow into a sinus were relatively harmless, while lesions with CVR could produce severe complications.

The 1980s were dominated by three extensive reports in the literature. In 1984, Malik et al. published their review of 223 cases with the message that restriction of venous outflow was a key factor; however, they did not emphasize the importance of CVR. Lasjaunias et al. published a meta-analysis of 191 cases, spreading the message that focal neurological symptoms were dependent on the territory of draining veins and that CVR carries a high risk of intradural bleeding. The third report by Awad et al. reviewed 377 cases, mostly taken from the literature. The latter introduced the term “aggressive” for lesions presenting with a hemorrhage or a focal neurological deficit and emphasized the importance of CVR, venous ectasias, and galenic drainage.

### 3.3.4.2 Pathogenesis

The etiology of cranial DAVFs is unknown, although much speculation has been published. It has already been mentioned that these lesions are generally accepted to be acquired, described after surgery, after head trauma, and in relation to sinus thrombosis; however, the exact pathway has never been unequivocally proven.

Two hypotheses of pathogenesis have been proposed. The first claims that cranial DAVFs arise from existing “dormant” channels between the external carotid circulation and the venous pathways within the dura mater. Histopathological and radio-anatomical studies have shown that these communications are normally present in the
dura. These channels open owing to the venous hypertension associated with sinus thrombosis or sinus outflow obstruction. A variation on this theme is the reported existence of thin-walled venous pouches within the dura, close to small arteries. Rupture of these fragile pouches easily induces arteriovenous communications within the dura.

The second hypothesis claims that DAVFs are the result of newly grown vascular channels due to provoked angiogenetic factors. These factors, such as VEGF and bFGF, originate either directly from the organization of a sinus thrombosis or indirectly induced by an increased intraluminal venous pressure through a mechanism of tissue hypoxia.

Histopathologically, the true arteriovenous fistula has no intervening capillary bed and consists of small venules with a diameter of approximately 30 μm. These vessels have been called “crack-like vessels,” because they look like cracks in the dural sinus wall after histological staining. Furthermore, intimal thickening of both dural arteries and dural veins has been observed. Although the fistula has initially been described within a thrombosed sinus, the general acceptance is that the fistula is located within the wall of the sinus. This also explains the existence of the type of DAVF that drains directly into the pial venous network, without drainage into the venous sinus.

### 3.3.4.3 Classification

In concert with several authors the terms “benign” and “aggressive” are used throughout this section in relation to the different types of cranial DAVFs and their typical signs and symptoms. In this concept, clinical features such as non-hemorrhagic neurological deficits (NHND), hemorrhage, and death are considered aggressive, while complaints of chronic headache, pulsatile bruit, and orbital symptoms including cranial nerve deficits owing to cavernous sinus involvement are considered benign, even though the complaints might be regarded as intolerable by the patient.

Several classification schemes for cranial DAVFs have been introduced, of which the classifications of Borden and Cognard are the most widely used (Tables 3.3.8, 3.3.9). Although the three-step classification of Borden has the advantage of being relatively simple to apply, the Cognard classification (a revision of the Djindjian classification scheme) is theoretically superior, as it incorporates the additional effect of the flow-direction in the dural sinus. Both classifications have been validated in the literature.

In this perspective, cranial DAVF categorized as Borden I, Cognard I or Cognard IIa are to be considered benign, while all higher Borden and Cognard grades are to be categorized as aggressive DAVFs, with all their consequences.

### 3.3.4.3.1 Benign DAVFs

The absence of CVR can be considered as a predictor of both a benign presentation and an uneventful natural disease course. Regarding benign DAVFs, few publications with clinical and angiographic follow-up data have been published. Davies et al. reported their experience with a cohort of 54 cases without CVR over a mean follow-up period of 33 months. Only one of the patients (2%) died after palliative endovascular treatment, without angiographic conversion into a lesion with CVR. This unusual course of a predicted benign disease was explained to be the result of venous hypertension owing to functional obstruction of the superior sagittal sinus. In the rest of their cohort Davies et al. found that the majority of cranial DAVFs without CVR behave in a benign fashion and that the focus of therapeutic efforts, if at all necessary, should be directed toward palliation rather than toward angiographic cure. Cognard et al. reported around 7 patients who initially had a DAVF without CVR, but following treatment experienced after a mean 7 years a worsening of the clinical symptoms. In a more recent study by Satomi et al., the chronological change in clinical symptoms and angiographic features of 117 patients with a benign cranial DAVF was evaluated. None of the cases presented with either intracranial hemorrhage or NHND; therefore, the preferred management of these lesions was observational. Palliative treatment, never aiming at cure,
was administered if the patient had intolerable symptoms or if there were pressing ophthalmologic indications. Using this conservative management 98% of the patients achieved a tolerable and often self-limiting disease.

### 3.3.4.3.2 Aggressive DAVFs
Cranial DAVFs with CVR are to be considered aggressive lesions (Fig. 3.3.19). Their behavior includes the high likelihood of intracranial hemorrhage, NHND, and death at presentation. However, for a long time the natural disease course after the aggressive presentation was less well understood, with the publication during the 1990s of several reports with contradictory messages. These reports all had their limitations, varying from a very short follow-up to mixing up benign and aggressive lesions. In 2002, Van Dijk et al. reported a prospective study on DAVFs with persistent CVR, with a mean follow-up of 4.3 years. It was found that the natural disease course of aggressive DAVFs had an annual mortality rate of 10.4%. In addition, the annual risks of subsequent intracranial hemorrhage or NHND after presentation were 8.1% and 6.9% respectively, adding up to a 15.0% annual event rate. These numbers mandate prompt diagnosis and treatment of these aggressive lesions.

### 3.3.4.4 Diagnostic Procedures

#### 3.3.4.4.1 CT
Due to the absence of CVR, benign DAVFs are nearly always occult on CT imaging. In the case of an aggressive DAVF, unenhanced CT images may show hypodensities, representing areas of edema or venous ischemia. Abnormally enlarged pial veins can be depicted due to their increased density in comparison to the brain parenchyma. Contrast-enhanced CT shows enhancement of the refluxing cortical venous network.

#### 3.3.4.4.2 MRI/MRA
On MRI, it is very challenging to detect a benign DAVF. MR angiography is more sensitive, although it still has its limitations in depicting the fistula. In the case of an aggressive DAVF, MRI is better able to visualize the abnormalities, characterized by flow voids on the cortex corresponding to dilated pial vessels. The brain parenchyma can show T2 hyperintensity in the white matter secondary to the venous hypertension leading to congestion of the brain, especially in the deep white matter. The venous hypertension will eventually lead to gliosis, which bears the same signal characteristics as edema on T2-weighted images. The differential diagnosis for T2 hyperintensity includes sinus thrombosis (with venous infarction or venous congestion), de/dysmyelination, and neoplasm. However, the combination of T2 hyperintensity and a surplus of pial vessels is highly suggestive of a vascular malformation and mandates prompt angiography.

#### 3.3.4.4.3 Digital Subtraction Angiography
Angiography still is obligatory for confirming the diagnosis of DAVF and for planning treatment. Selective contrast medium injections into the different branches of the external carotid artery will reveal rapid arteriovenous shunting through the fistula into the cerebral venous system. The transit time of contrast medium injected selectively into the internal carotid artery is usually delayed, compatible with venous congestion. The main goal in the imaging of cranial DAVFs is definitely the scrutinizing of the venous phase when there is CVR. Other important findings are outflow obstruction owing to venous sinus occlusion, which can result in extracranial drainage via collateral routes, including the orbital system, and augments the risk of retrograde flow into the cortical and cerebellar veins.

Finally, in diagnostic imaging, the existence of multiple DAVFs within one patient should be considered a possibility, since this scenario is reported to have a frequency of 7–8%.

### 3.3.4.5 Therapeutic Options
In general, treatment of a lesion is only to be performed if this treatment is expected to ameliorate the natural disease course. The natural history of cranial DAVFs is
related to the venous drainage pattern, especially the existence of CVR.

In benign cranial DAVFs, a 98% beneficial disease course without curative treatment has been reported, indicating that observation with timely angiographic re-evaluation is the best available treatment. Therefore, only in those patients who suffer intolerable symptoms should treatment be limited to diminishing focal symptomatology with palliative arterial endovascular embolization. The sacrifice of a venous sinus is contra-indicated at all times.

Aggressive cranial DAVFs demonstrate severe complications in their natural disease course, thus mandating aggressive treatment. Disconnection of CVR is obligatory to protect the patient from the sequelae of intracranial hemorrhage or NHND. Since partial treatment will not lead to risk reduction, the achievement of a cure by treating the CVR is essential. With both endovascular embolization and surgery it is possible to cure DAVFs. Surgery used to be the gold standard, but with the introduction of liquid adhesive embolics (NBCA) showing a durable result without recanalization, both techniques are regarded as equal. It is not necessary to achieve a complete resection or obliteration of the fistula; simple disconnection of the refluxing cortical veins to the brain parenchyma will yield the same result.

Although reported occasionally, radiosurgery plays no role in the treatment of cranial DAVFs, with or without CVR. Benign cranial DAVFs need no treatment and any additional risk from radiosurgery is too great. Aggressive cranial DAVFs have a bad disease course after their presentation, with, untreated, an annual event rate of 15%, often leading to severe disability or death. Since the expected results of radiosurgery come only years after treatment, this delay is unacceptable.

### 3.3.4.6 Pearls

- Cranial DAVFs can be classified as benign or aggressive based on the presence of cortical venous reflux to the brain parenchyma (CVR).
- DAVFs without CVR have a benign presentation and disease course; as a consequence they can be observed, with only palliative measures in patients with intolerable signs and symptoms.
- Be aware of the small chance of a benign DAVF converting into an aggressive DAVF; timely clinical and angiographic re-evaluation is mandatory.
- If untreated, an aggressive DAVF carries an annual event rate of 15%, with an annual mortality rate of 10.4%.
- Selective disconnection of the CVR, either by endovascular embolization or surgery, is the treatment of choice in aggressive DAVFs.

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**3.3.5 Stenotic and Occlusive Vascular Disease**

**VLADIMIR BENĚŠ**

### 3.3.5.1 Pathogenesis

#### 3.3.5.1.1 Physiology and Pathophysiology

The disease underlying 90–95% of ischemic strokes is atherosclerosis. Since atherosclerosis is a systemic disease, the majority of stroke patients suffer other atherosclerosis-related diseases as well – ischemic heart disease, diabetes mellitus, arterial hypertension, and ischemic disease of the lower extremities. Fat metabolism imbalance is frequent among these patients.

The brain represents only 2% of the total body weight, but consumes 15% of the cardiac output (approximately 750 ml of blood/min) and utilizes 20% of oxygen. Cerebral blood flow (CBF) averages 50 ml/100 g brain tissue/min. Brain utilizes 90–100% of glucose supplied by oxidative phosphorylation. Glucose consumption under normal conditions is 4.5–5.5 ml/100 g brain tissue/min and oxygen consumption is 3.0–3.5 ml O₂/100 g brain tissue/min. Most sensitive brain cells (hippocampal area CA1) survive some 3–5 min without oxygen. Brain–blood flow autoregulation is the ability to compensate for fluctuating levels of systemic arterial pressure. CBF remains stable within the range of systemic arterial pressure of 60–160 torr in healthy patients. The brain's vascular supply consists of a system of collaterals: four major arteries (bilateral internal carotid arteries – ICAs and bilateral vertebral arteries – VAs) constitute the circle of Willis, which is able to redistribute blood supply (in some cases even if only one of the main arteries is patent). This system is strengthened by collaterals between extra and intracranial vascular regions (ophthalmic artery, muscle branches of the VA, etc.). The most important part of the brain – the brainstem – is mainly supplied by the basilar artery (BA), which is supplied by both VAs and secured by both posterior communicating arteries (PcomA). Occlusion of one VA is almost always asymptomatic. On the other hand, untreated BA thrombosis is almost always fatal. Rapid thrombosis of the ICA usually causes a major stroke with ischemic lesions in the whole middle cerebral artery (MCA) territory. Slow progressive occlusion allows for enlargement and creation of collateral vessels, blood redistribution by the anterior communicating artery (AcomA) and PcomA, and thus may pass asymptptomatically. Occlusion of the basal ganglia and brainstem perforators almost invariably causes permanent neurological lesions.

The clinical picture depends on the rapidity of occlusion, and the depth and length of ischemia. Neurological deficit appears if the CBF decreases to < 30 ml/100 g brain tissue/min. EEG disappears with CBF < 18 ml/100g brain
Macroangiopathy (major vessels’ disease – both “artery-to-artery” embolization and hemodynamic strokes (in the vascular region of certain vessels or “watershed” strokes)

- Atherosclerotic
- Non-atherosclerotic (dissection, moy-a-moya disease, fibromuscular dysplasia, etc.)
  - Microangiopathy (perforating arterioles’ disease)
  - Embolization from the heart (mitral valve stenosis, atrial fibrillation, foramen ovale patens, etc.)
  - Stroke of unknown origin (non-lacunar ischemic lesions on CT of unknown origin – e.g., in the case of normal angiographic findings)

There is another heterogeneous group of strokes of rare origin (migrainous strokes, resistance to APC, hyperhomocysteinemia, antiphospholipid syndrome, sickle-cell anemia, MELAS syndrome, vasculitis) that are important in the differential diagnosis.

According to “Stroke Data Bank NIH” up to 40% of strokes are of unknown origin; 27% are attributed to microangiopathy, 19% to embolization from the heart, and 14% to macroangiopathy (major extra- and intracranial vessels). It seems that a large proportion of strokes of unknown origin are actually embolic.

The risk of ischemic stroke depends on the incidence of the risk factors. The best known risk factors are non-modifiable (age, gender, genetic predisposition, weather influence, race) or modifiable (arterial hypertension – the single most important risk factor, hypotension, heart disease, atherosclerosis, diabetes mellitus, hypercholesterolemia, dyslipoproteinemia, smoking, alcohol consumption, obesity, polycythemia).

### 3.3.5.2 Epidemiology

The stroke incidence is 300–600/100,000 inhabitants/year, and is the third most common cause of death or severe disability. In the USA 700,000 inhabitants suffer a stroke every year (80% an ischemic one). In the USA every year 150,000 persons die of stroke, even though the mortality rate of stroke in the USA is the lowest in the world. At present, approximately 4.4 million stroke survivors live in the USA, and two-thirds of them are disabled to some extent. The total cost (direct and indirect) of treating these patients is estimated at $51 billion/year. Stroke incidence is somewhat higher in Europe. The worst epidemiological data are encountered in the satellites of the former USSR (stroke incidence up to 650/100,000 inhabitants/year, mortality 273/100,000 inhabitants/year) and in Finland. Switzerland and France are countries with a very low stroke incidence.

### 3.3.5.3 Symptomatology

From the neurosurgical point of view, ischemic events can be divided into several groups.

#### 3.3.5.3.1 Asymptomatic Patients

The finding is incidental (during investigation of some other disease) or targeted (e.g., investigation due to carotid bruit).

#### 3.3.5.3.2 Transient Neurologic Deficit

There are clinical symptoms of amaurosis fugax, hemispheric transient ischemic attack (TIA), reversible ischemic deficit (RIND), and so-called vertebro-basilar insufficiency. Both singular and repeated events occur.
“Crescendo” TIAs, cumulated transient attacks, represent the same type of reversible ischemia and repeated embolization. They are important from the point of view of intervention timing. Clinically, the most frequent symptoms of TIAs are: contralateral hemiparesis, hemihypesthesia, and homonymous hemianopia. Speech, gnostic, and practical disorders are caused by attacks in the dominant hemisphere.

3.3.5.3.3 Completed Stroke
Any permanent neurologic deficit following stroke (even if the only finding is abnormal reflexes, or minimal deficit) should be quoted as a completed stroke (CS). Completed strokes are divided into minor and major ones. In minor stroke the patient is fully ambulatory and he/she is able to care for him/herself; in major stroke the patient needs another person’s help with routine daily activities.

3.3.5.3.4 “Stroke in Evolution” or “Progressing Stroke”
The neurological deficit is fluctuating or changing in time. Deficit usually increases and leads to completed stroke, even if aggressive conservative treatment is applied.

3.3.5.3.5 Global Ischemia
Dementia and psychological changes are dominant in the clinical picture. Other causes of dementia have to be ruled out.

3.3.5.4 Clinical Picture

- Asymptomatic patient (with occluded or stenotic magistral or brain vessel)
- Symptomatic patient
  - Transient deficit
  - Fixed deficit
  - Minor stroke
  - Major stroke
  - Dynamic deficit
  - Global deficit

The source of embolization (from carotid artery stenosis – “artery-to-artery,” from the heart – “heart-to-artery,” and small vessel disease – “lacunar infarctions”) usually cannot be distinguished by clinical findings only.

3.3.5.5 Diagnostic Procedures

3.3.5.5.1 Doppler Ultrasonography
Doppler ultrasonography (DUS) is the most important screening procedure. Well-conducted and precise investigation is sufficient for an indication for intervention on cervical carotid arteries. Non-invasivity, simplicity, low price, and the ability to repeat the investigation frequently are the advantages of DUS. It is extremely useful in post-intervention check-ups and in the monitoring of the dynamic changes of atherosclerotic disease. The information about the structure of the atherosclerotic plaques is important. DUS (or TCD) does not provide sufficient data on intracranial circulation beyond the M2 and A1 segments.

3.3.5.5.2 CT Angiography
Computed tomographic angiography (CTA) is a non-invasive technique – stenosis is displayed on axial scans, and the shape of the plaque and calcifications is appreciated. 2D and 3D reconstructions are very useful. CTA can display intracranial vessels as well. The indication for intervention for both magistral and intracranial vessels can be based on CTA findings only.

3.3.5.5.3 MR Angiography
Magnetic resonance angiography (MRA) is a non-invasive technique; both intracranial and extracranial vessels can be shown. The treatment indications can be based on MRA findings only as well. MRA contraindications are placement of a pacemaker, a vascular clip of unknown origin, an artificial metallic heart valve, etc.

3.3.5.5.4 Digital Subtraction Angiography
Digital subtraction angiography (DSA) is still considered the golden standard. The disadvantages of DSA – invasivity, procedural complications – have to be added to the interventional complications. Morbidity/mortality of DSA is reported to be within the range 0.5–1.5%. The main advantages are obtaining precise information about both the aortic arch and the extracranial and intracranial vessels, and easy interpretation of the findings. The possibility of conversion into a therapeutic session is another major advantage.

3.3.5.5.5 Computed Tomography
Computed tomography is a mandatory investigation in all patients with cerebrovascular disease. The information about brain morphology, the extent and age of the ischemic changes are displayed, and other brain diseases are excluded (tumor, chronic subdural hematoma, etc.). CT provides information about small vessel disease as well (status lacunaris). CT is a must in the acute phase of stroke: normal brain or minimal/major changes can be shown (sulci smoothening, density changes, loss of gray/white matter differentiation, expansive behavior of ischemic lesions, etc.). The sign of dense artery provides in-
formation about thrombus in major vessels (in one-third of major strokes, usually MCA).

3.3.5.5.6 Magnetic Resonance Imaging
With magnetic resonance imaging (MRI) morphological information is even more precise. Perfusion/diffusion studies can be performed in the acute phase of stroke (tool to differentiate a penumbra – hypoperfused, but still viable brain from the necrotic regions).

3.3.5.5.7 Functional Diagnostic Studies
Perfusion parameters (CBF) under the basal condition and after stimulation (CO₂ inhalation, i.v. acetazolamide, etc.) are appreciated. In specific cases, the utilization of certain metabolic substances and information about specific functional areas can be acquired. This is necessary when the revascularization procedure is considered (EC–IC bypass).

3.3.5.5.8 Transcranial Doppler
Transcranial Doppler (TCD) follows the changes in major brain vessels (vasodilatation does not appear during stimulation in these vessel’s segments). Any blood flow change is dependent on changes in the distal vascular territory. Blood flow velocity changes and their dynamics can be appreciated in real-time investigation. Hyperventilation can be used to evoke hypocapnia, which leads to distal vasculature vasoconstriction (if not, this can be a sign of complete vasoparalysis – important information if a high-flow bypass is considered).

3.3.5.5.9 Single Photon Emission-Computed Tomography
In single photon emission-computed tomography (SPECT) a 3D image is reconstructed from 2D (planar) images of local concentrations of radionuclide (⁹⁹mTc – hexamethyl-propylenamino-oxime labeled by Technetium). The level of radionuclide agent concentration depends on the CBF.

3.3.5.5.10 Xenon CT
⁹⁹Xe is a low-energy γ-emitter that is freely diffusible throughout the brain. Its washout or clearance is used to measure CBF. When small concentrations are used, the hazards of radiation to the patient and operating room personnel are minimized.

3.3.5.5.11 Perfusion CT
An axial brain slice at the level of all three vascular territories is performed. Contrast agent is applied under constant velocity and every second new axial slice at the same brain level is acquired (usually lasting 40 s). The brain density is a marker of CBF. Time-to-start and time-to-peak of maximal flow can be calculated (in semiquantitative fashion), as well as blood volume and cerebral blood flow.

3.3.5.5.12 Positron Emission Tomography
The presence or degree of hemodynamic impairment due to occlusive cerebrovascular disease is inferred from measurements of CBF, cerebral blood volume (CBV), oxygen extraction fraction (OEF), and the cerebral rate for oxygen metabolism (CMRO₂). For studies ¹⁵O-labelled carbon monoxide and ¹⁵O-labelled water are used. There is a two-stage classification of chronic hemodynamic impairment for patients with atherosclerotic carotid artery disease – stage I (autoregulatory vasodilation), identified as an increase in CBV or mean vascular transit time (mathematically equivalent to the CBV/CBF ratio) in the hemisphere distal to the occlusive lesion, with normal CBF, OEF, CMRO₂, and stage II (autoregulatory failure), characterized by reduced CBF and increased OEF with normal oxygen metabolism.

3.3.5.6 Surgical and Neurointerventional Treatment

3.3.5.6.1 Aortic Arch and Its Proximal Branches
3.3.5.6.1.1 Steal Phenomenon
Stenosis or occlusion of the brachial trunk (right) or subclavian artery (left) causes the blood-flow reversal in the opposite VA. The patients exhibit the signs of vertebrobasilar (VB) insufficiency – vertigo, dizziness – which is usually more pronounced during the increased physical exertion of the ipsilateral upper limb.

3.3.5.6.1.1.1 Diagnosis
Doppler ultrasonography and DSA can be used for diagnosis. The blood-flow reversal in the opposite VA is documented.

3.3.5.6.1.1.2 Indication
Empiric, individual.

3.3.5.6.1.1.3 Treatment
Stenting of the brachial trunk or subclavian artery is sometimes possible, even in patients with vessel occlusion. Carotido-subclavian bypass is the surgical option.

3.3.5.6.1.1.4 Complications
In the case of endovascular treatment complications are minimal (dissection, arterial thrombosis with possible stroke); in the case of surgery complications include inju-
ry to the surrounding structures (nerves, lymphatic duct) and vessel/graft occlusion.

3.3.5.6.1.2 Thoracic Outlet Syndrome
External pressure on the subclavian artery and/or brachial plexus causes diminished blood-flow in the upper limb, pain, and, rarely, symptoms of brachial plexus compression. The pressure is caused by cervical rib, scalene muscles, etc.

3.3.5.6.1.2.1 Diagnosis
Plain X-ray, DSA, and electrophysiology are used.

3.3.5.6.1.2.2 Indication
Empiric, individual.

3.3.5.6.1.2.3 Treatment
Pressure release by rib resection, scalene muscles section, etc.

3.3.5.6.1.2.4 Complications
Injury to the surrounding structures (nerves, lymphatic tract).

3.3.5.6.2 Carotid Bifurcation/Internal Carotid Artery Stenosis
The most typical site of atherosclerotic disease. Carotid endarterectomy (CEA) is the third most frequent surgical procedure. The atherosclerotic plaque causes stenosis but the clinical symptoms are caused by plaque fragmentation and/or blood aggregation on the plaque surface and distal embolization. Hemodynamic origin of symptoms is extremely rare. CEA is a tool of secondary prevention and surgery/intervention is considered in asymptomatic patients and in patients with transient deficits or minor stroke. Patients after a major stroke are less frequent surgical candidates.

3.3.5.6.2.1 Diagnosis
Doppler ultrasonography, CTA, MRA, and DSA are used.

3.3.5.6.2.2 Indication
Indications are evidence-based, on large multi-institutional randomized trials (NASCET, ECST, ACAS, ACST).

3.3.5.6.2.3 American Heart Association Recommendations
Surgery is indicated in symptomatic patients with stenosis above 50%, provided the institutional MM rate is below 6% and patients’ life expectancy is at least 5 years. In asymptomatic patients with stenosis above 60%, the MM rate is below 3% and life expectancy is 5 years at least.
In symptomatic patients the surgery should not be delayed (maximum benefit was observed in patients undergoing surgery less than 2 weeks after the last event), provided no large recent infarction is found on either CT or MR. If so, surgery should be postponed for 6 weeks.

The same criteria apply to carotid stenting (with distal protection). CEA is superior to stenting with regard to durability. Stenting should be considered as a treatment option in poor surgical candidates and in older patients.

3.3.5.6.2.4 Treatment
Endarterectomy could be performed under either general or regional anesthesia (cervical block). Neurological functions should be closely monitored (EEG, SSEPs). Stenting procedures are done under local anesthesia and/or mild sedation.

A skin incision runs along the anterior border of the sternocleidomastoid muscle, the carotid bifurcation is dissected free, the vessels closed by temporary clips and the vessel is incised from the common carotid artery (CCA) to the internal carotid artery (ICA). The use of an intraluminal shunt depends on institutional policy and varies from never to always. The plaque is removed. Extreme care is focused at the distal end of the CEA where the intima must be closely inspected and eventually sutured to the carotid wall to prevent dissection. Suture of the arteriotomy is performed either directly or with the use of a graft.

3.3.5.6.2.5 Restenosis
Restenosis occurs in 5% of patients. If necessary, restenosis is treated predominantly by stenting.

3.3.5.6.2.6 Complications
Stroke, carotid occlusion, dissection, postoperative hematoma, peripheral nerve (PN) injuries (VII, X, XII), and infection.

3.3.5.6.3 Carotid Pseudo-Occlusion
In certain cases the ICA behind the plaque is not thrombosed, but has collapsed. The lumen remnants can often be detected on DSA. The stenosis is arbitrarily quoted as 95%.

3.3.5.6.3.1 Diagnosis
Digital subtraction angiography.

3.3.5.6.3.2 Indication
Carotid endarterectomy can be attempted.

3.3.5.6.3.3 Treatment
Standard CEA.

3.3.5.6.3.4 Complications
Stroke, carotid occlusion, dissection, wound hematoma, PN injuries (VII, X, XII), infection, and monocular blindness.
3.3.5.6.4 Carotid Kinking and Coiling
Two types of carotid kinking are seen. The first type is probably based on hereditary elongation of the vessels; the second is seen in patients with atherosclerotic disease. Symptoms (usually TIAs) are caused either by embolization or by the hemodynamic effect of vessel occlusion during ipsilateral head rotation. Surgery is usually considered only in patients in whom best medical treatment (BMT) fails to prevent further TIAs.

3.3.5.6.4.1 Diagnosis
Doppler ultrasonography, CTA, MRA, and DSA (including forced positions) are used.

3.3.5.6.4.2 Indication
Empiric, individual.

3.3.5.6.4.3 Treatment
The carotid bifurcation is dissected free, mobilized, and in the case of minor kinking, the vessels are pushed downward and fixed to the surrounding structures. In more extensive kinks, the diseased part of the vessel is resected and the distal stump is either sutured end-to-end or replanted into the CCA. In the case of carotid coiling, the surgical approach is identical. Both procedures can follow routine CEA.

3.3.5.6.4.4 Complications
Stroke, carotid occlusion, dissection, wound hematoma, PN injuries (VII, X, XII), and infection.

3.3.5.6.5 Stump Syndrome
Emboli from the carotid stump can travel via natural or artificial (EC–IC bypass) collaterals and lodge either in the retina or cerebral vasculature, resulting in amaurosis fugax or TIAs. Only patients with repeated attacks who are not responding to BMT are considered for surgery.

3.3.5.6.5.1 Diagnosis
Doppler ultrasonography, CTA, MRA, and DSA are used.

3.3.5.6.5.2 Indication
Empiric, individual.

3.3.5.6.5.3 Treatment
The carotid bifurcation is dissected and an arteriotomy performed from the CCA to the ECA. Endarterectomy is performed and the orifice of the occluded ICA is closed by a running suture. The ICA flow can be restored in few cases, even if the vessel is thrombosed. In patients with retrograde flow reaching the carotid canal, an attempt at carotid recanalization can be performed. The Fogarty catheter is advanced to the region of the carotid canal and inflated. By gentle catheter withdrawal the thrombus is removed.

3.3.5.6.5.4 Complications
Peripheral nerve injuries (VII, X, XII), stroke, infection, and monocular blindness.

3.3.5.6.6 Extracranial Vertebral Artery

3.3.5.6.6.1 Vertebral Artery Origin
The origin of the VA is the typical location of VA stenosis. Patients usually exhibit symptoms of VB insufficiency (vertigo, dizziness, etc.). Alternatively, symptoms from the PCA territory can be seen (homonymous hemianopia). VA stenosis is also frequently found during the work-up for carotid territory ischemic symptoms. The symptoms are not only embolic. A hemodynamic origin can be suspected in some patients. It appears in patients with an aplastic or hypoplastic opposite VA and insufficient PCOM collaterals.

3.3.5.6.6.1.1 Diagnosis
Doppler ultrasonography, CTA, MRA, and DSA are used.

3.3.5.6.6.1.2 Indication
Empiric, individual, only higher degree stenoses are considered for treatment.

3.3.5.6.6.1.3 Treatment
An endovascular approach is the first-line treatment. Stenting may be performed, but simple percutaneous transluminal angioplasty is preferred at this location. Alternatively, VA–CCA transposition can be employed. The vessels are approached via the incision along the lower half of the anterior border of the sternocleidomastoid muscle. The VA is severed at its origin and sutured end-to-side to the CCA. Extreme care is to be focused on the recurrent nerve and lymph tract (left side).

3.3.5.6.6.1.4 Complications
In the case of endovascular treatment, there are virtually no complications (dissection, arterial thrombosis); in the case of surgery injury to the surrounding structures (nerves, lymphatic tract), vessel/graft occlusion.

3.3.5.6.6.2 Middle Portion of the VA (C6–C2)
The presenting symptoms are as in Sect. 3.3.5.6.6.1. Only individual cases are encountered. Either the external pressure on the VA is caused by hypertrophic uncovertebral joints in patients with degenerative spine disease or VA kinking between the two foramen can be found.

3.3.5.6.6.2.1 Diagnosis
Doppler ultrasonography, CTA, MRA, and DSA are used.
3.3.5.6.6.2.2 **Indications**
Individual.

3.3.5.6.6.2.3 **Treatment**
The VA can be decompressed via routine anterior diskectomy in patients with uncovertebral osteophytes. The preferred approach is, however, lateral. The spine is approached either anterior or posterior to the sternocleidomastoid muscle, posterior to the carotid artery and jugular vein. Osteophytes can be selectively removed, the VA exposed to its desired length (removing the two adjacent foramina and allowing VA exposure to the length of some 45–50 mm) for kinking resection or straightening. Atherosclerotic changes in this region are extremely rare. If necessary, these should be treated endovascularly.

3.3.5.6.6.2.4 **Complications**
Root injury, PN injury, thrombosis, and embolization.

3.3.5.6.6.3 **Upper Segment (C2 to the VA Junction)**
Sclerotic occlusive disease is more frequent in this region. Only symptomatic lesions can be considered for endovascular or surgical treatment.

3.3.5.6.6.3.1 **Diagnosis**
Doppler ultrasonography, CTA, MRA, and DSA.

3.3.5.6.6.3.2 **Indication**
Rare and strictly individual.

3.3.5.6.6.3.3 **Treatment**
Endarterectomies are not performed; bypass procedures (CCA–VA being the most frequent one) are now replaced by endovascular procedures (angioplasty, stenting).

3.3.5.6.6.3.4 **Bow–Hunter Syndrome**
In a maximal head rotation, the contralateral VA is stretched and thus stenosed or occluded. In a rare condition of hypoplastic or aplastic opposite VA and insufficient PCOM collaterals, VB–PCA ischemia can be encountered. The symptoms can be transient or permanent (homonymous hemianopia). Few fatal cases have been described.

3.3.5.6.6.3.4.1 **Diagnosis**
Digital subtraction angiography in a neutral and maximal head rotation is used.

3.3.5.6.6.3.4.2 **Indication**
Individual.

3.3.5.6.6.3.4.3 **Treatment**
C1–C2 fixation or VA deliberation from the posterior approach is the treatment used. In the case of VA deliberation, the bone forming the C1 vertebral foramen is resected and the VA dissected free from the surrounding structures.

3.3.5.6.3.4.4 **Complications**
Injury to the surrounding neural structures.

3.3.5.6.7 **Direct Revascularization**

3.3.5.6.7.1 **ECIC Bypass**
End-to-side anastomosis between the donor (superficial temporal artery – STA) and recipient (opercular branch of the MCA) provides some 18 ml/min of blood. The International Cooperative ECIC Bypass Study Group failed to prove any beneficial role of bypass procedures in stroke prevention (particularly in patients with MCA stenosis). A new randomized study (COSS – Carotid Occlusion Surgery Study) has recently been running and the indication for ECIC bypass is studied in patients with impaired cerebrovascular reserve capacity (CVRC) according to PET.

3.3.5.6.7.1.1 **Indication**
Unavoidable ICA/MCA sacrifice for a tumor or aneurysm.

3.3.5.6.7.1.2 **Uncertain Indication**
Occlusion of the ICA/MCA in patients with impaired cerebrovascular reserve capacity (proven by SPECT, PET, perfusion CT studies) and no/small ischemic lesion (usually watershed infarction).

3.3.5.6.7.1.3 **Diagnosis**
Clinical, DSA, CT/MRI, and CVRC study are used.

3.3.5.6.7.1.4 **Surgery**
The STA branch is dissected free. A small craniotomy is centered 6 cm above the tragus and a dural incision in a “Y shape” is made. The recipient artery is identified, between two temporary clips linear arteriotomy is performed and the donor artery (with an ostium prepared in a “fish-mouth” shape) is sutured in an end-to-side manner using a 10/0 suture. Extreme care is to be focused on wound closure because of CSF leak, donor vessel distortion or occlusion by pressure of the bone flap.

3.3.5.6.7.2 **Bypass Using Venous/Arterial Graft**
In the case of insufficient STA, a graft is used to create a bypass between the CCA/ECA and the intracranial ICA or proximal MCA – a flow-through bypass >100 ml/min is rarely needed in occlusive disease patients as there is an extreme danger of hyperemic breakthrough. The alternative ICA petrous segment (C2 segment) graft inter-
position is used in cases of intracavernous ICA stenosis, aneurysms, and ICA tumor involvement.

3.3.5.6.7.3 Posterior Circulation Bypasses
Posterior circulation bypasses are performed in selected cases with posterior circulation ischemia of hemodynamic origin. They consist of the STA – superior cerebellar artery bypass, and the STA/occipital artery – posterior inferior cerebellar artery bypass.

3.3.5.6.7.3.1 Diagnosis
Clinical diagnosis, DSA, CT/MRI, and CVRC studies are used.

3.3.5.6.7.3.2 Indication
Rare and individual, recently often replaced by endovascular angioplasties and stenting procedures.

3.3.5.6.7.4 IC–IC Bypass
Mainly side-to-side anastomosis between both ACA arteries – in the case of, for example, an A2 segment fusiform aneurysm.

3.3.5.6.7.4.1 Indication
Indications are individual. In general, many variations of bypass procedures are described, with both low and high flow (e.g., the ELANA technique). Until now, no randomized trial has shown any proof of bypass procedure benefit in any subgroup of patients.

3.3.5.6.7.4.2 Complications
Stroke, hyperemic breakthrough, and wound healing problems.

3.3.5.6.8 Indirect Revascularization

3.3.5.6.8.1 Encephalo-Duro-Arterio-Myo-Synangiosis
Encephalo-duro-arterio-my-o-synangiosis (EDAMS) and its variations (EMS, EDAS) – isolated temporalis muscle and uninterrupted STA branch are laid on the surface of the brain with exposed vessels. Neovascularization with the development of EC-IC collaterals can be proved angiographically in patients with moya-moya disease.

3.3.5.6.8.1.1 Indication
Individual, mainly moya-moya disease.

3.3.5.6.8.1.2 Complications
Infection and wound healing problems.

3.3.5.7 Non-Atherosclerotic Occlusive Disease

3.3.5.7.1 Moya-Moya Disease
Spontaneous stenosis/occlusion of intracranial carotid arteries (VB territory is rarely involved). Collateral flow develops through abnormal transdural anastomoses, known as rete mirabile.

3.3.5.7.1.1 Presentation
Ischemia occurs predominantly in children (mental retardation, IQ decrease, neurological deficit, seizures); intracerebral/intraventricular hematoma occurs predominantly in adults.

3.3.5.7.1.2 Diagnosis
Computed tomography, DSA – stenosis/occlusion of the distal ICA/proximal MCA+ACA, rete mirabile, and abnormal intraparenchymal anastomoses in the basal ganglia (moya vessels).

3.3.5.7.1.3 Treatment
Encephalo-duro-arterio-my-o-synangiosis and its variations.

3.3.5.7.2 Fibromuscular Dysplasia
Fibromuscular dysplasia is the second most common cause of extracranial carotid stenosis (in 80% bilateral).

3.3.5.7.2.1 Presentation
Cerebral ischemia, mental distress, tinnitus, vertigo, and carotidynia.

3.3.5.7.2.2 Diagnosis
Doppler ultrasonography, CTA, MRA, and DSA – multiple concentric narrowings (“string of pearls”) are seen.

3.3.5.7.2.3 Treatment
Primarily medical, but in the case of medical treatment failure, endovascular procedures and bypass surgery can be considered as well.

3.3.5.7.3 Dissections and Dissecting Aneurysm
Dissection is the extravasation of blood between the intima and the media (most common intracranially); dissecting aneurysm is the extravasation of blood between the media and the adventitia (most frequently extracranially).

Dissections are frequently associated with fibromuscular dysplasia, Marfan’s syndrome, Takayasu’s disease, etc. Dissection can be post-traumatic and iatrogenic (DSA) as well.
3.3.5.7.3.1 Presentation
Ischemic events owing to embolization or compromised CBF and SAH.

3.3.5.7.3.2 Diagnosis
Computed tomography, MR, and CTA/MRA/DSA are used.

3.3.5.7.3.3 Treatment
Medical treatment, anticoagulation, endovascular stenting, vessel occlusion, and bypass procedure.

3.3.5.7.3.4 Complications
Ischemia and intracerebral hemorrhage.

3.3.5.7.4 Intracranial Arterial Stenoses
(Including ICA Cavernous Segment, Intradural VA, BA)
Such lesions are rarely the source of emboli. In comparison with, for example, ICA stenosis at CCA bifurcation, the plaque surface is extremely small. Ulcers are not seen and lesions are harder. When symptomatic, the underlying pathophysiology is most likely, hemodynamic. In the past patients with such lesions were considered candidates for bypass surgery. After the ECIC Bypass Study, however, the procedures were abandoned. Recently, patients with intracranial arterial stenoses are frequently treated by neurointerventional methods – angioplasty with possible stenting.

3.3.5.7.4.1 Diagnosis
Computed tomography angiography, MRA, DSA, and CVRC studies are used.

3.3.5.7.4.2 Indications
Empiric, individual. No evidence-based support is available and endovascular procedures should not be indicated outside the experimental protocol. The indication criteria should be similar to those of the ECIC bypass (CVRC evaluation).

3.3.5.7.4.3 Treatment
Angioplasty, stenting procedures with dedicated intracranial stents are employed, no distal protection is necessary. The neuroradiologist must be ready to use thrombolytic agents or mechanic means in the case of vessel thrombosis.

3.3.5.7.4.4 Complications
Vessel occlusion, vessel rupture, dissection, stent migration, etc.

3.3.5.8 Mass Effect-Producing Ischemic Lesions
Acute occlusion of the major cerebral artery results in ischemic changes leading to a breakdown of the blood–brain barrier, causing malignant cerebral edema in some cases. Neurological deterioration caused by herniation can be very rapid.
- Infratentorial – the posterior inferior cerebellar artery (PICA) or superior cerebellar artery (SCA) territory is most frequently affected
- Supratentorial – the MCA territory is typically affected

3.3.5.8.1 Diagnosis
Computed tomography or MRI is used.

3.3.5.8.2 Indication
The indication is absolute in cerebellar infarction with rapid neurological deterioration and an ischemic mass lesion on CT (similar to an epidural hematoma).
Some of the recent studies support decompressive craniotomy in supratentorial MCA infarction (even in the dominant hemisphere), especially in young patients with rapidly deteriorating neurological status.

3.3.5.8.3 Treatment
- Infratentorial – ischemic lesion resection, decompressive craniectomy, and external ventricular drainage in the case of acute hydrocephalus
- Supratentorial – large decompressive craniectomy with a dural patch

3.3.5.9 Acute Phase Treatment of Ischemic Stroke

3.3.5.9.1 Thrombolysis
Urgent neurological and CT examinations are mandatory in every case of cerebral stroke that does not last longer than 3 h. If the ischemic stroke is confirmed and no contraindication for thrombolysis occurs, the patient should be transferred to the stroke ICU and thrombolytic therapy should be started immediately – rt-PA i.v. (dose of 0.9 mg/kg, maximal dose of 90 mg, with 10% of the dose as a bolus, followed by 60 min of infusion of the remaining drug). Thrombolytic therapy contraindications (only the basic ones are mentioned): intracerebral hematoma, stroke history longer than 3 h, unknown length of history, subarachnoid hemorrhage, NIHSS < 4, or rapidly improving neurological deficit, NIHSS > 25, or rapid progression of neurological symptoms, brain ischemia in more than
one-third of the MCA region on CT, the seizure at the beginning of the stroke (suspected Todd’s paresis), pre-existing serious neurological deficit, repeated stroke within 3 months, history of intracerebral hemorrhage, brain disease in history (tumor, aneurysm, etc.), hemorrhagic retinopathy, hemorrhagic diathesis, liver failure, compensated diabetes mellitus, major surgical procedure, or major trauma within 3 months, international normalized ratio (INR) > 1.7, thrombocytes < 100,000/mm³. The effect of intravenous thrombolysis is documented within 4.5 h after the stroke as well (the odds ratios are lower, but statistically significant).

Intra-arterial thrombolysis may be a treatment alternative in patients with proximal MCA occlusion and a history shorter than 6 h. Intra-arterial thrombolysis of acute BA thrombosis is a treatment option. The indication is not based on randomized study. This treatment should be performed within multi-institutional studies or within an experimental protocol.

Mechanical embolectomy is a new treatment option of acute cerebral vessel occlusion (e.g., Merci Retriever). Randomized study is underway in patients with a stroke history shorter than 8 h, in whom intravenous thrombolysis is not indicated. The lower risk of intracerebral hemorrhage is the major advantage of this approach. The acceleration of occluded cerebral vessel recanalization by TCD is another new treatment option and constitutes the clinical phase of the investigation. Thrombolysis is performed in up to 15% of acute stroke patients in the USA, and in Europe this figure varies among different countries (0.5–3%).

3.3.5.9.2 Timing of Procedures

3.3.5.9.2.1 Emergency (Range of Dozens of Minutes)
Thrombolysis, posterior fossa decompression for mass effect ischemic cerebellar lesion.

3.3.5.9.2.2 Urgent (Range of Single Days)
Carotid endarterectomy or stenting for symptomatic ICA stenosis. Surgery/stenting should be delayed for approximately 6 weeks in the case of larger ischemic lesions on CT (due to the risk of hemorrhagic conversion of ischemic lesions).

3.3.5.9.2.3 Elective (Range of Weeks)
Other vascular procedures.

3.3.5.10 Conservative Therapy

The following treatment strategies can be applied for the acute stroke patients who are not candidates of thrombolysis: volume expansion with hemodilution (usually crystalloids in combination with volume expanders, glucose should not be administered within the first 2 days due to the risk of lactate acidosis in the region of the ischemic lesion). Venepuncture can be considered in the case of hematocrit levels higher than 0.5 and if hemodilution therapy has failed. Either heparin (twice daily 5,000 IU subcutaneously) or low molecular weight heparins should be given. The effect of nootropic agents is not fully confirmed.

3.3.5.10.1 Primary Prevention

3.3.5.10.1.1 Arterial Hypertension
Arterial hypertension is the most important modifiable risk factor. Systolic pressure exceeding 160 torr and diastolic pressure exceeding 90 torr increases significantly the risk of ischemic stroke. The relationship between increasing blood pressure and the risk of stroke is linear. Blood pressure should be kept under 140/90 torr, in patients with diabetes mellitus under 130/85 torr.

3.3.5.10.1.2 Smoking
The pathophysiological sequelae of smoking are multifactorial, the elasticity of red blood cells is decreased, the level of fibrinogen is increased, the aggregability of thrombocytes is increased, the HDL level is decreased, and the hematocrit level is increased. Smoking increases the risk of ischemic stroke 2-fold.

3.3.5.10.1.3 Other Risk Factors – Diabetes Mellitus, Hyperinsulinemia, and Insulin Resistance
The incidence of other atherogenic risk factors is high among insulin-dependent patients, especially hypertension, obesity, and dyslipidemia (syndrome X). Hyperinsulinemia with resistance to insulin is typical in these cases. Strict compensation of glucose levels is mandatory, and hypertension should be treated strictly (with the use of ACE inhibitors).

3.3.5.10.1.4 Atrial Fibrillation
Atrial fibrillation is a serious risk factor of stroke (approximately 3–5%). Stroke is caused by embolization from the heart in approximately 70% of patients with atrial fibrillation. There is a closed relationship among atrial fibrillation, the age of the patients, and the risk of stroke. Anticoagulation or anti-aggregation therapy should be applied in primary stroke prevention in patients with atrial fibrillation. Other heart diseases increasing the risk of stroke include mitral valve stenosis, mitral valve prolapse, artificial valves, dilatatory cardiomyopathy, patent foramen ovale, atrial septum defect, and atrial aneurysm.
3.3.5.10.1.5 Hyperlipidemia
The dysbalance of blood fat levels are related to an increased risk of stroke; nevertheless, the relationship is weaker. Medication of statins reduces the risk of atherosclerotic disease of extracranial vessels. The dietary measures should be started in patients with hyperlipidemia, medication with statins is fully recommended in patients with ischemic heart disease and increased levels of LDL.

3.3.5.10.1.6 Other Risk Factors
Obesity, hyperhomocysteinemia, drug abuse, physical inactivity, the presence of antiphospholipid antibodies, hormone replacement therapy in climacterial women, and peroral contraception.

3.3.5.10.2 Secondary Prevention
The treatment of risk factors is mandatory. Anticoagulation is indicated in patients with cardio-embolic stroke (heart-to-artery) and atrial fibrillation (INR within the range 2 to 3). Anti-aggregation therapy by acetylsalicylic acid (ASA) is indicated (dose 50–325 mg/day), if anticoagulation is contraindicated (Table 3.3.10).

Anti-aggregation therapy is indicated in patients with an atherothrombotic event from extracranial vessels or in the case of stroke of unknown origin.

3.3.5.10.2.1 Acetylsalicylic Acid
A dose of 50–325 mg/day is accepted, as the ideal dose of ASA is unknown. The FDA (US Food and Drug Administration) recommends the above-mentioned range of doses; for secondary prevention the FDA prefers a full dose of 325 mg/day.

3.3.5.10.2.2 Ticlopidine
Recently, ticlopidine has become a less accepted medication due to the incidence of side effects, especially neutropenia. The incidence of side effects is 10% lower among Afro-Americans, and serious neutropenia has not been observed at all.

3.3.5.10.2.3 Clopidogrel
Clopidogrel is chemically related to ticlopidine. The efficiency is equivalent to ticlopidine and ASA. The low incidence of side effects is the major advantage of this drug.

3.3.5.10.2.4 Combination of Dipyridamole, Phosphodiesterase Inhibitor and ASA, Cyclooxygenase Inhibitor
There is a theoretical advantage of this combination compared to single drug medication.

3.3.5.11 Anesthesia, Preoperative and Postoperative Management, Monitoring
Surgencies are performed under either general or local anesthesia (e.g., extracranial carotid arteries – cervical block applied).

If general anesthesia is used, neuroprotective anesthetics are recommended (barbiturates, thiopental or pentobarbital) – especially in intracranial reconstructive vascular surgery (for example, a high-flow bypass to the M1 segment of the MCA). Burst suppression on the EEG can be reached whenever necessary. Etomidate (ultrashort acting derivate of imidazole) is another neuroprotective anesthetic agent. The major advantage of etomidate is the less frequent incidence of intraoperative hemodynamic side effects. Isoflurane is an example of an inhalatory, neuroprotective anesthetic agent.

Other drugs can be considered as well: a “Sendai cocktail” (phenytoin, mannitol, dexamethasone, vitamin E), and nootropic agents. Hypothermia can be considered in complex arterial reconstructions.

Continuous intra-arterial blood pressure monitoring is mandatory. Blood pressure should be raised by 10–30 torr above the patient’s normal pressure.

The monitoring of SSEPs, the spectral analysis of EEG, or TCD are considered as appropriate intraoperative adjuncts.

Table 3.3.10 Anti-aggregation and anticoagulation therapy in patients after transient ischemic attack (TIA) or stroke. DP dipyridamole, ASA acetylsalicylic acid, INR international normalized ratio

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Recommended therapy</th>
<th>Alternative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic</td>
<td>ASA 50–325 mg/day</td>
<td>DP 200 mg + ASA 25 mg 2× daily Clopidogrel 75 mg/day Ticlopidine 250 mg 2× daily ASA 50–1,300 mg/day</td>
</tr>
<tr>
<td>Atherothrombotic event in the event of intolerance or allergy to ASA, or repeated event on ASA medication</td>
<td>DP 200 mg + ASA 25 mg 2× daily clopidogrel 75 mg/day</td>
<td>Ticlopidine 250 mg 2× daily Anti-coagulation (INR 2–3) ASA 50–1,300 mg/day</td>
</tr>
<tr>
<td>Cardio-embolic</td>
<td>Anticoagulation (INR 2–3)</td>
<td>ASA 50–325 mg/day</td>
</tr>
</tbody>
</table>
Interventional procedures are usually performed under minimal sedation of the patient, and procedures under general anesthesia are less frequent. The anesthetist should be standing by in case of potential complications. Electrophysiological monitoring should be applied, if the interventional procedure is performed under general anesthesia.

For postoperative care, continuous/frequent blood pressure measurement is important, the detection of post-intervention risk factors, and thorough preoperative medical investigation. Patients should be monitored at least 24 h in an ICU bed, or semi-ICU after surgery/intervention. The parameters of the utmost importance are: GCS monitoring, neurological picture examination, direct blood pressure monitoring (which should be higher than a normal patient’s pressure), fluid balance, frequent surgical wound check-ups, etc.

### 3.3.6 Spontaneous Intracerebral and Intracerebellar Haemorrhage in Adults

**Daniel Hänggi, Hans-Jakob Steiger**

#### 3.3.6.1 Pathogenesis

Depending on the underlying cause, it is useful to distinguish between primary (about 80%) and secondary intracerebral and intracerebellar haemorrhage [1].

Primary (spontaneous) haemorrhages usually occur intraparenchymally and can be subdivided into deep and lobar haemorrhages [2–4]. They are usually located in the basal ganglia, the thalamus, the brain stem (predominantly the pons), the cerebral lobes (lobar) and the cerebellum [5].

#### 3.3.6.2 Causes

The most important cause of spontaneous intracerebral haemorrhage seems to be a pathophysiological wall vessel change and in consequence the rupture of small penetrating arteries and arterioles 50–200 µm in diameter that originate from the major cerebral arteries [6–9]. Degenerative changes induced by chronic hypertension as a risk factor or cerebral amyloid angiopathy [10] increase the likelihood of rupture of these vessels [11].

The older theory of microaneurysms of Charcot–Bouchard [12] as an aetiology of spontaneous intracerebral haematomas seems to be debatable and has not been proven [7, 9].

Cerebral amyloid angiopathy plays another major role in the pathogenesis of intracerebral haemorrhage, even in patients with more evident risk factors [10, 13, 14]. Other arteriopathies are rare, but as well documented as an aetiological factor for intracerebral haemorrhage. These include lipohyalinosis [6], fibrinoid necrosis [15] and cerebral arteritis [16].

Coagulopathies and induced clotting disorders must be ruled out as a potential aetiology for spontaneous bleeding. Particularly noteworthy is the iatrogenic pathway in patients on therapy with acetylsalicylic acid or other antiplatelet agents [17], the risk of anticoagulation [18, 19] and thrombolytic therapy with rt-PA [20, 21]. On the other hand, patients with leukaemia or thrombocytopaenia are also at risk of spontaneous cerebral bleeding.

Other obvious and occasional causes of cerebral haemorrhage include vascular anomalies such as aneurysms, arteriovenous malformations and venous angiomas, central sinus thrombosis, hyperperfusion (locally and globally) [22], haemorrhagic brain tumours, trauma, cranial surgery and sepsis.

#### 3.3.6.3 Epidemiology

##### 3.3.6.3.1 Incidence

Spontaneous intracerebral haemorrhage accounts for 10–20% of all stroke-related sudden onset neurological deficits [23].

##### 3.3.6.3.2 Risk Factors

The risk factors can be divided into two major groups, epidemiological risk factors and non-epidemiological risk factors.

#### 3.3.6.3.2.1 Race

The incidence of non-traumatic intracerebral haemorrhage worldwide ranges from 10 to 20 cases per 100,000 among whites [24, 25]. It is more common among certain populations including blacks and Japanese [26, 27]. For example, the incidence of intracerebral haemorrhage among blacks is more than twice that of the white population [26].

#### 3.3.6.3.2.2 Age

Five cohort studies have reported a significant relationship between age and the risk of intracerebral haemorrhage [28]. The incidence is expected to increase in the future because of the increasing age of the population.

#### 3.3.6.3.2.3 Sex

Men have a higher incidence of spontaneous intracerebral haemorrhage than women, especially those over 55 years of age [28, 29].
3.3.6.3.2.4 Education
Another epidemiological risk factor seems to be the level of education [26], the lower the level, the higher the incidence of a spontaneous bleeding. An explanation of this correlation could be the lack of awareness of primary health care.

3.3.6.3.2.5 Hypertension
The most important non-epidemiological risk factor for spontaneous intracerebral haemorrhage is hypertension [11, 28]. Hypertension increases the risk of intracerebral haemorrhage, especially in the older population [30]; an antihypertensive treatment with blood pressure control showed a reduction in the incidence of spontaneous intracerebral haemorrhage [25]. Hypertension was defined in one study as diastolic blood pressure of at least 95 mmHg [31], whereas another study defined hypertension as systolic blood pressure over 160 mmHg [32].

3.3.6.3.2.6 Alcohol
Alcohol consumption also increases the risk of spontaneous intracerebral haemorrhage [33, 34]. This was shown for recent moderate to heavy use and for chronic abuse [35, 36].

3.3.6.3.2.7 Smoking
Cigarette smoking as a risk factor for intracerebral haemorrhage shows controversial results [28, 37–39].

3.3.6.3.2.8 Hypercholesterolemia
Four case-control studies tended to show an association between low cholesterol and a higher risk of intracerebral haemorrhage [28, 40].

3.3.6.3.2.9 Physical Activity
Two cohort studies comparing active versus inactive patients showed no significant relationship concerning the risk of intracerebral haemorrhage [28].

3.3.6.4 Symptomatology

3.3.6.4.1 Primary Symptomatology
In cases in which the complete history was obtained, some patients described prodromal TIA-like symptoms with numbness and tingling or weakness [41].

The clinical features are in general different from ischaemic or embolic cerebrovascular accidents.

In the Harvard Stroke Registry and the Michael Reese Stroke Registry 51–63% of patients reported a mild progressive onset over minutes to hours combined with headache, nausea and vomiting and additional alterations in the level of consciousness in contrast to a rapid onset in 34–38% patients with ischaemic or embolic cerebrovascular accidents [42].

In general, the initial neurological findings at presentation of patients with supratentorial and infratentorial haemorrhages are dependent on the location and the size of the haematoma (see also Sect. 3.3.6.1).

It is useful for the classification to differentiate between specific and non-specific symptoms.

Patients with intracerebral haemorrhage involving the putamen, caudate and thalamus have contralateral sensory motor deficits of varying severity. Patients with large haematomas usually suffer rapid deterioration with a decreased level of consciousness as a result of increased intracranial pressure and direct compression of the thalamic and brain stem reticular activating system [43, 44].

It is also known that small and deep haematomas can lead to altered levels of consciousness. One explanation postulates decreased central benzodiazepine receptor binding on cortical neurons [45].

Dysfunction or loss of higher cortical function like aphasia, dysphasia, contralateral hemisensory deficit or mild hemiparesis and hemi-anopia are typical of lobar haemorrhages [42].

Patients with cerebellar haematomas show a different clinical symptomatology. In general, local cerebellar symptoms and signs of a brain stem dysfunction are in the foreground. Ataxia, nystagmus and dysmetria show the involvement of the cerebellum [46]. Brain stem signs include abnormalities of gaze, cranial nerve abnormalities and contralateral motor deficits [46].

Headache, nausea, vomiting and neck stiffness are non-specific symptoms [43, 47].

3.3.6.4.2 Secondary Deterioration
The risk of delayed or secondary deterioration concerns about one-third to one-half of all patients with intracerebral haematoma and the frequency of neurological deterioration was greatest within the first 24 h [48].

The reason for secondary deterioration is any combination of re-bleeding, oedema, hydrocephalus and seizures.

3.3.6.4.2.1 Rebleeding
The risk of rebleeding is well documented, is between 10 and 14% and decreases over time [49, 50]. Rebleeding is usually accompanied by clinical deterioration [50]. Worsening cerebral oedema is also implicated in delayed neurological deterioration [48]. Late deterioration during the second and third weeks is also observed and explained by oedema with unclear clinical significance [51].

3.3.6.4.2.2 Hydrocephalus
The presence of ventricular blood and the development of obstructive hydrocephalus definitely increase the risk of secondary deterioration or death [48, 52].
3.3.6.4.2.3 Seizures

Patients with spontaneous intracerebral haematomas are at higher risk of developing seizures than ischaemic stroke patients [53]. Seizures may be non-convulsive and are associated with neurological worsening and an increased midline shift [54]. The risk of epilepsy is higher in the first year after the index event and overall corresponds to about 8 per 100 patient years. The risk is probably higher in those with lobar haemorrhage, which more commonly involves the cerebral cortex [53].

3.3.6.4.3 Outcome

The functional outcome is similar to that of cerebral infarction [55].

Twelve community-based studies reporting a 1-month case fatality indicated a pooled estimate mortality of 42% [56].

A low score on the Glasgow Coma Scale, a large volume of the haematoma and the presence of ventricular blood on the initial CT are predictive factors of a high mortality rate [57–59].

3.3.6.5 Diagnostic Procedures

Besides a clinical examination with control of the vital signs and a check of the coagulation status, a conclusive distinction between cerebral infarction and intracerebral haemorrhage requires some sort of brain imaging [60].

3.3.6.5.1 CT

Computed tomography easily and immediately demonstrates blood as high density and the tendency towards a mass effect is also shown. In addition, a rapid manual method of measuring the haematoma volume on CT has been developed and validated. The volume is half the product of the diameters A, B and C (for each dimension) [57].

3.3.6.5.2 MRI

Magnetic resonance imaging also demonstrates intracerebral haemorrhage excellently. There is a time-dependent variation in MRI appearance and it may be difficult to detect an intracerebral haemorrhage within the first few hours [61, 62].

Further investigations are sometimes necessary to differentiate between primary and secondary intracerebral haemorrhage.

One study reported abnormalities on angiography in 48% of patients younger than 45 years who did not have hypertension.

Therefore, additional diagnostics may be recommended in all patients with isolated intraventricular haemorrhage and lobar haemorrhage, independent of their age. On the other hand normotensive patients under 45 years with putaminal, thalamic or cerebellar haemorrhage should undergo conventional angiography.

Computed tomographic angiography should be reserved for emergency situations with mass effect; MRA can also be used the sensitivity is not well established [64].

3.3.6.6 Treatment

3.3.6.6.1 Initial Management and Conservative Therapy

The initial work-up should concentrate on a basic examination including the evaluation of airways and breathing, circulation and a focused neurological status.

3.3.6.6.1.1 Oxygenation

The evaluation of adequate ventilation and the observation of a decreasing level of consciousness or airway protecting reflexes due to brain stem dysfunction are important clinical markers. Intubation is indicated for all patients with respiratory insufficiency as indicated by hypoxia (pO₂ < 60 mmHg or pCO₂ > 50 mmHg) or an obvious risk of aspiration (level of evidence A; Table 3.3.11) [65].

3.3.6.6.1.2 Blood Pressure

There is still considerable controversy regarding the initial treatment of blood pressure after intracerebral haemorrhage. One rationale is that hypertension in patients with intracerebral haemorrhage increases the risk of ongoing bleeding, which is associated with a poor outcome [66]. The data for this relation remains unclear with regard to the question whether hypertension predisposes to haematoma expansion or is a consequence of this event [67]. The opposite rationale is that elevated blood pres-

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<th>Table 3.3.11 Levels of evidence</th>
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<tbody>
<tr>
<td>Level of evidence Grade A</td>
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<tr>
<td>Level of evidence Grade B</td>
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<tr>
<td>Level of evidence Grade C</td>
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<tr>
<td>Level of evidence Grade D</td>
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ure has protective properties as it preserves cerebral perfusion (Cushing–Kocher response), especially in the case of elevated intracranial pressure [68].

To reconcile these rationales, our recommendation for patients with a history of hypertension is a moderate control of mean arterial blood pressure below 130 mmHg (systolic arterial blood pressure below 170 mmHg; level of evidence D; Table 3.3.11) [69]. If intracranial pressure is available, cerebral perfusion pressure should be maintained over 70 mmHg (level of evidence D; Table 3.3.11) [23].

3.3.6.6.1.3 Fluid Management
Normovolemia with a central venous pressure between 5 and 12 mmHg is the aim of the treatment. Electrolytes (sodium, potassium, calcium) should be controlled and substituted into a normal range.

3.3.6.6.1.4 Seizures
Most seizures develop at the onset of intracerebral haemorrhage or within the first 24 h [70]. There is a trend towards increased poor outcome in patients with post-haemorrhagic seizures [54]. Therefore, our recommendation is the treatment of seizures with anticonvulsants and discontinuing the antiepileptic therapy if no seizure activity occurs after 1 month (level of evidence D; Table 3.3.11) [71].

3.3.6.6.1.5 Medical Therapy: Randomized Trials
Two small randomized trials comparing steroids versus placebo treatment showed no significant benefit [72, 73]. In fact, one of these studies demonstrated that the patient group treated with steroids developed more infectious complications than the placebo group.

Likewise, one randomized trial using glycerol versus placebo [74] and another using haemodilution versus best medical therapy [75] ended without demonstration of a significant beneficial effect.

Ultra-early haemostatic therapy to minimise the increase in haemorrhage volume is currently thought to improve the outcome [76].

Several agents including fresh frozen plasma, prothrombin concentrate, factor IX concentrate, human and recombinant factors VIII and IX, cryoprecipitate, aminocaproic acid, aprotinin and activated recombinant factor VII theoretically influence the rebleeding rate [76].

Activated recombinant factor VII with probably the highest potential was investigated in patients with spontaneous intracerebral haemorrhage and published in February 2005 [77]. In the course of a multicentre, prospective and randomized study in patients with intracerebral haematoma, the investigators compared one group treated with recombinant activated factor VIIa (rFVIIa) and another group treated with placebo. The results in 399 patients documented that treatment with rFVIIa, within 4 h after the onset of intracerebral haemorrhage, limits the growth of the haematoma, reduces mortality and improves functional outcomes after 90 days, despite a small increase in thromboembolic adverse effects (level of evidence A; Table 3.3.11).

3.3.6.6.1.6 Intracranial Pressure Management
Elevated intracranial pressure is considered to be a major contributor to mortality after intracerebral haemorrhage [23].

Elevated intracranial pressure for adults is defined as intracranial pressure more than 20 mmHg over 5 min. The therapeutic target is intracranial pressure below 20 mmHg and cerebral perfusion pressure over 70 mmHg [69].

Initial treatment for intracranial hypertension should include an optimised head position, moderate hyperventilation and osmotic agents (level of evidence D; Table 3.3.11) [78].

Few data are available on mannitol. There are no randomised trials documented in literature; however, mannitol 0.25–0.5 g/kg every 4 h is often used in patients with large haematomas in combination with increased intracranial pressure for up to 5 days [23].

Corticosteroids should be avoided as mentioned before (level of evidence A; Table 3.3.11) [72, 73].

Experience with high doses of barbiturates to induce a barbiturate coma is limited. They can be chosen as a last resort to control intracranial hypertension, provided there is tolerance, but further investigation is needed [79].

3.3.6.6.2 Surgical Therapy
The surgical therapy of intracerebral haemorrhage is one of the most debated and controversial areas of neurosurgery.

Theoretically, haematoma evacuation should be beneficial due to volume reduction and lowering of intracranial pressure [80–82]. Therefore, perfusion in the surrounding areas should be improved by evacuation of the haematoma [83–85].

Additionally, secondary enlargement of the haematoma and the results of toxic products could be avoided [51].

However, clinical results in a number of different trials have not established a generally accepted treatment strategy so far [86, 87].

The major questions are whether, on whom, when and how should we operate?

3.3.6.6.2.1 Removal of Intracerebral Haemorrhage
In 1961, McKissock and Taylor reported the first prospective randomised trial that showed that operative treatment was associated with worse patient outcome [88]. More than 25 years later the second prospective random-
ized controlled trial documented the opposite result for endoscopic clot removal [89] and was disproven by another group in the same year [90].

These initial trials were followed by studies of Batjer and colleagues [91], Morgenstern and colleagues [92], Zuccarello and colleagues [93] as well as smaller trials and meta-analyses.

Congruent results with clear treatment guidelines are not available [94], even the results of the latest prospective randomised study, the STICH trial, published in January 2005, have been obtained [95]. In this international trial, early surgery and initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas were compared. A total of 1,033 patients were included and randomized for conservative management (530) or early surgery (503). The authors concluded that there was no overall benefit from early surgery when compared with initial conservative therapy [95].

However, going into the study in more detail there was a subgroup of patients clearly profiting from early surgery. These were patients with superficial large lobar haematoma in a better neurological condition. As known from earlier trials, prognosis was additionally related to age.

Therefore, our recommendation to operate on intracerebral haematomas is dependent on age, neurological condition and trend, haematoma location and volume as well as radiological tentorial herniation and coagulation disorders.

Compose a cross sum of these above-mentioned factors is important in the decision process.

An age of over approximately 65 years inclines more to initial conservative management (level of evidence A–D; Table 3.3.11).

Patients with a GCS score below 4 should be treated with supportive care because of a high chance of poor functional outcome that cannot be improved by surgery (level of evidence A–D; Table 3.3.11).

Secondary neurological deterioration in patients after intracerebral haematoma is an indicator surgery (level of evidence B–D; Table 3.3.11).

Patients with large haematomas measuring more than 50 ml are potential surgical candidates (level of evidence A–D; Table 3.3.11) particularly in case of superficial or lobar haemorrhages (level of evidence A–D; Table 3.3.11).

Patients with coagulation disorders should first be treated with conservative therapy.

### 3.3.6.6.2.2 Cerebellar Haemorrhage

There has been up to now no documented randomised trial on the treatment of intracerebellar haemorrhage.

Non-randomised trials reported in patients with cerebellar haemorrhage larger than 3 cm in diameter or signs of brain stem compression or hydrocephalus have reported good outcomes [46, 96–98]. In these patients, medical treatment alone resulted in poor outcome [99].

For this reason, we recommend surgical removal as soon as possible in patients with a cerebellar haemorrhage larger than 20–30 ml or 3 cm in diameter who are neurologically deteriorating, or patients with brain stem dysfunction or with obstructive hydrocephalus [98] (level of evidence B–D; Table 3.3.11).

### 3.3.6.6.2.3 Minimally Invasive Surgery

There is evidence that classical craniotomy for intracerebral haematoma additionally traumatises brain tissue and influences the functional outcome negatively [100, 101]. Therefore, minimally invasive surgery was developed to achieve clot removal with minimal side effects.

One of the first documented studies to use ultrasound-guided endoscopic clot removal was published by Auer and colleagues [102]. The following randomised trial resulted in the improved outcome of a surgically treated group [89].

An even less invasive technique was introduced by using plasminogen activator for clot lysis in combination with minimally invasive surgery.

So far, to investigate the efficacy of stereotactic treatment for primary intracerebral haematoma, case reports, a couple of small trials [93, 103–105] as well as the randomised SICHPA trial [106] have been published and documented an improved functional outcome.

Therefore, particularly for deep haematomas, the stereotactic approach is favoured, while a small focused craniotomy allows complete and immediate removal of the haematoma in superficial haemorrhages (level of evidence B–D; Table 3.3.11).

### References

3.3.6 Spontaneous Intracerebral and Intracerebellar Haemorrhage in Adults


3.3 Vascular Diseases


86. Hankey GJ (Evacuation of intracerebral hematoma is likely to be beneficial against. Stroke 34(6):1568–1569


3.3.7 Pediatric Vascular Lesions


3.3.7 Pediatric Vascular Lesions*

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3.3.7.1 Pediatric Intracranial Arteriovenous Shunts

3.3.7.1.1 From Adults to Children

Cerebral arteriovenous (AV) shunts have different characteristics in children from those in adults. Children can have multifocal lesions, induced remote AV shunts, large venous ectasias, high-flow lesions and single-hole arteriovenous fistulas (AVF), venous thrombosis, brain atrophy, and systemic phenomena. Conversely, high-flow angiopathic changes are rare in children as are flow-related arterial aneurysms, while proximal occlusive arteriopathy is more frequent. For this reason, management protocols derived from experience in adults should not be applied to the pediatric population. In particular, adult-based classifications and AVM grading according to the expected surgical outcome is particularly inappropriate in children, in whom:

- Cerebral eloquence is difficult to assess, particularly in the first few years of life.
- Most lesions are fistulas or multifocal.
- Drainage usually affects the entire venous system.
- The potential for recovery is different.

In addition to the conventional objectives, the decision-making process in children must take into consideration additional specific details pertaining to the veins and the myelination process. Neurocognitive evaluation is the key follow-up criterion in children even without deficits, hemorrhage or seizures, as it helps in the assessment of treatment quality and success. Failure to obtain a normal maturation process may constitute a therapeutic failure if the optimal moment for intervention has been missed (therapeutic window).

Lesions in children are divided into non-proliferative and proliferative lesions. The former group comprises vascular malformations, the latter hemangiomatous lesions. In fact such a distinction, which has been helpful during the past 20 years, has also greatly benefited from recent biological contributions as well as the recognition of shear stress mechanisms in vascular modeling and remodeling.

3.3.7.1.2 Types and Disease Groups of Vascular Lesions

Even in an apparently single disease category such as CAVMs, several entities must be distinguished, as their predictable presentation or evolution requires different management at different times. The generic name regrouping of artificially different situations expresses the use of a single key (the arteriovenous shunt, for example), where two or three would reveal the differences (familial disorder for hereditary hemorrhagic telangiectasia [HHT], metameric disease for CAMS, proliferative activity for proliferative angiopathy, PHACE [posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities] syndrome, etc.) (Fig. 3.3.20).

3.3.7.1.2.1 Non-Proliferative Lesions

3.3.7.1.2.1.1 AV Lesions

The AV lesions that can be encountered depend on the meningeal space from which they primarily develop: dural, pial, “subarachnoid” or choroidal. These locations give rise to several subtypes and may be unifocal, multifocal, hereditary, etc.
3.3.7.1.2.1.2 **Isolated Brain AVMs**

Isolated brain AVMs can be small (micro-AVM) or large (macro-AVM), and this distinction is of nosological interest as the passage from one type to the other cannot be demonstrated. Of interest is the distinction between the nidus type (with an arteriolar network) and the fistulous type (single or multiple large, direct AV communication). Finally, there is no gender dominance in CAVM in children.

3.3.7.1.2.1.3 **Vein of Galen Aneurysmal Malformations**

Vein of Galen aneurysmal malformations (VGAM) constitute a unique, well-defined group of malformations that occur at the end of the embryonic period. They make up a separate group from other lesions such as CAVMs, which are often called non-Galen vein AV malformations, particularly in neonates and infants. In the VGAM group, there is a 2–3:1 male predominance.

3.3.7.1.2.1.4 **Cerebrofacial Arteriovenous Metameric Syndrome**

Features of the cerebrofacial arteriovenous metameric syndromes (CAMS), as originally described and common to all, include arteriovenous malformations of the brain and orbit (with retinal and/or retrobulbar lesions) (Bonnet–Dechaume–Blanc or Wyburn–Mason syndrome) and maxillo-facial lesions. We have suggested segmental patterns of involvement in what is likely to be a disease of the neural crest and/or adjacent cephalic mesoderm. A newly proposed rational classification reflects the putative, underlying disorder and calls for a new acronym: CAMS.

3.3.7.1.2.1.5 **Dural Lesions**

Dural lesions can be encountered at any age in children, but represent different disease entities (Fig. 3.3.21). They can present as true malformations in very young children or as secondary AV shunts in older children. The former are encountered in neonates and infants and can be diagnosed in utero. The latter are usually multifocal and contain large sinuses and high-velocity flow phenomena, but are originally associated with low pressure in the dural sinuses.

3.3.7.1.2.1.6 **Telangiectasias**

Telangiectasias are usually included in the malformation group and they are occasionally described in children at autopsy. They are likely to represent improper capillary remodeling.

3.3.7.1.2.1.7 **Blue Rubber Bled Nevus Syndrome**

The blue rubber bled nevus (BRBN) or Bean syndrome can produce multiple types of CNS (central nervous system) involvement. These features consist of multiple VMs (venous malformations similar to large telangiectasias), DVAs (developmental venous anomalies) in supratentorial brain, the cerebellum, and the tectum mesencephali. Although BRBN can be sporadic, its familial transmission is frequent and the link with HHT1 unlikely, despite the involvement of the same chromosome (Chr9p).

3.3.7.1.2.1.8 **Venous Malformations (Cavernomas)**

Venous malformations (cavernomas) are located outside the nervous tissue and therefore do not contain nervous or glial elements. They are referred to as being cavernous and can be isolated or multiple. In the latter case, they
are often familial with autosomal dominant transmission. These lesions are malformations and can be found in autopsy series in any location within the intradural space (subarachnoid, subpial). They increase in size following intralesional hemorrhage. They occasionally have the appearance of a tumor (particularly in children) or a cyst, through confluence of recurrent hematomas. They can be associated with venous anomalies or other malformations such as dural sinus AV malformations (DSM) and can be induced by radiation therapy.

3.3.7.1.2.1.9 Developmental Venous Anomalies

So-called venous angiomias or developmental venous anomalies (DVA) are anatomic variations that can involve one or both hemispheres and be located infratentorially. They do not exist at the spinal cord level or where no secondary germinal matrix migration has occurred. DVAs should therefore never be a target for treatment.

3.3.7.1.2.1.10 Cerebrofacial Venous Metameric Syndrome

Cerebrofacial venous metameric syndrome (CVMS, formerly Sturge–Weber syndrome). The syndrome consists of cutaneous, facial, port-wine stain (venular malformation), subcutaneous lymphatic malformations (with secondary maxillo-facial bone and soft tissue hypertrophy), and cerebral, cortical vein thrombosis with cortical atrophy, secondary angiogenesis and transhemispheric venous drainage, with or without choroid plexus hypertrophy. The facial involvement represents the distal destination of the migrating neural crest cells, contributing to the vascular network rather than the "trigeminal dermatome."

3.3.7.1.2.1.11 Induced Pial Shunts

Induced pial shunts are unique in juvenile dural arteriovenous lesions and occur only in children. They develop with the sump effect from the abnormal dural sinus, retrograde to the cerebral vein, with subsequent pial AV shunt formation.

3.3.7.1.2.1.12 Spinal Cord AVM

Spinal cord AVM and spinal cord cavernous malformations present the same characteristics as those mentioned in the brain. Similar to the cranial region, SAMS are recognized, enriching the historical description of Cobb's syndrome.
3.3.7.1.2.2 Proliferative Lesions
Proliferative vascular lesions in children form a distinct group of disorders; the name angiomatous is often given indiscriminately to all apparently congenital, non-ischemic vascular lesions.

3.3.7.1.2.2.1 Hemangiomas
The name angiomatous (vascular growth) should be abandoned or reserved for hemangiomas, which are benign tumors of blood vessel origin in infants. Some hemangiomas can be seen intracranially, but such localization is rare and usually associated with superficial hemangiomas. Yet some of them keep a capillary angioarchitecture and are named NICH (non-involuting capillary hemangiomas).

3.3.7.1.2.2.2 PHACE Syndrome
PHACE or PHACES are acronyms for a syndrome of variable phenotypic expression comprising posterior fossa malformations, facial hemangiomas, arterial anomalies, coarctation and other cardiac disorders, eye abnormalities, and stenotic artery disease; many of the elements of this disorder may reflect an underlying abnormality of cell proliferation and apoptosis.

3.3.7.1.2.2.3 Proliferative Angiopathy
Moya-moya disease, moya-moya-like syndromes, and proliferative angiopathy in children are the most typical disorders in this group. They combine neoangiogenesis (production of the lumen) and angioectasia (production of the vessel wall), which may be difficult to differentiate; however, in such instances there is a discrepancy between the apparent size of the “nidus-like” network of vessels and the draining veins that are often normal or slightly enlarged.

In proliferative angiopathy, while seizures are the most common clinical symptom at presentation, headaches and progressive deficits are also possible, whereas hemorrhage is exceptional. In our experience, the risk of hemorrhage being low at presentation, the risk of recurrence once a hemorrhagic episode has occurred is significantly higher than in CAVM. Transdural supply in remote locations (supra- and infratentorial, bilateral) confirms the diffuse character of the angiogenetic activity of the disease, suggesting an unpressed response to cerebral sub-ischemic manifestations. Proliferative angiopathy is still often confused with CAVMs and thought to represent a diffuse nidus. Treatment should therefore not be emollient (or surgery or radiation therapy) unless areas of the angio-architecture suggest zones of weakness or demonstrate obvious constraints to the eloquent brain. Today, perfusion MRI has reinforced the suspicion of chronic ischemic disease with angiogenetic activity, as in moya-moya, and similar treatment with burr holes has already been performed in a handful cases with immediate good clinical results on both the headaches and the seizure response to medical treatment.

3.3.7.1.2.2.4 Moya-Moya Disease
Moya-moya disease is a primary vascular disease characterized by progressive stenosis and eventual occlusion of the supra-oculoid portion of the internal carotid artery and the adjacent segments of the middle and anterior cerebral arteries. In response, an abnormal vascular network of small collateral vessels develops to bypass the area of occlusion. The most frequent symptoms in childhood are multiple transient ischemic attacks, with permanent residual following some episodes. Seizures occur in 33% of children under the age of 6 years. Moya-moya represents 10–20% of strokes in children, and is grouped into primary and secondary moya-moya. Many pseudo-moya-moya patterns can be seen, with slowly progressing large-vessel vasculopathy with collateralization in childhood. Moya-moya syndrome or the moya-moya phenomenon can be considered to be responses to different triggers of different weaknesses, rather than true diseases. Specific vulnerability includes a familial occurrence noted in 10% of cases with linkage to Chr17q25, and 3p24.2–26.

3.3.7.1.2.2.5 Hemorrhagic Angiopathy
Hemorrhagic angiopathy is another entity that we encounter in some rare cases of intracerebral hematomas in children. Often, after the age of 5, they correspond to a network of intracerebral subcortical arterioles with normal morphological and sequential venous drainage. They may re-hemorrhage and can therefore be partially embolized when the area of weakness in the angioarchitecture can be identified. The response to radiation therapy is amazingly rapid and efficient.

3.3.7.1.3 Classification of CAVMs by Age Group

3.3.7.1.3.1 Fetal Age
Intrauterine antenatal ultrasound or MRI diagnosis of a large fetal intracranial mass as a pseudocystic, non-echogenic or poorly echogenic spherical image, depending on its topography, either represents a VGAM or a dural sinus malformation (DSM). With regard to the fetal brain, macrocrania can be seen in both VGAM and DSM, but the two types differ with regard to prognostic value. In VGAM, macrocrania (in the absence of ventricular enlargement) is usually a benign observation without a negative impact on the prognostic neonatal score. In contrast, macrocrania in DSM indicates an already active sinus dysfunction with water and venous effect; if present, the prognosis, which is already not good, would become even worse. The only finding that has the same importance at the fetal stage, regardless of the type of AV shunt, is the presence of encephalomalacia. The presence
of isolated cardiomegaly has no impact on prognosis. On the other hand, cardiac failure in fetuses with VGAM is known to be pejorative (Fig. 3.3.22).

3.3.7.1.3.2 Neonatal Age
At the neonatal stage there is a fundamental difference between VGAM and non-Galenic AV malformations (pial). Early neurological symptoms in VGAM are of major negative prognostic value, to the extent that treatment may be withheld. On the other hand, similar symptoms are an indication for emergency management in non-Galenic AVMs (Table 3.3.12).

The systemic symptoms in neonatally diagnosed CAVM are usually better tolerated than in VGAM, probably because the veno-dural junction is relatively well preserved and protects the cardiac function. Hemorrhage in VGAM does not occur in this age group. A hemorrhagic episode or convulsion in a neonate should steer one away from the diagnosis of VGAM.

3.3.7.1.3.3 Infancy
Infancy is dominated by hydrovenous disorders. The granulations are not yet functional, and their maturation is likely to be delayed if increased pressure is present in the dural sinuses.

The signs of water retention start with macrocrania without ventriculomegaly. Clinical consequences are almost consistently neurocognitive delay without any direct relationship to the degree of the increase in the head circumference. If left untreated, this water dysfunction progressively leads to ventriculomegaly. Ventricular shunting at that time is associated with significant morbidity.

Venous changes have a direct impact at this age. In non-Galenic AVMs, local congestion rapidly leads to focal ischemia, as revealed by convulsions and later hemorrhage. In VGAM, pial congestion is absent for a long time and depends on whether maturation of the venous drainage at the skull base occurs (cavernous sinus capture). The dysmaturation and subsequent closure of the jugular foramen in VGAMs, in some CAVMs and in DSM patients are unlikely to be related to high-flow venous angiopathy, and more likely to lead to impaired postnatal development. The slowly developing end result of hydrovenous dysfunction at the posterior fossa level will be progressive tonsillar prolapse. This prolapse is reversible for a long time with adequate treatment of the AV shunt.

This supports the concept of a therapeutic window during which to intervene at the optimal moment, permitting treatment to result in a normally developing child.

3.3.7.1.3.4 After the Age of 2 Years
Children who have not presented with systemic and hydrovenous disorders will reveal their vascular lesions with neurological symptoms. Venous thrombosis may start to

**Fig. 3.3.22** Natural history of vein of Galen aneurysmal malformations
Vascular Diseases

Thus, two high-flow lesions, both apparently located on the surface of the brain, may have different effects on the underlying cerebral tissue depending on whether they open directly into subpial or subarachnoid outlets, almost independently of the flow they carry. The clinical interaction with young children and adolescents will be particularly challenging and entirely different from that in adults; information for parents also requires thorough knowledge of the consequences of the diseases involved rather than the techniques available (Table 3.3.13).

3.3.7.1.4 Melting Brain Syndrome

Melting brain syndrome consists of the rapid destruction of the brain, usually the white matter, with secondary ventricular enlargement. This phenomenon is associated with severe neurological manifestations and no signs of increased intracranial pressure, although they are usually present before the morphological damage is seen. When the brain suffering leads to trophic changes these are usually bilateral and symmetrical; they correspond to a regional decrease in the cerebral blood flow caused by retrograde venous hyperpressure, leading to hydrovenous dysfunction. Arterial steal is not present or an accessory in this syndrome. The local atrophy around a PAVM can represent focal expression of this phenomenon. These findings are never encountered in adults. This mechanism is progressive and once it starts, develops fairly rapidly, although it is slow enough to result in a loss of substance rather than a hemorrhagic infarct, which supports the role played by water in the maintenance of brain tissue. In contrast, the subarachnoid veins travel directly into the peri-cerebral spaces with little impact on the intrinsic water physiology as long as the dural sinuses are sufficiently patent. Thus, two high-flow lesions, both apparently located on the surface of the brain, may have different effects on the underlying cerebral tissue depending on whether they open directly into subpial or subarachnoid outlets, almost independently of the flow they carry.

### Table 3.3.12 Bicêtre Neonatal Evaluation Score

<table>
<thead>
<tr>
<th>Points</th>
<th>Cardiac function</th>
<th>Cerebral function</th>
<th>Respiratory function</th>
<th>Hepatic function</th>
<th>Renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Overload, no med tt.</td>
<td>Subclinical isolated EEG Abn’s</td>
<td>Tachypnea, finishes bottle</td>
<td>No hepatomegaly, normal function</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>Failure – stable with med tt.</td>
<td>Non convulsive intermittent neurologic</td>
<td>Tachypnea does not finish bottle</td>
<td>Hepatomegaly, normal function</td>
<td>Transient anuria</td>
</tr>
<tr>
<td>2</td>
<td>Failure – not stable with med tt.</td>
<td>Isolated convulsion</td>
<td>Assisted ventilation, normal saturation FIO2 &lt; 25%</td>
<td>Hepatomegaly, normal function</td>
<td>Transient anuria</td>
</tr>
<tr>
<td>1</td>
<td>Ventilation necessary</td>
<td>Seizures</td>
<td>Assisted ventilation, normal saturation FIO2 &lt; 25%</td>
<td>Moderate or transient hepatic insufficiency</td>
<td>Unstable diuresis with treatment</td>
</tr>
<tr>
<td>0</td>
<td>Resistant to med tt.</td>
<td>Permanent neurological signs</td>
<td>Assisted ventilation, desaturation</td>
<td>Abn coagulation, elevated enzymes</td>
<td>Anuria</td>
</tr>
</tbody>
</table>

Maximal score = 5 (cardiac) + 5 (cerebral) + 5 (respiratory) + 3 (hepatic) + 3 (renal) = 21

### Table 3.3.13 Bicêtre Admission and Outcome Score*

<table>
<thead>
<tr>
<th>Score</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal (N)</td>
</tr>
<tr>
<td>4</td>
<td>Minimal non-neurological symptoms, not treated (MS) and/or asymptomatic enlargement of the cardiac silhouette</td>
</tr>
<tr>
<td>3</td>
<td>Transient neurological symptoms, not treated (TNS) and/or asymptomatic Cardiac overload under treatment</td>
</tr>
<tr>
<td>2</td>
<td>Permanent minor neurological symptoms, mental retardation of up to 20%; Non-permanent neurological symptoms under treatment (MNS) Normal School with Support and/or Cardiac failure stabilised with treatment</td>
</tr>
<tr>
<td>1</td>
<td>Severe neurological symptoms, mental retardation of more than 20% (SNS); Specialised School and/or Cardiac failure unstable despite treatment</td>
</tr>
<tr>
<td>0</td>
<td>Death (D)</td>
</tr>
</tbody>
</table>

* Does not apply to neonates
3.3.7.2 Intracranial Aneurysms in Children

3.3.7.2.1 Introduction
Aneurysms are not congenital, in the respect that they are not present at birth. Yet, they reflect various types of structural or functional weaknesses already present in utero and expressed at a later age. Aneurysm is therefore a generic name encompassing various disorders involving the vessel wall. Aneurysm formation is likely to require both a local target (vessel wall structure or function) and systemic triggers that are more or less specific for that arterial segment.

Aneurysmal vasculopathies in the pediatric age group are significantly different from those in adults:
- There is a male dominance of 2–3:1.
- There is a higher incidence of unusual sites (posterior circulation > 30%).
- There is a predilection for a carotid bifurcation location (31–54%).
- There are a greater number of large and giant aneurysms (20%).
- There is a lower incidence of multiple aneurysms (<10%).
- The morbidity rate is lower.
- There is a higher incidence of traumatic, dissecting, and infectious etiologies.
- There is a higher incidence of spontaneous thrombosis.
- Aneurysms are 1.6 times more frequently responsible for intracranial hemorrhage (ICH) than CAVMs in white populations.
- Aneurysms are four times less frequently responsible for ICH than CAVMs in some Asian populations.

These differences are more pronounced in early childhood and become less obvious toward adolescence.

3.3.7.2.2 Incidence
Intracranial aneurysms in the pediatric age group represent less than 5% (0.6–4.6%) of the total number of intracranial aneurysms in the general population. The higher incidence of intracranial aneurysms in women in the adult population is reversed in the pediatric population, in which the male to female ratio varies from 2:1 in infants up to 8 years of age, to a nearly equal ratio of 1.2:1 in the 10–20 age group.

3.3.7.2.3 Presentation
When assessing the entire pediatric age group, about 70% of patients with intracranial aneurysms present with subarachnoid hemorrhage. The incidence of hemorrhage, however, is reported to be as high as 82% if only infants and children below 5 years of age are considered. The incidence appears to progressively decrease and to be as low as 45% if only children over 5 years of age are considered. Other clinical presentations, such as seizures and stroke, are uncommon and occur in less than 10% of cases. Many of the children in our studies presented with a neurological deficit or headaches. The type of presentation with subarachnoid hemorrhage (SAH) or intracerebral hematoma varied depending upon the age of the child and was increased below 2 years of age and between 6 and 15 years of age, which coincided with the peak incidences of dissections and saccular aneurysms (Fig. 3.3.23).

3.3.7.2.4 Etiology
In our patient groups, clear known causes were found in less than 50% of the aneurysms. However, various subgroups of aneurysms can be identified: traumatic (5–10%), infectious (15%), saccular (30%), and dissections (about 50%). Such numbers must be adjusted to the age at the time of referral as dissection will be dominant during the first 5 years of life and saccular ones occurring between the ages of 6 and 15 (Fig. 3.3.24).

3.3.7.2.4.1 Traumatic Aneurysms
3.3.7.2.4.1.1 Traumatic
The majority of children with traumatic aneurysms present with a hemorrhagic episode about 3–4 weeks after the original injury. Twenty percent healed spontaneously. A mortality rate of 31% has been reported in children with traumatic intracranial aneurysms that were not operated upon.

3.3.7.2.4.1.2 False or Pseudo-Aneurysm
In this group of post-traumatic AA, a false or pseudo-aneurysm from a ruptured vessel can occur, which corresponds to an extravascular space, usually within a hematoma. Evolution of such lesions can sometimes be favorable, with spontaneous healing of the leakage point.

3.3.7.2.4.2 Infectious Aneurysms
Today the term “infectious arterial aneurysm” (IAA) seems more appropriate. While they can be caused by fungal infections, they are most often bacterial. They account for 1.5–9% of all intracranial aneurysms (pediatric and adult), but represent less than 1–2% of our interventional practice. The most common organism has been Staphylococcus, followed by Streptococcus and other Gram-negative organisms. They often complicate bacterial endocarditis in infants with congenital or rheumatic heart disease. IAA’s may involve the intracavernous ICA by contiguity, following severe sphenoid sinus infections with osteomyelitis and cavernous sinus thrombophlebitis.
Yet, the concept of “infectious” is too narrow to account for the complexity of the disorders encountered under this heading. In fact “infectious and immune” indicates the agent and the host, describing the two components of the same disorder. Several reports of aneurysms associated with the human immunodeficiency virus (HIV) can be found in the literature.

We observed similar features in chronic mucocutaneous candidiasis (CMCC). CMCC is a familial disease with a primary immunodeficiency disorder that should be distinguished from the opportunistic candidiosis seen in globally immunocompromised patients (steroid therapies, chemotherapies).
3.3.7.2.4.3 Saccular Aneurysms
The saccular type of aneurysm remains as controversial in the pediatric age group as they are in adults. Between 50 and 70% of aneurysms in the pediatric population are believed to be of this type. Despite their location at the bifurcation of various vessels, intrinsic hemodynamic factors almost certainly play less of a role than in adults. Mural or systemic factors are considered to be more important.

Ehlers–Danlos syndrome, Klippel–Trenaunay syndrome, polycystic kidney disease, tuberous sclerosis, moyamoya syndrome, co-arctation of the aorta, and fibromuscular hyperplasia have all been documented to occur in association with aneurysms in children.

3.3.7.2.4.3.1 Familial Occurrence
Familial occurrence has been reported in children, but appears to be less frequent than in adults.

The association of autosomal dominant polycystic kidney disease (PKD) with intracranial aneurysms (IA) is a well-known occurrence in the adult age group, but is rare in children. The combination of the recessive form and AA is exceptional.

No data exist regarding the outcome of non-operated children presenting with saccular AA. Most of the familial diseases associated with AA do not occur during childhood, as though additional triggers with subsequent alteration of the disease or loss of compensation (“second hit”), is needed for the AA to develop.

3.3.7.2.4.3.2 Multiple Saccular Aneurysms
The incidence of multiplicity is higher in children with aneurysms of infectious origin. In fact, the multiplicity is low in saccular aneurysms in comparison to adult groups, but is high if the dissection etiology group is considered and is even higher among the infectious and immuno-compromised ones.

3.3.7.2.4.3.3 Flow-Related Aneurysms
Flow-related aneurysms associated with CAVMs are not seen in the pediatric population.

3.3.7.2.4.3.4 Additional Aneurysms
Additional aneurysms seen in children and likely to correspond to an underlying specific dysplastic disease are those associated with PHACE and CAMS. These two syndromes illustrate the angiogenetic nature of some aneurysmal vasculopathies.

3.3.7.2.4.4 Dissecting Aneurysms
The dissecting aneurysm group is related to a specific type of mural damage, non-infectious and non-immune in this section, which may actually ignore the fact that spontaneous dissections in babies may result from an unrecognized immune type of segmental aggression or segmental vascular failure. The frequency of dissecting aneurysms in the pediatric age group is four times that of the adults. The mean age of the child with dissecting aneurysm is 6 years.

Focal arterial stenotic segments are often observed proximal or distal to the dissecting aneurysm, suggesting mural damage. Impaired vessel wall with stenosis can induce spontaneous damage. Some of the dissecting aneurysms heal spontaneously, leading to associated occlusion of the parent artery. This is often well tolerated in the child owing to good collateral circulation via the circle of Willis or pial collateral anastomoses.

Dissecting aneurysms of the MCA (M1), or ACA (A1) are the most difficult cases to manage because of the absence of a neck and the involvement of perforating arteries arising from the dissected aneurysmal wall. These tend to be unstable and rebleed rapidly. Dissecting aneurysms presenting with deep-seated ischemic infarcts should therefore be analyzed with great care.

Schematically, two types of dissections can be encountered:

- Extensive vessel wall damage (fusiform or wide neck “saccular” aneurysms) without evidence of mural hematoma; they may present with a deep-seated stroke or an SAH. Early recurrence of rupture often occurs during the first few days. Aggressive treatment is recommended.
- Focal lesions that can be of large size (giant or large “saccular” aneurysms), with evidence of recent mural hematoma on CT or MRI. Presentation is often ischemic and spontaneous healing with completion of the lumen thrombosis is frequently observed and medical treatment with aspirin or even anticoagulation is recommended; anti-inflammatory treatment may have to be discussed.

3.3.7.2.4.5 Giant Aneurysms
Giant aneurysms, as seen in adults, should not only be distinguished because of their size, but also as a group within the dissection category. They seem to constitute a specific type of mural failure (perhaps disease). Their frequency is higher in children. Giant-sized aneurysms are about four times more common in children than in adults.

3.3.7.2.5 Location
Recent reviews demonstrate that depending on the type of referral the most frequent location will in fact vary. This observation accounts for the wide range of numbers quoted in the literature and which did not discriminate amongst the various etiologies. In particular among infectious, immune and saccular aneurysms there is a clear preference for involvement of the anterior circulation, whereas the posterior circulation is predominantly in-
volved by the dissections. The age profile of the referred children will also have an impact on the type of etiology faced and consequently the location of the aneurysms. The likelihood of the multiplicity of the lesions in a given child will also depend on the etiology of the aneurysm (Fig. 3.3.25).

3.3.7.3 Pearls

3.3.7.3.1 Pial AV Shunt in Children
- Micro/Macro AVM
- Micro/macro AVF
- Multifocal
- CAMS
- Familial
- Proliferative angiopathy
- Hemorrhagic angiopathy
- False and induced AV shunts

3.3.7.3.2 Galenic Vascular Lesions in Children
- Choroidal VGAM
- Mural VGAM
- VGAD
- Dural VGAV shunt
- Venous dilatation

3.3.7.3.3 Dural AV Shunt in Children
- Sinus malformation
- High-flow lesions
- Multifocal
- “Adult” types
- Post-traumatic

3.3.7.3.4 Intracranial AV Shunt in Children: In Utero Manifestations
- Congestive cardiac failure (CP > 200/min, ventricular extrasystoles, tricuspid insufficiency)
- Macrocrania
- Ventriculomegaly
- Brain loss

3.3.7.3.5 Intracranial AV Shunt in Children

3.3.7.3.5.1 Systemic Manifestations
- Cardiac failure
- Pulmonary hypertension
- Renal dysfunction
- Hepatic insufficiency
- Coagulation disorders

3.3.7.3.5.2 Hydrodynamic Manifestations
- Macrocrania
- Ventriculomegaly
- Tonsillar prolapse
- Melting brain syndrome
- Hydromyelia

3.3.7.3.5.3 Cerebral Manifestations
- Venous congestion
- Venous ischemia
- Hemorrhagic infarct
- Melting brain syndrome
- Arterial steal

3.3.7.3.5.4 Neurological Symptoms
- Mental retardation
- Epilepsy
- Deficit
- Hypertony
- Headaches

3.3.7.3.6 Familial Diseases
- Seldom symptomatic in the pediatric age
- Arterial aneurysm (PKD, Chr16, Chr4, etc.)
- Pial arteriovenous shunts (HHT, Chr12, Chr9)
- Usually high-flow multifocal AVFs
- ED Chr2, NF1 Chr17: “spontaneous” AVFs, parachordal AVFs
- Cavernomas Chr7: often multiple in the brain and the cord
- BRBN Chr1, Chr9

Fig. 3.3.25 Location of 112 intracranial pediatric aneurysms (Bicêtre hospital series)
3.3.7.3.7 **Sporadic or “Primitive” Diseases**

- Vein of Galen aneurysmal malformations (30% diagnosed in utero)
- Dural sinus malformation (50% diagnosed in utero)
- Pial arteriovenous shunts (cerebral or cord; 1.3% diagnosed in utero)
- CAMS/SAMS (Bonnet–Dechaume–Blanc, Wyburn–Mason, Cobb)

- Single cavernoma
- CVMS (Sturge–Weber)

3.3.7.3.8 **Acquired or Secondary**

- Dural arteriovenous shunt (juvenile and adult types)
3.4 Infectious Disease

M. NECMETTIN PAMIR

3.4.1 Infection of the Scalp

3.4.1.1 Basics

- The layers of scalp are the Skin, Subcutaneous tissue, Galea aponeurotica, Loose connective tissue and the periosteum.

3.4.1.2 Aetiology/Epidemiology

- These lesions are mostly a complication of craniotomy incisions. Other factors are trauma, pin placements (halo or stereotactic frame), or cosmetic surgery for hair loss.
- The scalp infection rate after craniotomy is 1–5%. Pre-disposing factors are long operating times, very tight closure of the skin, remnant of the necrotic tissues, penetration of the paranasal sinuses and decreased blood supply to the skin flap.
- The responsible organisms are usually Staphylococcus aureus, Staphylococcus epidermidis, streptococci and Gram-negative bacilli. Anaerobic microorganisms can be found in traumatic lacerations.

3.4.1.3 Symptoms

- The main signs are tissue swelling, erythema, tenderness and local heat.
- Systemic signs of infection such as fever and fatigue can be seen. If the infection spreads into the deep tissues such as bone and the intracranial space the clinical picture can be more serious.

3.4.1.4 Diagnostic Procedures

- The diagnosis mainly relies on physical examination.
- Elevated white blood cell count and erythrocyte sedimentation rate can be found.
- Plain radiographic films may show swollen tissue and additional osteomyelitis (Fig. 3.4.1). CT and MR are seldomly used for diagnosis. They aid in ascertaining whether there is any intracranial component of the infection.

3.4.1.5 Therapy

- The superficial infections can be treated with antibiotics.
- If there is a subcutaneous abscess, reopen the wound, drain the pus, take a culture of the pus, remove the necrotic tissues, clean the area with antiseptic solutions, place a drain and close the wound with monofilament nylon or wire. Close inspection of the infected area and anti-infection therapy are mandatory.
- Analgesics, antipiretics
3.4.2 Osteomyelitis of the Skull

3.4.2.1 Aetiology/Epidemiology
- The infection of the calvarium is mainly due to craniotomy, trauma (compound depression fractures) or the spread of scalp infection.
- Basal skull infections may develop due to infection of the paranasal air sinuses.
- The most common pathogens are *Staphylococcus* and *Streptococcus*. Fungal infections, anaerobic microorganisms, Gram-negative bacilli are rarely reported.
- The rate of osteomyelitis in clean surgery is less than 1%.

3.4.2.2 Symptoms
- Pain, erythema and local increased heat over the infected bone. If there is an accompanying scalp abscess, pus may drain from the wound.
- The systemic signs of infection can be found.

3.4.2.3 Diagnostic Procedures
- Postsurgical or post-traumatic acute osteomyelitis should be suspected in a patient with the above-mentioned symptoms. Chronic osteomyelitis may only demonstrate slight swelling and pain. Osteomyelitis of the skull base may cause cranial nerve palsies.
- Plain films: spotty areas of demineralisation, resorption of the bone flap. In chronic cases, oedema and swelling may become detectable on X-rays and this is called "Pott's puffy tumor" (Fig. 3.4.2).
- CT: may show bony changes at an earlier stage.
- MR: helpful in showing additional soft tissue changes.
- Bone scintigrams: gallium-67 citrate accumulates in inflammatory tissues, and shows osteomyelitis. Technetium-99m methylene diphosphonate also detects osteomyelitis.

3.4.2.4 Therapy
- Removal of all infected and necrotic bone is mandatory. Cultures should be taken.
- Antibiotic therapy should be given for at least 6 weeks.
- Hyperbaric oxygen therapy can be used.
- Cranioplasty for the bone defect is performed 6–12 months after completing antibiotic treatment.
- Response to the treatment can be monitored with bone scintigraphy.

3.4.3 Epidural Abscess

3.4.3.1 Definition
- An abscess between the bone and the dura mater. The dura is a strong barrier to the spread of the abscess. These lesions are mostly well localised.
3.4.3.2 Aetiology/Epidemiology

- This condition mostly accompanies osteomyelitis of the skull.
- Aetiological factors are: craniotomy, trauma and para-nasal air sinus infections.
- Incidence in clean craniotomies is less than 1%.
- The organisms responsible are *Staphylococcus* and *Streptococcus*. Gram-negative micro-organisms and anaerobics are rare.

3.4.3.3 Symptoms

- Systemic signs of infection, signs of the additional infections such as scalp infection and osteomyelitis.
- Because of the strong barrier feature of the dura, symptoms and signs are mostly related to the mass effect of the abscess.

3.4.3.4 Diagnostic Procedures

- CT: hypodense epidural mass, may demonstrate contrast enhancement at the rim of the purulent mass. Small abscesses are sometimes not be visible on CT.
- MR: demonstrates more anatomical details. Additional subdural empyema and cerebral infection can easily be detected.

3.4.3.5 Therapy

- Remove the infected and devitalised bone, and drain the abscess. Place a drain and close the skin with non-absorbable nylon suture. Do not open the dura unless there is an existing subdural empyema.
- Culture for aerobic and anaerobic micro-organisms. Begin antibiotics and analgesics.
- Subgaleal and epidural antibiotic irrigation and suction drain system may preserve the bone flap in some cases.

3.4.4 Subdural Empyema

3.4.4.1 Definition

- A subdural empyema (SDE) is an infectious condition between the dura and the arachnoid membrane. Empyema refers to an infection within a pre-existing normal space.

3.4.4.2 Aetiology/Epidemiology

- Subdural empyema constitutes 13–23% of the localised intracranial bacterial infections.
- The most common predisposing factor for SDE is paranasal air sinus infections. In infants, SDE usually follows meningitis. SDE secondary to craniotomy or trauma is rare. Evacuation of chronic subdural haematoma may predispose to SDE.
- Aerobic and anaerobic micro-organisms may be responsible for the infection. In SDE following meningitis in infants, the most common organisms have been *Haemophilus influenzae* and *Streptococcus pneumoniae*.

3.4.4.3 Symptoms

- Patients with SDE may have a more dramatic clinical picture. They are seriously ill and febrile. Headache and nuchal rigidity can be seen. Seizures can be seen in up to 60% of the patients. Hemiparesis, sensory deficits, homonymous hemianopsia and alterations in the mental state can be seen.
- The reasons for this septic condition in these patients are cerebral venous thrombosis, oedema, cerebral venous infarct and small subcortical abscesses. SDE is more fulminant and fatal than epidural abscess.

3.4.4.4 Diagnostic Procedures

- Skull films may help to demonstrate predisposing factors such as paranasal air sinus infections (Fig. 3.4.3).
- CT may not show the thin collections at the subdural space.
- MR is the preferable screening method. It shows the detailed spread of the pus and additional cerebral and cerebellar infection.
- Lumbar puncture may be dangerous and adds little critical information.

3.4.4.5 Therapy

- Acute SDE is treated with systemic antibiotics and burr holes. In the early stage of SDE, the purulent material flows freely and burr holes usually suffice.
- If loculations are encountered and drainage is inadequate, then a craniotomy will be required. Drains can be used 24–48 h postoperatively.
3.4 Meningitis

3.4.5.1 Definition

- Meningitis is an acute, fulminating febrile illness caused by infection of the subarachnoid space. May be caused by bacteria, viruses or fungi.

3.4.5.2 Aetiology/Epidemiology

- Micro-organisms may reach the meninges and CSF by dissemination through the bloodstream, by retrograde propagation from the nasopharynx, or by direct spread from contiguous foci of infection.
- The most common causative agents are:
  - In normal adults 15–50 years: *Neisseria meningitidis*, *Streptococcus pneumoniae*
  - In normal adults >50 years: *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes* and aerobic Gram-negative bacilli.
  - In old, debilitated or alcoholic patients: *S. pneumoniae*, enterococci, *Listeria*.
  - In immunocompromised patients fungi, tuberculosis and aseptic HIV meningitis may be seen in addition to those conditions found in adults.
- In a post-neurosurgical setting or after craniocerebral trauma: *Staphylococcus aureus*, enterobacteriae,*Pseudomonas* and *S. pneumoniae*.
- Shunt infection: foreign body provides microbes with a favorable site for colonisation while at the same time hampering host defences. Almost one-fourth of the shunt patients develop infection. Most shunt infections are caused by *S. epidermidis* and diphtheroids.

Other micro-organisms such as *S. aureus*, *Pneumococcus*, *Haemophilus* and Gram-negative bacilli can be the causative organisms.

3.4.5.3 Symptoms

- The classic triad is fever, headache and nuchal rigidity.
- Photophobia, anorexia, nausea, vomiting, back pain and myalgias are frequently present and may be severe.
- Focal neurological signs or altered mental status will indicate meningoencephalitis and is seen in 75% of the cases. Coma occurs in about 5–10% of cases, seizures in 20% and cranial nerve palsies in 5%.
- Increased ICP is common: 90% have an opening pressure of >180 mmHg, and 20% have opening pressures of >400 mmHg. Herniation occurs in 1–8%.

3.4.5.4 Diagnostic Procedures and Treatment

- Blood cultures are drawn and antibiotic treatment started immediately. Antibiotics do not alter CSF examination within the first few hours.
- Immediate CT to rule out mass effect is followed by emergency lumbar puncture.
- Lumbar puncture will indicate a high progressive multifocal leukoencephalopathy (PML) count, increased protein (>45 mg/dL) and decreased glucose (<40 mg/dL and/or CSF/serum glucose ratio of <0.4). Gram stain demonstrates micro-organisms in >60%, and CSF cultures are positive in >80%.
### 3.4.6 Brain Abscess

#### 3.4.6.1 Aetiology/Epidemiology
- Brain abscess may be caused by haematogenous spread (cardiac, pulmonary or dental foci, which are common in IV drug abusers), direct extension (from the temporal bone or paranasal sinus infections) or by penetrating injury (may also be post-surgical).

#### 3.4.6.2 Symptoms
- Generalised signs of elevated intracranial pressure and focal neurological deficit. Rapid onset and progression.

#### 3.4.6.3 Diagnostic Procedures
- Pathology and CT imaging evolves through four phases. Early cerebritis (0–4 days), late cerebritis (4–10 days), abscess (early capsule stage) and abscess (late capsule stage; Figs. 3.4.4, 3.4.5).
- Leukocytosis.
- Lumbar puncture is rarely conclusive and carries the risk of herniation.

### 3.4.7 Encephalitis

#### 3.4.7.1 Definition
- Parenchymal infection of the brain. May be acute or chronic.
- Commonly associated with meningitis (meningoencephalitis)

#### 3.4.7.2 Aetiology/Epidemiology
- Acute cases are commonly caused by viral or toxic agents.
- Acute encephalitis in immunocompetent adults is most commonly due to herpes simplex, which causes a fulminant, necrotising, haemorrhagic meningoencephalitis. It has a preference for the temporal lobe.
- Other non-infectious acute causes include Reye's syndrome and acute disseminated encephalomyelitis.
- Various forms of chronic encephalitis may be encountered including progressive multifocal leukoencephalopathy (PML) in immunosuppressed adults or subacute sclerosing pan-encephalitis (SSPE) in children aged 5–12 years.
- It is a complication of the measles infection with long latent periods.

#### 3.4.7.3 Symptoms
- Focal or diffuse neurological symptomatology occurs in addition to the febrile illness and meningeal involvement. The most common signs are aphasia, ataxia, hemiparesis, seizures and cranial nerve deficits.

#### 3.4.7.4 Diagnostic Procedures
- If not contraindicated because of elevated ICP, lumbar puncture reveals lymphocytic pleocytosis, slightly elevated protein and normal glucose. Steroids may blur the picture. PML strongly indicates a non-viral cause. Erythrocytes in the absence of a traumatic tap will indicate herpes simplex virus (HSV) encephalitis.
• PCR has 98% sensitivity and 94% specificity for HSV.
• MRI reveals focal changes in 90% of cases.
• Brain biopsy is reserved for patients who have focal abnormality, a negative PCR study and continue to deteriorate despite antiviral therapy.

3.4.7.5 Therapy

• Intravenous acyclovir is empirically started in suspected cases of viral encephalitis.
• Supportive treatment with suppression of seizures and fever is initiated.

**Selected Reading**


**Fig. 3.4.5a–d** Brain abscess
Neurosurgery began with the treatment of head injuries. Around the world we find skulls with healed trephinations, some of them several thousand years old (Fig. 3.5.1). The treatment of patients with head injuries consisted mostly of war surgery performed by general surgeons until the end of World War II. Industrialisation and in particular the increase in motor-driven vehicles after World War II were accompanied by a rapid increase in head injuries. The neurosurgical community met that need. Shortly after World War II neurosurgeons specialised in trauma care and developed the first Intensive Care Units in the 1950s and early 1960s in various countries. They started to perform tracheostomies, recommended drugs to treat spasticity, and also started to cool patients with an acute midbrain syndrome and increased body temperature. Mechanical ventilators became more and more readily available in the 1960s in most hospitals and also central i. v. lines and gastric tubes to apply parenteral and enteral nutrition. This brought anaesthesiologists onto the scene as major players in the treatment and management of head trauma victims. Together with neurosurgeons they developed regimens for treatment. With the increasing number of patients and the spreading of ICUs in developed countries in conjunction with the limited neurosurgical resources, it was evident that neurosurgeons could not handle these patients alone. Figures for Germany indicate that neurosurgeons care for approximately 30% of all patients with severe head injuries, whereas patients with minor injuries are mainly looked after by staff from other disciplines.

Computed tomography (which was introduced in the mid-1970s) has dramatically changed the treatment of traumatic brain injury (TBI). When this method became available it rendered defunct echosonography (Fig. 3.5.2) and angiography (Fig. 3.5.3) as well as woodpecker surgery with exploratory burr holes to detect an intracranial hae-

matoma. It also enabled neurosurgeons to detect intracranial haematomas before patients developed clinical signs of herniation and as such further improved outcome.

Systematic research (both clinical and laboratory) has improved our knowledge and understanding of the dynamic processes within the brain that are initiated by the primary trauma. Laboratory research has led to the invention of devices and new drugs to monitor and treat our patients. Clinical research in conjunction with the increasing use of computers has resulted in large so-called Coma Data Banks, which help to identify patients at risk, to improve prognosis and to compare different treatment strategies.

As a result of these developments, nowadays, unfortunately, novices (and sometimes even experienced neurosurgeons) tend to rely mainly on pictures and data instead of on clinical examination and judgement when treating patients with head injuries. They often forget that careful history-taking and clinical examination is still the basis for treatment.

Using the fundamental rule "patient first – pictures second", careful study of Fred Plum’s and Jerome Posner’s wonderful textbook *Coma and Impaired Consciousness* and assuming the personal attitude of the late J. Douglas

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**Fig. 3.5.1** Neolithic skull found in Mecklenburg-Vorpommern (Germany) with a parietal trephination performed approximately 2,400 years BC
Fig. 3.5.2a,b Detection of a midline shift by echoencephalography in the 1960s (courtesy of Professor Collmann, Department of Neurosurgery, University of Würzburg, Germany). a Siemens electroencephalograph. b Displacement of the midline (M) due to a developing epidural haematoma.

Fig. 3.5.3a,b Detection of an epidural vertex haematoma by cerebral angiography (single-shot, direct puncture of the carotid artery) in the 1970s. Note the displacement of the cerebral vessels (red arrow) caused by the haematoma. No vessels are visible in the region of the haematoma. a Antero-posterior view. b Lateral view.
Miller (1937–1995) to neurotrauma comprise the personal advice I would give to them!

### 3.5.1.2 Definitions, General Principles and Pathophysiology

#### 3.5.1.2.1 Definitions

If a force from outside hits the head this force may result in various injuries possibly involving scalp, skull, dura, brain and their supplying vessels. This explains why in various papers different terms are used for such injuries. While some authors exclusively focus on “brain injuries” (i.e. trauma to the central nervous system), others use the term “head injury (HI)” to include injuries to the soft tissue, the skull, as well as to the facial fractures.

If a patient has sustained a traumatic brain injury, this fact will alter his level of consciousness in some way. Level of consciousness is usually examined by applying the Glasgow Coma Scale (see later). As TBI is a dynamic process, definition of its severity is problematic. In accordance with most authors, a head injury is called “severe” if the worst GCS score within the first 48 h is between 3 and 8 points. Head injuries are called “moderate” with the worst GCS score of 9–12 points, and “mild” if the worst score is 13 or better. Together with the anatomical description of the structures involved (e.g. “moderate TBI with a left temporal epidural hematoma and a right zygomatic fracture”) this definition is usually sufficient to describe the injury.

#### 3.5.1.2.2 General Principles and Pathophysiology

Traumatic brain injury (TBI) is a very common disease in all countries with long-term, often life-long consequences for the patient involved. It is essential to understand that TBI is a dynamic process that is initiated by the initial trauma. This means that individual situations, particularly in the early period, can vary from minute to minute. The so-called “primary” damage happens at the scene of the accident and determines outcome in a large proportion of the patients. It is estimated that even in countries with a sophisticated rescue and emergency system like Germany, 30–50% of all patients with TBIs die at the scene of the accident or during transport to the hospital as a result of their primary damage. Primary brain damage cannot be treated, it can only be prevented. Therefore, neurosurgeons involved in neurotrauma care should also feel responsible for the prevention of TBI. “Secondary” injuries to the brain may have intracranial as well as extracranial causes (Fig. 3.5.4). Avoidance and treatment of these secondary insults is the core of neurotrauma care. As a chapter like this cannot cover all aspects of treatment, it mainly focuses on the clinical examination, operative treatment and on some general aspects. For detailed information (in particular on pre-hospital treatment, treatment of brain oedema and raised intracranial pressure, general ICU treatment, as well as on rehabilitation) the reader should refer to the different textbooks mentioned in the suggested literature.

---

**Fig. 3.5.4** Pathophysiology of traumatic brain injuries: Primary damage vs secondary insults
There are no world-wide data on the epidemiology of head injuries as the incidence, the types of injury, and their causes vary widely from society to society and also over time. For the United States and European countries it is estimated that approximately 2% of the whole population are affected by TBI per year. Between 200 and 300 patients per 100,000 inhabitants are hospitalised every year for a traumatic brain injury.

From a large population-based study on 6,783 patients performed 2000 by Rickels et al. it can be calculated that in Germany 331 patients per 100,000 inhabitants per year suffer a head injury severe enough to be admitted to a hospital. (Patients dead at the scene of an accident are not included). According to these data, 90.9% of the injuries are mild, 3.9% moderate and 5.2% severe. Of the patients, 58.4% were male and 41.6% were female. In patients aged 16–35 years, however, men constituted two-thirds of all victims. Detailed data on age and mechanism are shown in Figs. 3.5.5 and 3.5.6. Data on accompanying injuries are shown in Fig. 3.5.7.

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From the data above and from a comparison with the older literature it is obvious that the epidemiology of the “typical” patient with a head injury has totally changed over the last few years, at least in central Europe, because of the introduction of various protective vehicle-related advice (use of helmets in motor-bikers, introduction of airbags, anti-lock braking systems, electronic stability programs). Falls account for more than 50% of our patients, shifting the age group to older patients, with all their accompanying internal diseases and problems for which the neurosurgeon has to be prepared.
3.5.3 Initial Assessment and Early Management

3.5.3.1 Introduction

Care for patients with head injuries is a dynamic process starting at the scene of the accident. During the early stages of hospital care, the patient may require management in a variety of locations, including the emergency room (ER), the operating room (OR), the radiology department and the intensive care unit (ICU). In the later course of the disease transfer of the patient to a rehabilitation facility has to be organised. Additionally, the patient may require further neurosurgical operations (e.g. for the treatment of post-traumatic hydrocephalus, closure of skull defects), even decades after the trauma (e.g. to treat late infectious complications). This continuum of care has to be ensured by the neurosurgeon responsible for the trauma patient.

3.5.3.2 Initial Assessment of the Head Injured Patient

The main aim of patient care in the early stages of management should be to prevent or minimise the risk of secondary brain injuries and to assess the full extent of the injury.

3.5.3.2.1 Clinical History

The importance of ascertaining a complete history in a patient with acute head injury is extremely important, but is often overlooked. Eye-witness reports of the mechanism of injury and the initial level of consciousness are of critical importance. The same is true of reports from the ambulance crew and emergency doctors. The following items should be checked in a standardised fashion:

- Past medical history (concomitant diseases, current medication)
- Suspected influence of drugs/alcohol
- Possible medical reason for the accident (e.g. seizure, heart attack, stroke)
- Time, place, mechanism and speed of the accident
- Use of airbags, seat-belts, crash-helmets etc.
- Vital parameters at the scene and during transport
- Neurological state (level of consciousness, pupillary response) at the scene and during transport
- Treatment at the scene and during transport

3.5.3.2.2 Physical Examination

It is well known that secondary insults to the already injured brain dramatically increase mortality and morbidity in head trauma victims. Therefore, the initial examination starts with checking and stabilising vital functions. Blood pressure should be kept normal and sufficient oxygenation has to be secured either by O₂ insufflation in minor injuries or by intubation and ventilation in unconscious patients (GCS < 9 points).

A careful head-to-toe examination should address the following points:

- Inspection of the entire scalp (as scalp wounds may be hidden by blood-clotted hair)
- Peri-orbital or retro-auricular bruising or haematomas (indicating the possibility of a basal skull fracture)
- Rhinorhoea or otorrhoea
- Open injuries of the cranial vault with CSF leakage or cerebral debris
- Gunshot wounds, stabbing, presence of foreign bodies (glass or metal splinters)
- Maxillofacial injuries
- Injuries to the eyes
- General examination of the whole body (front and back!) to identify extra-cranial injuries
- Breathing pattern (e.g. abnormal respiratory pattern indicating cerebral damage, diaphragmatic breathing indicating lower cervical spinal cord injury)
- Priapism in males may indicate lesions to the cervical spinal cord

Due to the fact that up to 10% of all patients with severe head injuries may also have a spinal fracture all patients should be managed and treated accordingly during the whole examination until such a fracture has been ruled out by radiographic studies. Dangerous mechanisms are road-traffic accidents and falls from heights.

3.5.3.2.3 Neurological Examination

A detailed neurological examination is not necessary during the initial examination. A neurological "mini-exam" is carried out focussing on the level of consciousness and to note the presence or absence of focal or lateralising neurological signs.

The level of consciousness is determined by applying the Glasgow Coma Scale Score (Table 3.5.1).

Cranial nerve deficits are examined by checking the pupils for symmetry, size and reaction to light (directly and indirectly) separately and in comparison to the opposite side, testing the corneal reflex and the brain-stem reflexes. Lateralising motor signs are tested by observing and testing the motor function independently for each limb and comparing it with that of the opposite side. The main cervical and lumbar deep tendon reflexes should be tested and compared, in order not to overlook peripheral nerve root injuries. A positive Babinski's sign is caused by lesions of the pyramidal tract.
3.5.3.3 Early Management

3.5.3.3.1 Monitoring
Basic monitoring is indicated in all patients admitted to the hospital for a significant head injury. It includes:
- 3-lead ECG in all patients
- Pulse rate and arterial blood pressure (non-invasive)
- Pulse oximetry
- Capnography (ventilated patients)

3.5.3.3.2 Neurological Monitoring
Repeated neurological examinations have to be performed for clinical monitoring in all patients admitted. Additional technical monitoring includes measurement of intracranial pressure (ICP), mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) in more severe head injuries (usually GCS <9 points). In specialised units this basic monitoring can be complemented by advanced methods of intracranial monitoring, which may give further insights into cerebral perfusion, oxygenation and biochemistry (local CBF, transcranial Doppler, brain-tissue PO\textsubscript{2}, jugular venous oxygenation, microdialysis) and electrophysiology (evoked potentials, transcranial Doppler). For details, refer to specialist neurosurgical ICU textbooks.

3.5.3.3.3 Catheters and More
Two peripheral i.v. cannulae are usually appropriate during initial evaluation and resuscitation. In patients with moderate or severe injuries and in multiple trauma patients a central venous catheter should be inserted after the first CT together with an arterial line. A naso-gastric tube (oro-gastric tube in the presence of facial or fronto-basal injuries) is also inserted. Patients with severe injuries or multiple trauma also require a bladder catheter for the monitoring of urine excretion and temperature.

3.5.3.4 Laboratory Investigations
In all patients who are going to be admitted to the hospital for further treatment/observation, the following laboratory values should be obtained during the initial resuscitation phase:
- Haemoglobin, haematocrit, leucocytes, platelets
- Sodium, potassium, blood glucose
- Coagulation parameters
- Blood urea, creatinine
- Liver enzymes
- Pregnancy test (if appropriate)
- Drug screening (if appropriate)

Patients with moderate or severe injuries also require determination of arterial blood gases and cross-matching of at least 4 units of blood.

3.5.3.4 Imaging

3.5.3.4.1 Computed Tomography
Details of the scanning procedure and the various types of intracranial pathology that might be detected after head

<table>
<thead>
<tr>
<th>Table 3.5.1 Glasgow Coma Scale score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye opening (E)</td>
</tr>
<tr>
<td>To voice</td>
</tr>
<tr>
<td>To pain</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Verbal response (V)</td>
</tr>
<tr>
<td>Confused</td>
</tr>
<tr>
<td>Inappropriate words</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Best motor response (M)</td>
</tr>
<tr>
<td>Localises pain</td>
</tr>
<tr>
<td>withdraws from pain</td>
</tr>
<tr>
<td>Abnormal flexion</td>
</tr>
<tr>
<td>Abnormal extension</td>
</tr>
<tr>
<td>None</td>
</tr>
</tbody>
</table>
injuries are described in detail in Sect. 3.5.4. In general, cranial CT should be obtained in:

- All patients with a GCS of 12 and lower on admission (i.e. moderate or severe head injuries)
- Patients with a GCS of 13–15 on admission (mild head injuries) if they present at least with one of the following risk factors:
  - Focal neurological symptoms and signs (hemiparesis, seizure, pupil inequality, other cranial nerve deficits)
  - Neurological deterioration
  - Alcohol or drug abuse/intoxication
  - Disturbances of blood coagulation (e.g. coumarins, aspirin)
  - Suspected penetrating injury
  - CSF leak
  - Age > 65 years
  - High-speed accidents
  - Amnesia > 30 min

As it is well known that a large number of patients may develop delayed intracranial haematoma (Fig. 3.5.8), the initial CT should routinely be repeated after 4–6 h.

### 3.5.3.5 Classification

As a head injury is a dynamic process, from a practical point of view, the initial evaluation should guide further treatment and allow patients with head injuries to be classified according to:

- Severity of the brain injury
  - Severe head injury (GCS score 3–8 points)
  - Moderate head injury (GCS score 9–12 points)
  - Minor head injury (GCS score 13–15 points)
- Type of brain injury
  - Focal or diffuse
  - CT classification (refer to Sect. 3.5.4)
- Open or closed injury
- Structures involved (skin, skull, brain, vessels, cranial nerves)

### 3.5.3.6 Treatment

#### 3.5.3.6.1 Severe and Moderate Injuries

Every patient with a severe or moderate head injury and every patient requiring an intracranial operation should be observed and treated in an ICU (preferably in a specialised neurosurgical intensive care unit). For detailed information about the broad and complex subject of ICU treatment in head injuries the reader should refer to specialised ICU textbooks, as this section can only cover the more general aspects of head injury treatment.

#### 3.5.3.6.2 Minor Head Injuries

There is a continuing debate as to which patient with a minor injury can be safely discharged and treated as an outpatient. Table 3.5.2 describes the current algorithm at the author's institution.

### 3.5.4 Diagnostic Procedures

#### 3.5.4.1 Computed Tomography

Computed tomography (CT) is the type of imaging that is the first choice in any head-injured patients in whom an intracranial lesion is clinically suspected. In Europe, CT scanners are available in all major trauma centres around the clock. The main advantages are their rapid imaging time, especially with the new generations of multi-slice CT scanners that allow scanning of the whole body of a multiple trauma victim in 1- to 3-mm slices within minutes. The other advantage over MRI scanners is that they can produce valuable images even in moving patients, which diminishes the need for sedation. It has also been
Table 3.5.2  Algorithm for the treatment of patients with minor head injuries (GCS 13–15 on admission)

<table>
<thead>
<tr>
<th>GCS (admission)</th>
<th>History</th>
<th>CT findings</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–8</td>
<td>Does not apply</td>
<td>Does not apply</td>
<td>Admit to ICU</td>
</tr>
<tr>
<td>9–12</td>
<td>Does not apply</td>
<td>Does not apply</td>
<td>Admit to ICU</td>
</tr>
<tr>
<td>13 and 14</td>
<td>Risk factors not present</td>
<td>Negative</td>
<td>Admit and observe on regular ward; repeat CT if clinical deterioration</td>
</tr>
<tr>
<td>13 and 14</td>
<td>Risk factors not present</td>
<td>Positive</td>
<td>Admit and observe on intermediate care unit; repeat CT after 4–6 hours or if clinical deterioration</td>
</tr>
<tr>
<td>13–15</td>
<td>Risk factor present</td>
<td>Negative</td>
<td>Admit and observe on intermediate care unit; repeat CT after 4–6 hours or if clinical deterioration</td>
</tr>
<tr>
<td>13–15</td>
<td>Risk factor present</td>
<td>Positive</td>
<td>Admit and observe on ICU; repeat CT after 4–6 hours or if clinical deterioration</td>
</tr>
<tr>
<td>15</td>
<td>Loss of consciousness</td>
<td>Does not apply</td>
<td>Admit and observe on regular ward; do CT, if clinical deterioration</td>
</tr>
<tr>
<td>15</td>
<td>No loss of consciousness</td>
<td>Does not apply</td>
<td>Discharge, if observed home*</td>
</tr>
</tbody>
</table>

*Patients with minor injuries who cannot be scanned (e.g. for technical reasons) should also be admitted and observed. Patients without sufficient supervision at home should also be admitted and observed. In patients who are discharged, a detailed instruction should be given to the patient's relatives, together with an emergency telephone number.

Table 3.5.3  Computed tomography classification of head injuries (Marshall et al., 1991, reproduced with permission)

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse injury I</td>
<td>No visible intra-cranial pathology on CT scan</td>
</tr>
<tr>
<td>Diffuse injury II</td>
<td>Cisterns are present with midline shift 0–5 mm, and/or lesion densities present</td>
</tr>
<tr>
<td></td>
<td>No high or mixed density lesion &gt; 25 cc</td>
</tr>
<tr>
<td></td>
<td>May include bone fragments/foreign bodies</td>
</tr>
<tr>
<td>Diffuse injury III (swelling)</td>
<td>Cisterns compressed or absent with midline shift 0–5 mm</td>
</tr>
<tr>
<td></td>
<td>No high or mixed density lesion &gt; 25 cc</td>
</tr>
<tr>
<td>Diffuse injury IV (shift)</td>
<td>Midline shift &gt; 5 mm</td>
</tr>
<tr>
<td></td>
<td>No high or mixed density lesion &gt; 25 cc</td>
</tr>
<tr>
<td>Evacuated mass lesion</td>
<td>Any lesion surgically evacuated</td>
</tr>
<tr>
<td>Non-evacuated mass lesion</td>
<td>High or mixed density lesion &gt; 25 cc, not surgically evacuated</td>
</tr>
</tbody>
</table>
demonstrated that the results obtained correlate closely with the clinical outcome of the patient. A practical CT classification of such injuries was given by Marshall in 1991 (Table 3.5.3).

Thus, CT has replaced skull radiography in most institutions as it does not only show skull fractures, intracranial air and foreign bodies (as plain radiographs do), but also show the parenchymal lesions of the brain itself, especially space-occupying haematomas requiring urgent evacuation.

A special scanning protocol should be instituted in every individual centre and should be strictly adhered to in all cases without exception in order not to miss any clinically important lesions. At our institution we obtain 0.5-mm axial slices from the foramen magnum up to the vertex angled parallel to the orbit-meatal line. The images are reconstructed and printed in various window algorithms for bone, soft tissue and blood. Intravenous contrast medium infusion is usually not indicated, but may be necessary if underlying diseases (example: head injury owing to a seizure caused by an intracranial tumour) or vascular lesions are suspected. Sometimes contrast enhancement may also be indicated to detect an isodense subacute or chronic subdural haematoma.

It should also be kept in mind that a marked number of patients with head injuries may have additional injuries to their spine that should be ruled out with a standardised protocol.

The following sections describe the most common findings in patient with acute head injuries.

3.5.4.1 Parenchymal Injuries
Parenchymal brain injuries result from laceration of smaller intracranial vessels owing to shearing forces. From a clinical point of view they are classified as present vs not present, single vs multiple, and are described with regard to their size, their location and their mass effect.

3.5.4.1.1 Contusions
Cortical contusions are found if the accelerated–decelerated brain hits the inner side of the skull. As most patients sustain their injury while moving in forwards, most of these contusions are located within the brain parenchyma at the floor of the anterior or the middle skull-base, resulting in contusional lesions of the frontal and the temporal lobe surface. In some cases additional contusions can be detected on the opposite side to that of the original impact (coup–contre coup lesions). Contusions are often bilateral and multiple (Fig. 3.5.9). They present as focal cortical hyperdense lesions. In some (older) cases they are accompanied by surrounding local oedema (Fig. 3.5.10). Usually, initial CT does not show the complete extent of the injury, as these contusions may “grow” (Figs. 3.5.11) within the few next hours or days (in up to 30% of all cases). Growing contusions are particularly

![Fig. 3.5.9](image1) Typical frontal and temporal location of cerebral contusions (arrowheads)

![Fig. 3.5.10](image2) Haemorrhagic contusion of the right temporal lobe (double arrowheads) with marked surrounding oedema (single arrowheads)
3.5.4.1.1.2 Diffuse Axonal Injuries

Diffuse axonal injuries (DAI; synonym – diffuse white matter shearing injuries) result from severe shear-strain forces during high-speed accidents. Clinically, the patients present in deep coma with midbrain or brain-stem symptoms. Most injuries occur along the midline with small punctual lesions in the deep lobar white matter, the corpus callosum, and the dorso-lateral brain stem (Fig. 3.5.12). In some cases, only small amounts of sedimented blood in one of the lateral ventricles caused by rupture of its ependyma will be visible on the CT, although without therapeutic consequences an additional MRI procedure (see later) will reveal the full extent of the injury.

3.5.4.1.1.3 Subcortical Grey Matter Injuries

Subcortical grey matter injuries (Fig. 3.5.13) are occasionally (3–5%) found in the basal ganglia and the thalami.

observed in patients with disturbances of blood coagulation. If a patient shows such a contusion on the first CT, it is therefore advisable to repeat this imaging procedure within the next 4–8 h or whenever clinical deterioration (drop in GCS score, new papillary abnormalities, ICP rise) occurs.

Fig. 3.5.11a–c “Growing” bifrontal contusions in a 47-year-old heavy drinker. The date of the examinations is indicated on the images.
They are usually associated with a poor prognosis. The postulated mechanism is a disruption of small arteries in this region by shearing forces.

3.5.4.1.4 Brain-Stem Injuries
Brain-stem injuries are best detected on MRI as CT will only show approximately 10% of these lesions. These severe injuries are usually observed in conjunction with severe diffuse axonal injuries. Isolated brain-stem injuries are found in less than 1% of all cases of severe head injuries (Fig. 3.5.14). They must be differentiated from secondary brain-stem haemorrhages due to prolonged transtentorial herniation.

3.5.4.1.2 Extra-Axial Haematomas

3.5.4.1.2.1 Epidural Haematoma
See Sect. 3.5.9.1.

3.5.4.1.2.2 Acute Subdural Haematoma
See Sect. 3.5.9.2.
Expanding supratentorial mass lesions initially cause obliteration of the ipsilateral cortical sulci followed by compression of the ipsilateral ventricle and subfalcine herniation. As the mass effect continues transtentorial herniation occurs followed by herniation of the cerebellar tonsils resulting in brain death. All these mass effects can be demonstrated on CT.

### 3.5.4.1.2.3 Traumatic Intracerebral Haematoma
See Sect. 3.5.9.3.

### 3.5.4.1.3 Traumatic Pneumoencephalus
The normal intracranial compartment does not contain air. The presence of air on the initial CT within the brain, the ventricles or the subdural/epidural space, therefore, indicates communication of the intracranial compartment with the paranasal sinuses, the mastoid, or direct communication with the external environment (Fig. 3.5.15). CSF fistulas are frequently found as a result of this type of injury. Small amounts of intracranial air will usually be resorbed and will disappear on the follow-up CT. Acute tension pneumoencephalus, however, is an emergency situation resulting from a valve gear mechanism where more and more endonasal air is entrapped via a fronto-basal lesion with every breath of the patient.

### 3.5.4.1.4 Secondary Effects of Head Injuries

#### 3.5.4.1.4.1 Brain Herniations
Displacement of the brain caused by an expanding mass results in typical CT findings that should be known to every neurosurgeon involved in neurotrauma care.
3.5.4 Diagnostic Procedures

3.5.4.1.4.1.3 Tonsillar Herniation
Tonsillar herniation (Fig. 3.5.18) results either from an expanding infratentorial mass or from prolonged transtentorial herniation. The cerebellar tonsils are displaced downwards into the foramen magnum. Obstructive hydrocephalus may accompany these findings.

3.5.4.1.4.2 Diffuse Supratentorial Brain Swelling
Diffuse supratentorial brain swelling (Fig. 3.5.19) can quite often be found in patients with severe injuries, especially in younger patients. Loss of the contour of the cerebral sulci, compression of the Sylvian fissures and the third ventricle, and obliteration of the basal cistern indicate high intracranial pressure. The whole supratentorial brain appears hypodense compared with the tentorium and the cerebellar hemispheres. The white–gray matter interface is usually lost. This finding may result either from diffuse injuries, accompanying hypoxia, or a combination of both.

3.5.4.1.4.3 Hydrocephalus
Communicating hydrocephalus is a frequent finding in severe head injuries. Acute, obstructive hydrocephalus (Fig. 3.5.20), however, is a very rare finding and is usually observed if a mass (e.g. intraventricular blood clot) blocks CSF outflow from the ventricles above.

Fig. 3.5.17 Transtentorial herniation of the medio-basal temporal lobe caused by a large acute subdural haematoma (ASDH)

Fig. 3.5.18 Typical CT of a patient with tonsillar herniation (single arrowhead) and brain-stem compression (double arrowheads)
3.5.4.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has several disadvantages and advantages compared with CT in the acute trauma setting. On the one hand, it is more sensitive in detecting small extra-axial and non-haemorrhagic lesions, especially in the deeper parts of the brain. On the other hand, factors like the need for non-magnetic monitoring equipment, its sensitivity to the patient’s motion and its longer scanning time limit its use in the acute care of a head trauma victim. At our institution we use additional MRI if the clinical picture is not fully explained by the CT obtained and in all cases in which diffuse axonal injuries are suspected. With the rapid development of high magnetic field scanners, the introduction of new scanning techniques and the shortening of the examination time it is certain that its role in neurotrauma will have to be re-defined during the coming years.

The examples in Figs. 3.5.21–3.5.26 show typical indications and examinations of patients with various post-traumatic pathological conditions.

3.5.4.3 Cerebral Angiography

Cerebral angiography is rarely indicated in the acute examination of a head injury patient. It should, however, be kept in mind that in the absence of a CT scanner or in an emergency situation percutaneous injection of a contrast medium into the common carotid artery followed by single-shot antero-posterior radiography will usually show larger space-occupying extracranial haematomas in typical locations.

Injuries to cerebral vessels (dissections, carotid-cavernosus fistulas; Fig. 3.5.27) may also be demonstrated by cerebral angiography, although CT or MRI angiography has already replaced it in most cases.

3.5.4.4 Skull Radiography

There is a continuing debate – particularly in patients with minor trauma – whether skull radiography should be obtained as the first diagnostic tool in head injuries. Although it is well known that the presence of a skull
Fig. 3.5.21 Magnetic resonance imaging in a patient with subacute epidural haematoma (arrowhead)

Fig. 3.5.22 Magnetic resonance imaging in a patient with chronic subdural haematoma (arrowheads)

Fig. 3.5.23 a CT and b MRI images of a patient with a hypodense right temporal contusion (arrowheads)
Fig. 3.5.24  a CT and b MRI images of a patient with a post-traumatic basal ganglia haemorrhage (arrowhead)
Fig. 3.5.25 a CT and b see next page
Fig. 3.5.25 (continued) b MRI images in a case of diffuse axonal injury. The initial CT only demonstrates some blood within the third ventricle and on the tentorium. The full extent of the cerebral damage is revealed by the corresponding MRI. These images show shearing lesions to the frontoparietal cortex (1), the dorsal corpus callosum (2), the dorsal right thalamus (3), both temporo-mesial lobes (4), the vermis (5), and the left dorso-lateral brain-stem (6)
Fig. 3.5.26  

a Follow-up CT of a young boy with an initial GCS score of 15 on admission who deteriorated 2 days after the trauma. Marked infarcts to both cerebellar hemispheres explain the clinical picture.  
b MRI angiography demonstrates the absence of the left vertebral artery with some irregularities in the upper basilar artery (dissection of the vertebral artery)

Fig. 3.5.27a,b  

Cerebral angiography in a patient with a carotid-cavernous fistula (arrowhead)  
apre- and b post-embolisation (radiologist: Dr. Jens Kröger)
fracture dramatically increases the risk of harbouring an intracranial haematoma, we have abandoned plain radiographs and perform CT instead. The indication for CT as the initial examination follows generally accepted rules in neurotrauma care and is shown in Table 3.5.4.

### 3.5.5 General Principles of Treatment

#### 3.5.5.1 Minor and Moderate Injuries

The main aim of treating patients with minor and moderate injuries is to prevent secondary insults to the injured brain. Anticipation of such insults and careful observation by experienced staff are the key-points during the early course. The current policy at our department is to follow patients with minor injuries and normal CT on the regular ward. Patients with moderate injuries or patients with minor injuries and abnormal CT are best observed on an intermediate care unit for at least 8–12 h. Vital signs, pupils and GCS score should be checked regularly (at our institution: patients with minor injuries and normal CT every 2 h; patients with moderate injuries or patients with abnormal CT at least every hour).

Any abnormal CT scan should be repeated within 4–6 h in order not to overlook a developing intracranial haematoma. Any drop in the GCS score of 2 or more points or any change in pupil reaction should also prompt follow-up CT.

#### 3.5.5.2 Severe Injuries

##### 3.5.5.2.1 General Remarks

Patients with severe injuries should be treated on a specialised neuro-intensive care unit. As the general principles of ICU treatment of patients with severe injuries are extensively discussed in Sect. 3.5.1, only some aspects should be mentioned in this section.

Virtually any medical complication can occur during the post-traumatic course of a patient with a severe head injury. The most frequent medical complications include disturbances of serum electrolytes with an estimated rate of 60%, pneumonia (40%), disturbances of blood coagulation (18%) and septicaemia (10%). Hypotension can occur during the pre-hospital phase (29%) and in hospital (21%). However, only some of these events are independent predictors of a negative outcome in this patient group. It has been estimated that the elimination of hypotension only can reduce the unfavourable outcome in patients with severe head injuries by 9.3%. The corresponding figures for pneumonia are 2.9%, for coagulopathy 3.1% and for septicaemia 1.5%.

Therefore, ICU treatment needs to focus on the prevention and aggressive treatment of these extracranial events.

##### 3.5.5.2.2 Circulation and Oxygenation

Adequate oxygenation needs to be ensured by early intubation and ventilation. Peripheral oxygenation of the patient should be monitored continuously and blood gases should be checked regularly. Although the exact threshold for arterial oxygenation is not known, \( S_\text{aO}_2 \) should be maintained at > 90%.

Blood pressure should be measured via an arterial line. Any hypotension (defined as systolic blood pressure < 90 mmHg) must be avoided if possible or corrected. If intracranial pressure (ICP) is monitored, the cerebral perfusion pressure (CPP) calculated should not be lower than 60 mmHg.

##### 3.5.5.2.3 Prevention of Infection

Prophylactic administration of antibiotics can be used in order to reduce the risk of pneumonia. This does not, however, change the length of stay or mortality. Early tracheostomy should be performed to reduce the number of ventilation days. Routine exchange of intraventricular catheters will not reduce the incidence of meningitis. Whether special catheters covered with silver or antibiotics will do so has to be proven yet.
3.5.5.2.4 **Prophylaxis of Deep Vein Thrombosis**

Graduated compression stockings combined with regular physical therapy are highly recommended. The administration of low molecular weight heparin or low unfractionated heparin (higher incidence of heparin-induced thrombocytopenia compared with low molecular weight heparin) may lower the incidence of deep vein thrombosis, but increase the incidence of intracranial haemorrhage. Therefore, the risks and benefits of this prophylaxis have to be calculated.

3.5.5.2.5 **Nutrition**

Even sedated patients with severe head injuries will have a resting energy expenditure of 120–160% compared with the normal level. Caused by severe catabolism, even patients with isolated injuries will lose up to 20–30 g of nitrogen per day during the first week. This must be matched by artificial nutrition. Full nutritional replacement should therefore be achieved within the first week after trauma. As these patients tend to develop hyperglycaemia with nutritional support one has to be extremely cautious not to overload patients with glucose calories. Blood glucose levels should therefore be kept normal as hyperglycaemia may worsen outcome in this patient group. Until now it has not been proven which kind of nutritional support (enteral vs parenteral) is superior.

3.5.5.2.6 **Intracranial Pressure Monitoring: Indications, Monitoring Technique, Thresholds for Intervention**

Intracranial pressure should be monitored in all salvageable patients with severe head injuries. This is especially true of patients in whom the initial CT shows any sign of raised intracranial pressure (absent or compressed subarachnoid spaces, compressed ventricles and basal cisterns) and in patients in whom the CT shows a midline shift or contusions.

Ventricular catheters connected to an external transducer are still the gold standard for monitoring ICP. They are cheap, reliable, can be re-calibrated in situ, and allow withdrawal of CSF to lower increased ICP. The risks of intracranial haemorrhages caused by puncture and their higher infection rate compared with other devices have to be taken into account. Parenchymal devices are as accurate, but more expensive and do not allow re-calibration in situ. Epidural, subdural and subarachnoid devices are less accurate.

There is no generally accepted upper threshold for any therapeutic intervention to lower increased ICP. Most studies, however, suggest that an ICP of higher than 20–25 mmHg should be treated. If CPP is calculated it should be maintained at least 50–60 mmHg. The attempt to increase CPP to >70 mmHg may adversely influence outcome owing to a higher rate of patients with acquired respiratory distress syndrome.

As a textbook like this cannot extensively cover all aspects of the conservative treatment of raised ICP, advanced neurological monitoring and general ICU treatment, the reader should refer to specialist ICU textbooks and published guidelines (see Selected Reading). A useful algorithm for the treatment of raised ICP is shown in Table 3.5.5.

The different treatment techniques should be performed in a stepwise fashion after having excluded an operable mass as the underlying cause by CT. Treatment thresholds at our institution are ICP >25 mmHg and CPP <60 mmHg (for further details refer to specialist ICU textbooks).

### Table 3.5.5 Algorithm for treatment of raised intracranial pressure

<table>
<thead>
<tr>
<th>Basic therapy</th>
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<tbody>
<tr>
<td>− Keep normal milieu interieur</td>
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<tr>
<td>• Glucose</td>
<td></td>
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<tr>
<td>• Electrolytes</td>
<td></td>
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<tr>
<td>• Osmolarity</td>
<td></td>
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<tr>
<td>• Body temperature</td>
<td></td>
</tr>
<tr>
<td>− Mild hyperventilation (p$_{a}$CO$_2$ 32–35 mmHg)</td>
<td></td>
</tr>
<tr>
<td>CSF drainage (if ventricular drain)</td>
<td></td>
</tr>
<tr>
<td>Mannitol (0.3–1.25 g/kg body weight)</td>
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<tr>
<td>Second tier therapies</td>
<td></td>
</tr>
<tr>
<td>− Decompressive (hemi)craniectomy</td>
<td></td>
</tr>
<tr>
<td>− Forced hyperventilation (p$_{a}$CO$_2$ 28–32 mmHg)</td>
<td></td>
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<tr>
<td>− Tris-hydroxymethyl aminomethane (THAM)</td>
<td></td>
</tr>
<tr>
<td>− Barbiturates</td>
<td></td>
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<tr>
<td>− Hypothermia</td>
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</table>

3.5.6 **Skull Fractures and Open Injuries**

3.5.6.1 **Linear Fractures**

Less than 1% of all patients admitted with a minor head injury and a GCS score of 15, but 75% of all patients dying from a head injury have a skull fracture. Most of these fractures are linear (Fig. 3.5.28). It must, however, be kept in mind that the presence of such a fracture increases the risk of harbouring an intracranial lesion, es-
3.5.6.2 Depressed Fractures

Depressed fractures were observed in up to 6% of all patients with severe head injuries and account for significant morbidity and mortality. If the overlying galea is disrupted they are called “open”. Additional dural tearing may then cause free communication of the intracranial space with the external environment. The incidence of post-traumatic infections and epilepsy is significantly increased in such cases.

“Simple” depressed fractures are covered by an intact galea. In some cases, depression of the bone fragments may act as a space-occupying mass. Obviously, the risk of infection is not increased in such cases, but the rate of post-traumatic epilepsy seems to be higher.

3.5.6.3 Treatment

Even extended linear fractures (“burst fractures”) heal spontaneously. Unless they are accompanied by an intracranial haematoma, surgical intervention is not indicated.

There is, however, a continuous debate whether and which type of depressed skull fractures should be operated on, as prospective, controlled, randomised trials covering this issue are lacking.

Simple depressed fractures require surgical intervention if they cause a significant mass effect, if they are depressed more than 1 cm below the adjacent intact skull or if they are accompanied by a haematoma beneath. The

**Fig. 3.5.28** Typical linear fracture (red arrowhead) on the lateral skull X-ray

pecially an extra-axial haematoma. The likelihood of a conscious patient with a skull fracture is 200-fold greater than it is in a patient without such a fracture. Special attention has to be paid to fractures that cross one of the cerebral sinuses or the middle meningeal artery with its branches.

**Fig. 3.5.29a–c** Surgical treatment of a compound skull fracture in a 10-year-old boy. a Preoperative CT scan (red arrowheads indicate the fracture). b, c see next page
surgical approach should be sufficient to cover the whole fracture. The depressed fragments are removed, the dura inspected and closed if necessary and re-implantation of the fragments should ensure the regular contours of the skull.

The rationale of the traditional management of compound fractures (Fig. 3.5.29) is their association with infection and epilepsy. Elevation of the fracture, debridement of the wound, removal of the bone fragments and meticulous closure of the dura constitutes the traditional approach in such lesions. There is also a debate as to whether or not the bone fragments should be replaced, as this traditional approach requires a second operation for cranioplasty. It seems that replacement of the bone fragments does usually not increase the rate of postoperative infections if performed within the first 12–24 h.

In some series, the rate of infection as well as that of post-traumatic epilepsy, was significantly reduced with the use of this traditional approach if the patients were operated on within the first 48 h of injury. Some authors, however, prefer a more conservative approach. They advocate simple closure of the scalp if the wound is clean, if there is no haematoma beneath the fracture, if there is no CT evidence of dural penetration, if there is no associated pneumoencephalus and if there is no involvement of the frontal sinus. In any case prophylactic antibiotic administration (e.g. second-generation cephalosporin) is recommended.

### 3.5.7 CSF Fistulas

#### 3.5.7.1 Introduction

Cerebrospinal fluid (CSF) leaks are caused by a tear of the basal dura and the arachnoid in conjunction with a basal fracture along the anterior or the middle of the skull base. They occur in approximately in 2–3% of all head injuries and in about 10% of basal skull fractures. Eighty percent of these CSF fistulas are caused by accidents, most of the remaining 20% following surgery (e.g. endonasal procedures). The severity of the initial head injury has no correlation with the appearance of a CSF fistula that might occur even in patients with no loss of consciousness or focal neurological signs. While most of the fistulas will cease with conservative (non-operative) management, some will persist and require surgical treatment.

#### 3.5.7.2 Clinical Presentation

About 98% of all fistulas occur within the first 3 months of trauma, most of them within the first 24–48 h. Delayed rhinorrhoea, even decades after trauma, however, has been reported in the literature. Delayed otorrhoea is a rarity.

Meningitis develops in 10–85% of all CSF fistulas. Bacterial strains from the nasal cavity are the main causative organisms (*Pneumococcus, Haemophilus influenzae*). In
some cases, recurrent episodes of meningitis are the only clinical signs.

Pneumoencephalus is present in about one-third of all cases. In most cases, this amount of intracranial air is small and does not cause any problems. Tension pneumoencephalus, however, is a life-threatening situation requiring immediate surgical relief. It is caused by a “valve” mechanism leading to entrapment of intracranial air with rapidly progressing brain compression.

3.5.7.3 **Physical Examination**

If a patient complains of a nasal discharge of clear fluid (Fig. 3.5.30) after a head injury he should be assumed to have a CSF fistula. Physical examination should therefore begin with a careful history-taking. Special attention should be given to any form of trauma, endonasal ENT procedures and episodes of fever in conjunction with disturbed consciousness or neck stiffness.

In acute cases, bilateral ecchymosis (Fig. 3.5.31) indicates a suspected fracture of the anterior skull base (raccoon eyes). Retro-auricular haematoma (Fig. 3.5.32) may indicate a fracture of the temporal bone (Battle’s sign).

Cranial nerve deficits are also suggestive of a basal skull fracture. Special attention should be paid to the olfactory and the vestibulo-cochlear system. Uni- or bilateral anosmia indicates an injury to the olfactory nerve, usually by a fronto-basal fracture and are suggestive of a CSF fistula, but is not a condition sine qua non. On the other hand, normal olfaction does not exclude a CSF leak. Impaired vestibular or cochlear function may be caused by fracture of the temporal bone, which may also cause ipsilateral facial nerve palsy.

Proof of the fistula itself, however, may be a difficult task. If the secretion is profuse and clear, the diagnosis is straightforward. But small and intermittent fistulas may cause major diagnostic problems. If the liquid is mixed up with blood, the secretion can be dropped onto cotton gauze. A clear corona surrounding a central red blood stain may indicate a fistula. Distinction from secretion due to “simple” rhinitis can be made by a paper strip test for glucose. If the paper strip test is negative for glucose, a CSF fistula can be excluded, because CSF usually has 30% of the glucose concentration in blood. More specific (and more expensive) is the test for β2-transferrin, a substance not present in normal ear and nose excretions.

**Fig. 3.5.30** Clinical presentation of a CSF fistula with discharge of clear fluid from the nose (arrow)

**Fig. 3.5.31** Bilateral ecchymosis in a patient indicating a fronto-basal skull fracture
3.5.7.4 Location of the Fistula

The clinical location of an anterior CSF fistula is not safe as about 10% of all patients will experience their rhinorrhoea on the opposite side of the anatomical leak. Conventional skull X-rays (Fig. 3.5.33) may show a bone defect, a fracture, intracranial air and foreign bodies that may direct further studies, but are not sufficient to prove the existence and the site of the fistula. Thin-slice CT (1.5 mm) in axial and/or coronal planes are the methods of choice to detect basal skull fractures and are superior to MRI.

In addition to trauma being the main cause of the CSF leak, differential diagnoses include tumours that destroy the skull base and occult encephalocele in anterior fistulas.

Intrathecal injection of positive contrast agents (CT cisternography) can only localise active fistulas. Other methods include radionuclide cisternography and lumbar injection of vital dyes (fluorescein, indigo carmine, methylene blue). At our institution we use intrathecal fluorescein in combination with nasal endoscopy in the ENT department. After a lumbar puncture 10–20 cc of CSF is withdrawn, mixed with 0.5–1.0 ml of 5% fluorescein in a syringe and re-injected.

3.5.7.5 Treatment

No prospective, randomised trials of operative vs non-operative treatment of traumatic CSF leaks have been published. Various studies describe an incidence of ascending meningitis in such cases of between 10 and 85%, mainly depending on the length of the follow-up period. Therefore, a careful risk–benefit analysis of conservative vs operative treatment has to be performed in each individual patient. Based on the personal experience of more than 200 such lesions, the diagnostic work-up and the indications for surgery at the author’s institution are summarised in Figs. 3.5.34 and 3.5.35.

3.5.7.6 Non-Operative Management

Non-operative management includes bed-rest in a semi-sitting position, repeated lumbar punctures, or continuous lumbar drainage. At our institution we only perform continuous lumbar drainage (100–200 ml/day) for 7 days if rhinorrhoea persists for longer than 24 h. If the fistula does not disappear afterwards, an operation is usually indicated. Otorrhoea is just observed for 7 days without any specific treatment, as these fistulas usually vanish within days.

3.5.7.7 Operative Treatment

The main goal of surgery is to seal the CSF leak and to prevent ascending meningitis. Other complications such as muco- or pyocele, chronic sinusitis, subdural empyema and brain abscess should also be prevented. Cosmetic aspects also play a role if the trauma has caused external deformity of the skull.

There is also a continuing debate on the timing of surgery, the best operative approach, and the material with which to close dural leaks and possible bone defects.

3.5.7.7.1 Timing and Approaches

All of the surgical goals mentioned above can only be achieved if a clear-cut diagnosis and an exact surgical plan are made. Proper diagnosis and surgical planning usually take time. It has also been shown that, with regard to outcome, delayed surgery in intracranial procedures is superior to immediate surgical intervention.

Cerebrospinal fluid fistulas caused by traumatic lesions of the anterior skull base are best managed by a collaborative interdisciplinary approach from the very beginning. The neurosurgeon, the maxillofacial surgeon, the ENT surgeon and sometimes the ophthalmologist are involved in the process of diagnosis, establishing the
Fig. 3.5.33a–c Skull X-rays and corresponding axial CT scan of a patient with marked pneumoencephalus following a minor head injury; note in particular the air-filled ventricles in a the antero-posterior view (arrow)
The advantages of an extracranial approach (Fig. 3.5.36) are less morbidity and mortality. The main disadvantage is the inability to address the adjacent brain damage. At our institution we use extracranial approaches only in small and circumscribed lesions (usually less than 1 cm in diameter) of the medial portion of the anterior skull base (endoscopic repair) and in fistulas of the parasellar region (paranasal incision). The operations are usually performed by the ENT surgeon with neurosurgical assistance.

The need for brain retraction to gain full visualisation of the whole anterior skull base carries a significant risk of injury to the olfactory nerves and the frontal lobes if a transcranial approach (Fig. 3.5.37) is chosen. Complex or larger fractures of the anterior skull base with associated CSF leaks, however, are still best addressed via the traditional intracranial, intradural approach, which allows full visualisation of the injury. We strongly advocate delaying the operation until the patient has recovered to some extent (GCS score at least > 5 points, infection-free, haemodynamic stability) and there is not any sign of brain swelling on the preoperative CT (status of the ventricles, basal cisterns). In order to minimise the risk of retraction, preoperative drainage of CSF by a lumbar drain or intraoperative puncture of the lateral ventricle can be used. If surgery is delayed in the way mentioned above, additional facial fractures can also be safely treated by the maxillofacial surgeon in the same procedure.

We usually first approach all lesions intradurally. Dural tears should be sutured whenever possible. If this is not possible, various methods have successfully been used for covering the dural defect (inferior-based galeal pericranial flaps, rotated flaps of the temporalis muscle, free flaps of the temporalis muscle, fascia lata etc.). Based on our experience of 34 re-operations, we do not feel that inferiorly based or rotated flaps are superior to free flaps. Because blood supply to the based flaps is very limited, both types of flap tend to shrink. In the author’s opinion it is more important to ensure that a flap is large enough to cover the leak more than 2 cm around its border to avoid recurrence of a fistula.

Larger bone defects (> 2 cm) should be covered by hard material to avoid recurrence of the fistula. Various materials can be used for this purpose (inverted temporal muscle + bone, free bone flap from split calvarium, titanium mesh). In our department, we mainly rely on titanium micro-meshes for closure.

As we strictly rely on the conservative management of otorrhoea, the author has only operated on two such fistulas during the last 20 years via a standard subtemporal approach.

### 3.5.7.2 Antibiotic Prophylaxis

Up to now there has been no clear evidence on the use of prophylactic antibiotics in patients with CSF fistulas. We routinely use a second-generation cephalosporin, starting on admission and stopping 3 days after definitive closure of the leak.
Fig. 3.5.36a–d Extracranial endoscopic assisted repair of a delayed CSF fistula (51 years following the initial trauma) in a 59-year-old lady. a Lateral MRI scan shows brain herniation (arrow) through the skull base into the nasal cavity and the fractured sphenoid. b Endoscopic view into the sphenoid with herniated brain (arrow). c Closure of the leak is performed with free muscle and fibrin glue (arrowhead). d Resected specimen of herniated brain
3.5.8 Penetrating Head Injuries

3.5.8.1 Introduction

Unlike in the USA, penetrating injuries in the civilian population are very rare in Central Europe. In Germany they account for less than 1% of all head injuries. The main causes are firearm injuries either by suicide/homicide or accidental. In rare circumstances penetrating injuries may be caused by assaults or accidents with sharp objects like knives, forks, screwdrivers etc.

3.5.8.2 Pathophysiology

Injuries from gunshot wounds are caused by transmission of the bullet’s energy to the head. The kinetic energy transmitted is a function of the bullet mass and the velocity of the missile. It follows the equation:

\[ E = M \times (v_{in} - v_{out})^2 \]

(E = energy, M = mass, \(v_{in}\) = entry velocity, \(v_{out}\) = velocity at exit).

Therefore, the extent of the cranial injury is influenced by a number of factors such as mass and velocity of the missile and design of the bullet. Brain injury, then, is caused by various mechanisms:

- The missile itself may cause laceration and tissue disruption along its way through the brain.
- Bone and tissue fragments may enter the brain acting as “mini missiles” causing further injuries.
- Vascular injuries may lead to intracranial haematoma.

The size of the intracranial cavity caused by penetrating gunshot wounds may be much larger than the diameter of the missile itself. The cavity is usually filled with bullet parts, driven in bone and tissue fragments, and necrotic brain. Associated pathological features include skull fractures at the entry and exit points, skull fractures of the skull base and dural lacerations at sites remote from these points, contusional lesions in the surrounding cavity, and injuries to major vessels.

On the other hand, non-missile penetrating injuries usually occur at very low velocities and large cavities do not exist.

**Fig. 3.5.37** Transcranial approach of a large defect (arrow) with subsequent CSF leak located in the right anterior skull base

**Fig. 3.5.38** Computed tomograph of a patient with a bihemispheric injury caused by a gunshot wound. The patient who tried to commit suicide was admitted with a GCS score of 3 points and unresponsive pupils. He died shortly after admission
3.5.8.3 Initial Examination

Clinical examination should be performed in a routine manner and is comparable to those in other head trauma victims. Additionally, one should not only focus on the obvious cranial gunshot wound, but also on further wounds that may have been caused by another bullet (chest, abdomen, oral cavity etc.). The whole head should be shaven to inspect entry and possible exit points. For legal purposes photo documentation of the injury is advisable.

A brief neurological examination includes determination of the level of consciousness (Glasgow Coma Scale), and pupillary and brainstem reflexes.

After systemic stabilisation a rapid radiological diagnosis should be established. Ideally, this should be accomplished by rapid CT, which will show the full extent of the intracranial injury (Fig. 3.5.38). Sometimes, performing CT may not be possible with large penetrating objects still sticking in the head. In such cases, skull X-rays will at least give an impression of the trajectory of the penetrating injury (Fig. 3.5.39).

In some cases it may be advisable to first obtain plain radiographs of the skull, to remove the object in the emergency room with the full back-up of a neurosurgical team and then perform CT, which might bring about further neurosurgical interventions. If vascular injuries are suspected, these films may be followed by cerebral angiography if necessary.

3.5.8.4 Operative Treatment

3.5.8.4.1 Salvageability

Patients with gunshot wounds tend to present at both ends of the GCS scale. This means that on the one hand we might have patients with low-velocity injuries who are usually in a good neurological condition (GCS score 13–15 points). On the other hand a large number of patients with mainly high-velocity missile injuries may present with an initial post-resuscitation GCS score of 3 or 4 points. If these patients do have non-reactive pupils and missing brain stem reflexes no treatment should be considered. This is also true of patients with a GCS of 4...
and 5 and bihemispheric injuries without a space-occupying haematoma.

3.5.8.4.2 Surgical Principles

Surgical repair of penetrating injuries is often demanding and requires an experienced surgeon. Such lesions are not for beginners!

As most of these lesions are unique, which is especially true of non-missile injuries, no standardised procedures can be applied. There are, however, general principles that should be followed when treating such lesions. The current principles of treatment of civilian gunshot wounds are mainly derived from military experience. Surgical treatment of such lesions should focus on the following goals:

- Debridement of necrotic scalp, muscle, dura and brain tissue
- Removal of driven in bone and bullet fragments if they are easily accessible and can be removed without causing any further neurological damage
- Evacuation of space-occupying intracranial haematomas
- Repair of injured vessels
- Meticulous haemostasis
- Meticulous closure of the dura and the scalp

Autologous grafts (e.g. fascia lata for dural repair) should be preferred, avoiding foreign material as much as possible. Bullets should be preserved for legal purposes.

Dural sinus injuries can result in massive intraoperative blood loss. They should be anticipated from the initial radiological evaluation. Several units of blood and plasma should be present in the OR before surgery starts. Dural sinus injuries should be addressed with adequate exposure, allowing proximal and distal control of the vessel. Ligation of the anterior third of the superior sagittal or a non-dominant transverse sinus is usually safe, but extensive and highly demanding microsurgical repair may be necessary in other cases.

3.5.8.5 Postoperative Treatment

Postoperative treatment follows the same rules and principles as for other kinds of head injuries. An ICP transducer should be inserted in patients with severe injuries who are judged to be salvageable. Although large randomised trials in the civilian population are lacking, most centres use antibiotic prophylaxis in penetrating injuries. At our institution we empirically apply penicillin plus a second generation cephalosporin for 7–10 days.

3.5.8.6 Outcome

A large number of patients with gunshot wounds will die at the scene or during transport to a hospital. Patients reaching the hospital alive will have an overall mortality of around 60%. Around 20% of all patients will have a satisfactory outcome. About half of the patients with higher GCS scores on admission (i.e. 9–15 points) will attain a satisfactory neurological result.

3.5.9 Traumatic Haematoma

3.5.9.1 Epidural Haematoma

3.5.9.1.1 Definition

An epidural (or extradural) haematoma (EDH) is an accumulation of blood in the epidural space between the inner side of the skull and the dura mater.

3.5.9.1.2 Pathogenesis

Traffic accidents and falls are the leading causes of epidural haematomas (EDHs) in the adult population. In children, falls account for approximately 50% of these lesions.

In most adult cases the underlying cause is a skull fracture crossing the middle meningeal artery or its branches in the fronto-temporal region. Rarely, a fracture may be associated with tearing of large veins at the vertex of the skull or of the venous sinuses of the brain itself. This explains why most EDHs (>95%) are located above the tentorium. Rare locations include the posterior fossa (hemispheric or retro-clival) and bilateral supratentorial haematomas. In about 60–70% of all patients with an EDH the EDH is the only intracranial injury (“pure” EDH), in 30–40% the EDH is associated with other intracranial lesions, mainly contusions and intracerebral haematomas (“complicated” EDH).

In the paediatric population venous bleeding accounts for about one-third of all EDHs and a bleeding source cannot be found during operation in another third. “Pure” EDHs occur more frequently in paediatric patients than in adults.

3.5.9.1.3 Epidemiology

The true incidence of EDH is not known. In large unselected series of patients with head injuries, its incidence is about 2–4% and may be around 10% in comatose patients. EDHs in very young (<5 years) and older (>65 years) patients are quite rare. They predominantly occur between the second and third decades of life. This is due to the fact that the dura in very young and older patients is usually tightly adherent to the skull and does not tear easily.
3.5.9.1.4 Clinical Signs
Inspection of the skull may show local bruises or skin abrasions as well as subgaleal swelling as a hint that a circumscribed force has hit the head of the patient. Ot- orrhagia and retro-auricular bleeding (Battle’s sign) may indicate a temporobasal skull fracture.

Secondary deterioration (i.e. a drop on the GCS scale) after a so-called “lucid interval” is the classical clinical course of a patient who develops a post-traumatic EDH. Nowadays, however, this “classical” course can be observed in less than 30% of all patients harbouring an EDH. Due to the initial impact on the brain in high-speed accidents most of the patients are already comatose on admission and deteriorate into deeper coma afterwards because of their developing epidural mass lesion. In some cases patients with EDHs remain conscious during the whole course until they are operated on. Clinical deterioration usually occurs during the first 4–8 h after injury as the haematoma evolves. In patients with tearing of the main trunk of the meningeal artery secondary deterioration may develop dramatically within some 10–20 min.

Local pressure on the ipsilateral central gyrus causes contralateral hemiparesis. Compression of the ipsilateral oculomotor nerve causes ipsilateral mydriasis. If the haematoma progresses further midbrain, compression due to transtentorial herniation is observed with the clinical signs of flexion/extension movements. Afterwards, compression of the brain stem leads to fixed bilateral pupils and subsequent brain death.

3.5.9.1.5 Diagnostic Procedures
Cranial CT is the diagnostic method of choice. In typical cases it shows a hyperdense, lenticular-shaped, space-occupying mass located under the inner side of the skull in the fronto-temporal region (Fig. 3.5.40). If CT is performed very early some portions of the haematoma may not have clotted yet, resulting in a hypodense/hyperdense appearance of the epidural mass (Fig. 3.5.41). Various EDHs in atypical locations are shown in Figs. 3.5.42.

3.5.9.1.6 Operation

3.5.9.1.6.1 Indication
Because of the natural course of the disease, there are no randomised controlled trials comparing surgical versus non-surgical treatment of EDHs. Therefore, indications for surgery mainly rely on the clinical conditions, the neurological status and the CT findings of the patient. It is well known that some CT factors like haematoma thickness, haematoma volume, and degree of midline shift are related to outcome. In general, all patients harbouring an EDH with a volume greater than 30 cm³, or a haema-
toma more than 15 mm thick, producing a midline shift of more than 5 mm, as well as all unconscious patients, should be operated on. As outcome has been proven to be closely correlated with the duration of brain herniation, these patients should be handled as emergencies. Only in rare cases (awake patients, haematoma thickness less than 15 mm, midline shift less than 5 mm, haematoma volume less than 30 cm³; Fig. 3.5.43) may conservative management (close neurological follow-up, repeated CT) be justified. The old neurosurgical saying “if in doubt, take it out” is still a reliable guideline for the operative treatment of EDHs. Even in patients with fixed and dilated pupils surgery of EDHs may have good clinical results, especially if no other cerebral lesions are visible on the preoperative CT.

### 3.5.9.1.6.2 General Principles of Surgery

In most cases the operation of an EDH is an easy, straightforward procedure. Details of the operation are described elsewhere (refer to Selected Reading). In my personal experience vertical skin incisions with small craniectomies/craniotomies are only justified in very circumscribed haematomas. Otherwise, the skin and the bone flap should always cover the entire extension of the haematoma to gain complete exposure of possible bleeding sources (main trunk of the meningeal artery, sinuses).

In extreme emergencies, where rapid decompression and relief of intracranial pressure is essential, the skin above the area of the maximal extension of the haematoma is opened first, a small craniectomy is performed to evacuate some parts of the haematoma by suction. The scalp incision and the craniectomy are then completed to evacuate the rest of the haematoma. In cases in which the haematoma is caused by laceration of a major sinus the surgeon (and the anaesthesiologist) should be prepared for major blood loss. After elevation of the bone flap the haematoma is removed by suction, irrigation and forceps. If the EDH is the only intracranial injury the dura is usually relaxed and the operation is completed in the typical fashion. If the dura remains tense or a bluish colour, this suggests an underlying subdural haematoma, and the dura has to be opened to address these lesions.

Meticulous haemostasis should be obtained by circumferential and bone flap dural tacking sutures and electric bipolar cautery of the dural vessels. In cases in which a lesion of the main trunk of the middle meningeal artery has caused the haematoma, haemostasis can easily be obtained by ligation of the vessel. In some cases the foramen spinosum has to be exposed and closed by waxing. I usually close the bone flap by leaving one or two (in larger haematomas) epidural suction drainages and an additional subcutaneous one. The bone flap is replaced and the scalp is closed in the routine manner (Fig. 3.5.44).

### 3.5.9.1.6.3 Postoperative Precautions

Routine control CT should be performed 4–8 h after the operation to show adequate expansion of the brain and to ensure complete removal of the haematoma. Control CT is particularly warranted in cases in which the EDH is associated with additional intracranial lesions, as even small contusions may grow enormously after pressure relief (Fig. 3.5.45).

### 3.5.9.1.6.4 Outcome

As mentioned previously, the outcome of a patient with an EDH depends on various factors (clinical condition, initial neurological status, neurological status at the time of surgery, duration of herniation, associated intracranial lesions). This is the reason why outcome varies so much. In general, a favourable outcome can be obtained in most patients with “pure” EDHs, even if they are comatose at the time of surgery. The estimated mortality derived from studies with larger patient groups is 35% for patients with a GCS score of 3–5 and a good clinical outcome in more than 90% of the cases in patients with a GCS score of 8–15.

### 3.5.9.2 Acute Subdural Haematoma

#### 3.5.9.2.1 Definition

A subdural haematoma (SDH) is an accumulation of blood in the subdural space between the inner side of the
Fig. 3.5.42a–d  Atypical locations of EDHs. a Left frontal EDH (red arrowhead). b Left occipital EDH (red arrowhead). c EDH located on the vertex. d EDH in the right posterior fossa (single red arrowhead) causing marked compression of the (hypodense) brain stem (double red arrowhead)
Fig. 3.5.43 Small EDH (red arrowhead) in the left frontal region that may be treated conservatively. Such small haematomas are usually caused by ruptured diploic veins from a linear skull fracture.

Fig. 3.5.44a–c Typical situs during operation of a right temporo-parietal epidural haematoma. a After incision of the scalp the skull fracture (white arrow) with the underlying haematoma is already visible. b Same situs after exposure of the haematoma. c Same situs after removal of the haematoma. Note the relaxed dura and the circumferential tacking sutures.
Fig. 3.5.45a,b  Growing contusion following removal of an epidural haematoma. a Initial CT scan demonstrating a left parieto-occipital EDH (arrowhead). b see next page
Fig. 3.5.45a,b (continued) Growing contusion following removal of an epidural haematoma. b Postoperative CT scan after removal of the epidural haematoma. A right-sided contusion has developed in the fronto-temporal region (single red arrowheads) as well as a small subdural haematoma (double red arrowheads).
3.5.9.2.2 Pathogenesis
Traffic accidents in younger patients and falls in the older population are the leading causes of acute subdural haematomas (aSDHs) in the adult population. In children, parental and child abuse are also common causes.

“Pure” aSDHs occur in a minority of cases. Rupture of a cortical artery or a bridging vein following minor trauma is the most common cause in these cases. In most aSDHs, associated intracranial lesions (rupture of cortical vessels – either arteries or veins – on the contused brain surface) are responsible for the development of such a haematoma. Associated lesions are found in approximately half of patients with a GCS score of 3–15. In patients with a GCS score of 8 or below, the percentage of associated intracranial lesions increases up to 60–80%. Most of these associated lesions are contusions and/or traumatic intracerebral haematomas. Traumatic subarachnoid haemorrhage (tSAH) can be observed in 10–20% of all aSDHs. As most of these lesions are the results of high-speed accidents, extracranial injuries (midface, thoracic, abdominal, extremities) are especially frequent.

Most aSDHs are located in the supratentorial space on the convexity of the brain with a special preference for the fronto-temporo-parietal region. Space-occupying interhemispheric SDHs are rare findings. Infratentorial aSDHs account for less than 1% of all cases.

3.5.9.2.3 Epidemiology
Combining the results of several studies, aSDHs occur in approximately 10% of all patients with a traumatic brain injury. In comatose patients the incidence is around 20%. The author’s own data on 1,136 patients with severe head injuries showed an incidence of 18.4% in cases of isolated head injuries and 30.4% in multiple trauma patients. aSDH may occur at any age, but are predominantly found in younger men between 30 and 50 years of age.

3.5.9.2.4 Clinical Signs
As in epidural haematomas, the skull should be inspected for local bruises or skin abrasions and subgaleal swelling as local signs of trauma.

Due to the fact that severe primary brain injury is present in the majority of all patients who are going to develop an aSDH as a secondary complication of their injury, most of these patients are already in a coma when admitted. At the time of admission 37–80% of all patients present with a GCS score of 8 or less. A lucid interval is reported in less than 20% of all cases. Roughly 50% of all patients with aSDH present with pupil abnormalities at the time of admission to the hospital.

As in other space-occupying haematomas secondary deterioration leads to a drop on the GCS scale, dilatation of the ipsilateral pupil, and contralateral hemiparesis, and is followed by clinical signs of midbrain and brain stem herniation.

3.5.9.2.5 Diagnostic Procedures
As in all trauma cases cranial CT is the diagnostic imaging of choice. In typical cases it shows a hyperdense, biconvex, lenticular, space-occupying mass located under the inner side of the skull in the fronto-temporal region (Fig. 3.5.46). Quite typical is the extension of the haematoma into the Sylvian fissure (Fig. 3.5.47). As already mentioned, an infratentorial aSDH is a very rare finding (Fig. 3.5.48). CT will not only demonstrate the aSDH itself, but will also reveal associated intracranial pathological features (Fig. 3.5.49).
3.5.9 Traumatic Haematoma

3.5.9.2 Operation

3.5.9.2.6 Indication

As with epidural haematomas, there have been no randomised controlled trials comparing outcome in surgical versus non-surgical treatment of aSDHs. Therefore, the indication to operate on such a patient also relies on the clinical condition, the neurological status and the CT findings of the patient. The thickness and volume of the haematoma, the degree of midline shift and the patency of the basal cisterns are closely to outcome in patients with aSDHs. Haematomas with a thickness greater than 10 mm or haematomas causing a midline shift of more than 5 mm should be operated on, regardless of the GCS score of the patient. Surgical evacuation of the haematoma should be performed as soon as possible because – as with EDHs – a delay in surgery usually worsens the individual outcome. In patients with smaller haematomas, but clinical deterioration of the patient, there is also a good indication for surgery. In general, it is advisable to measure ICP in all patients who are comatose and who have been operated on for an aSDH. Because age (as in all TBI patients) is a strong predictor of outcome in patients with aSDH, various studies have focused on outcome after surgery for an aSDH in older patients. From these studies it can be stated that a good functional outcome in comatose patients above the age of 70 years is very unlikely. Therefore, with regard to the

**Fig. 3.5.47** Computed tomograph with a large aSDH on the right side. Note the extension of the haematoma into the Sylvian fissure (arrowhead)

**Fig. 3.5.48** Acute subdural haematoma above the right cerebellar hemisphere (red arrowheads)

**Fig. 3.5.49** Typical CT picture of an acute subdural haematoma (single red arrowhead) accompanied by a temporal contusion (double red arrowheads)
indication to operate this fact also needs to be taken into account.

3.5.9.2.6.2 General Principles of Surgery

There are various methods of evacuating an aSDH. Burr-hole trephination, craniotomy or craniectomy (both with and without additional duraplasty), and subtemporal decompression are the most frequent. There are very few studies in the literature that have prospectively compared the influence of those various surgical methods on outcome. The only consequence that can be derived from these findings is that evacuating an aSDH via a burr-hole is usually not a good idea. Subsequently, in most centres, the decision which method is to be used in the individual patient is mainly influenced by the clinical status of the patient and the evaluation of the CT scan. At our institution we use a large standardised “trauma flap” (i.e. a large fronto-temporo-basal-parietal craniotomy) in order to evacuate an aSDH in a typical location. It cannot be overemphasised that both the skin and the bone flap, as well as the opening of the dura, have to be large enough (which means that the entire fronto-lateral, temporal and parietal cortex have to be exposed down to the temporal skull base and as close as 2 cm away from the superior sagittal sinus) to address all intracranial pathologies and bleeding sources as well as to gain sufficient ICP relief. After elevation of the bone flap and opening of the dura, removal of the haematoma is performed by suction and irrigation. We do not routinely remove brain that appears to be functional, but severely contused brain as well as space-occupying clots in the frontal and temporal region should also be removed.

Fig. 3.5.50a–c Typical operative steps during operation of a large acute subdural haematoma. a After incision of the scalp and removal of the bone flap the tense bluish dura already indicates the underlying haematoma. b Same situs after exposure of the haematoma. c Same situs after removal of the major part of the haematoma. Note red colour of the surface due to traumatic subarachnoid haemorrhage and multiple contusions of the brain
If the brain is relaxed and there is no tendency towards brain swelling, we implant a parenchymal ICP transducer and complete the operation with meticulous haemostasis, closure of the dura, re-implantation of the bone flap and closure of the scalp. If the brain, however, tends to swell (as a general rule: if it has reached the dural level at the end of the intracranial part of the operation) we routinely perform a duraplasty and remove the bone flap (Fig. 3.5.50).

3.5.9.2.6.3 Postoperative Precautions
As in all cases of operated traumatic haematomas, routine control CT should be performed after the operation to ensure complete removal of the haematoma and to exclude an evolving haematoma away from the operation site.

3.5.9.2.6.4 Outcome
Owing to the fact that most patients with an acute traumatic SDH have sustained a severe primary trauma, outcome in general is poorer than in patients with epidural haematomas. Clinical condition, initial neurological status, neurological status at the time of surgery, duration of herniation and associated intracranial lesions are extremely significant predictors of outcome. In general, mortality in comatose patients varies from 45 to 70%, with a rate of good functional outcome of between 10 and 20%.

3.5.9.3 Parenchymal Lesions

3.5.9.3.1 Introduction
Parenchymal mass lesions (Figs. 3.5.51–3.5.53) occur in approximately 10% of all head injuries and in about one-third of all severe injuries. Most of these lesions are (and remain) small without any space-occupying effect and can be managed conservatively. Some of them, however, develop a mass effect, placing the patient at risk of further deterioration, herniation and subsequent brain death. Different from epidural and acute subdural haematomas, which are usually present within the first 8 h of the initial injury, parenchymal lesions tend to evolve, sometimes even within days, making it difficult to decide when to operate on them. Research, therefore, has mainly focused on defining subgroups of patients who are at risk of developing such a lesion, on the indications for surgery and on the best time to operate.

3.5.9.3.2 Definition
Head injuries can be classified into diffuse vs focal. In most cases, patients present with a mixture of both. With this distinction, parenchymal lesions represent focal le-
sions. The distinction between a contusion, a traumatic intracerebral haematoma and an infarction is somewhat artificial. From a practical point of view, such lesions are best classified according to their CT appearance as hyperdense, hypodense or mixed. Most of these lesions are visible on the initial CT. Because approximately 30% of them will grow within the few hours or days after the initial injury the need for repeated CT and continuous monitoring of such patients cannot be overemphasised. A special entity is a delayed intracranial haemorrhage (DTICH), which develops in about 2% of all cases in a region of initially "normal" brain tissue. Special attention must also be paid to small contusions that are accompanied by an extra-axial haematoma, as a remarkable amount of these lesions will "grow" after evacuation of the initial mass lesion. Therefore, it is desirable to perform routine CT following evacuation of such lesions within 4–8 h of surgery.

3.5.9.3.3 Indications for Surgery
Many prognostic factors have been defined in parenchymal lesions such as location, size, mass effects, timing of surgery, GCS score on admission and prior surgery and many more. Such prognostic factors may help to define patients at risk of transtentorial herniation from such a lesion and may guide surgical decision making. Additionally, continuous monitoring of ICP and repeated CT may be helpful in deciding whether to operate or not.

Useful parameters to guide surgical treatment are:
- Progressive neurological deterioration
- Raised ICP resistant to conservative treatment
- Signs of mass effect on repeated CT (midline shift, compromised basal cisterns, obliteration of the third and the lateral ventricles)

Given these parameters patients with focal parenchymal lesions should be operated on if:
- The lesion volume is larger than 20 cm$^3$
- The lesion causes an increase in ICP $>20–25$ mmHg that is refractory to conservative therapy
- The patient has a GCS score of 6–8 points, and the lesion:
  - Is located frontally or temporally
  - Causes a midline shift of more than 5 mm or the basal cisterns are obliterated
  - Is larger than 20 cm$^3$

3.5.9.3.4 Surgical Technique
Although attempts have been made to evacuate such lesions by stereotactic needle aspiration, the best treatment is still open craniectomy and evacuation.

3.5.9.3.5 Decompressive Craniectomy
According to EBIC and ABIC guidelines for severe head injuries, decompressive craniectomy is one therapeutic option for brain oedema after diffuse lesions that do not respond to conventional therapeutical measures. Decompressive craniectomy has experienced a revival during the last decade. Whereas class I studies of this subject are still lacking (but on the way), there is good evidence from prospective uncontrolled trials that such an operation improves outcome in general and also has beneficial effects on various physiological parameters known to be independent predictors for a bad outcome. The additional volume gained by this procedure is remarkable and shifts the ICP pressure–volume curve to the right.

3.5.9.3.5.1 Indications
"Therapeutic" decompressive craniectomy should be performed in a "protocol-driven" fashion as a second-tier therapy in deteriorating patients with a rise in ICP refractory to conventional pharmacological treatment. There are hints that ICP thresholds in these patients may vary depending on their clinical state. Whether "prophylactic" decompression improves outcome is questionable, but there is some evidence that such decompression may produce good clinical results too. Such procedures may be the only methods available of preventing patients from
suffering from herniation in developing countries with a lack of ICU and monitoring resources for brain trauma victims. Best clinical results are obtained in young patients, but there is no evidence from the literature for a certain age limit. For age, the actual overall agreement is that patients above 50 years should be decompressed with caution. Primary or secondary signs of brain stem damage (pupils fixed and dilated; GCS score 3 points) are clear contraindications for the procedure.

3.5.9.3.5.2 Surgical Technique
Different techniques exist for surgical decompression (bifrontal, temporal/subtemporal, hemicraniectomy, with or without removal of brain tissue, with or without duraplasty). At our institution we perform a standardised hemicraniectomy with subtemporal decompression in combination with duraplasty without removing brain tissue (Fig. 3.5.54). If the swelling is unilateral, the procedure is limited to the affected side. In cases of general oedema, the decompression is performed bilaterally.

3.5.9.3.5.3 Outcome
Given the indications and contraindications above, approximately 70% of the patients undergoing this procedure will survive and two thirds of those survivors will have a favourable outcome (GCS 4 or 5).

3.5.10 Selected Reading

Books
3.5 Trauma


3.5.11 Head Injuries: Specific Aspects in Children

LUCA MASSIMI, ANTONIO CHIARETTI, ORAZIO GENOVESE, CONCEZIO DI ROCCO

3.5.11.1 Peculiar Aspects of Paediatric Traumatic Brain Injuries

3.5.11.1.1 Epidemiology

Traumatic brain injury (TBI) accounts for most neurosurgical admissions to hospital and remains the most common cause of death in the paediatric population. The estimated incidence of TBI among children aged 0–14 years in the United States is about 800/100,000/year [4]. Head trauma results in emergency department (ED) consultations in 731 cases per 100,000, hospitalisation in 63 per 100,000, and death in 4.5 per 100,000. Children less than 4 years of age have the highest rate of ED consultations (1,035/100,000), hospitalisation (80/100,000), and death (5.7/100,000), if compared with those aged 5–9 years and 10–14 years.

Falls are the leading cause of TBI in the paediatric population, followed by transportation-related injuries and inflicted injuries. In about 5% of cases the mechanisms of the trauma remain unknown. The causes of head injury by age are listed in Table 3.5.6.

Boys and adolescents are more likely to have a TBI than girls. The mortality rate among children with GCS 3–8 at onset ranges from 20 to 40%.

3.5.11.1.2 Head Traumas in Newborns and Infants

Traumatic brain injury occurring in this subset of patients differs from those of older counterparts owing to the characteristics of infantile cranio-encephalic structures. The main differences from older children and adults can be summarised as follows:

- Young children have a larger and heavier head in relation to body size, but weaker cervical muscles and ligaments, consequently suffering more severe lesions for a given acceleration/deceleration of the body or for an impact with the same energy.

Articles


Guidelines

1. Guidelines for the Prehospital Management of Severe Traumatic Brain Injury, 2nd edn
2. Guidelines for the Management of Severe Traumatic Brain Injury, 3rd edn
3. Guidelines for the Surgical Management of Traumatic Brain Injury
4. Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents
5. Early Indicators of Prognosis in Severe Traumatic Brain Injury

Guidelines can be ordered or accessed via www.brain-trauma.org

Useful Links

1. World Federation of Neurological Societies: www wfns org
2. European Association of Neurological Societies: www eans org
3. American Association of Neurological Surgeons: www aans org
4. Congress of Neurological Surgeons: www cns org
5. European Brain Injury Consortium: www ebic ni

Table 3.5.6 Causes of paediatric traumatic brain injury (TBI) by age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Main causes of TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>Delivery, falls</td>
</tr>
<tr>
<td>Infants</td>
<td>Inflicted injuries, falls</td>
</tr>
<tr>
<td>Toddlers</td>
<td>Falls, transportation-related injuries, inflicted injuries</td>
</tr>
<tr>
<td>Young school-aged children</td>
<td>Falls, transportation-related injuries (mainly bicycle crashes)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>Transportation-related injuries (mainly motor vehicle crashes), sporting injuries, falls</td>
</tr>
</tbody>
</table>
• Newborns have thin and pliable chondral skull bones, with open sutures, that can result in typical skull fractures after a traumatic impact. The pliability of the skull together with the absence of internal bone ridges usually limits the occurrence of contre-coup contusions.

• The immature brain shows increased water content (especially within the white matter) because of the still immature myelination (most of the pattern of myelination, indeed, is completed by the second year of age). Subsequently, it is more susceptible to the mechanical alterations that can result in more intense brain tissue displacement. The brain lacerations are the most common lesions resulting from such a mechanism. They consist of haemorrhagic lesions of the white matter, usually parallel to the overlying cortex, occurring only during the first months of life as a consequence of major closed and/or shaking traumas.

• Newborns and infants are prone to developing hyperaemia after TBI because of an increased cerebral blood flow resulting from impairment of the autoregulation. Hyperaemia has been postulated to be the major mechanism underlying diffuse cerebral swelling (DCS). Other possible mechanisms are vascular congestion (increased blood volume) and/or increased water content (but different from post-traumatic vasogenic oedema). DCS often complicates a TBI in very young children, even following mild brain injuries. It appears in the early post-traumatic phases, usually after a period of normal vigilance. The early medical treatment of DCS is of paramount importance. In fact, it can be complicated by intracranial hypertension and secondary hypoxic insults favouring further impairment of the autoregulation and interference with the neural metabolism.

• The developing brain is more "plastic" to the external stimuli compared with the adult one. The brain plasticity is a very complex molecular and cellular event (neuronal migration, dendritic arborisation, axonal growth, synaptogenesis) taking place during the first two decades of life, even though most of the neuronal changes occur within the first decade. The neuroplasticity is thought to give the young children significant advantages for functional recovery after a TBI compared with adolescents and adults. However, infants often show the worst developmental outcome after severe TBI (chronic and behavioural disturbances) and, as do the older children, have a higher incidence of post-traumatic epilepsy. Such a paradoxical result may be the consequence of prolonged and abnormal physical (e.g. hypoxia, ischaemia) and/or environmental stimuli (e.g. poor parents’ compliance, inadequate child rehabilitation) that alter the processes of brain plasticity making it ineffective or even deleterious. A further hypothesis is that TBI, occurring in a critical phase of the brain development, may severely interfere with cerebral maturation.

• Functional recovery, especially after moderate/severe TBI, is often limited and most children suffer from some degree of neurological, cognitive, or behavioural alteration. Very young patients appear to be more affected than older children, which results from the pathophysiology of the injury rather than from the age or the cause of the trauma. Indeed, delayed medical attention, hypoxia, and ischaemia seem to be the main causes of the poor outcome in this subset of patients [5]. Predictors of poor outcome include multiple trauma, early hypoxia or shock, GCS, CT pattern, and ICP values. The common use of different coma scales, such as the Children’s Coma Scale (CCS), the Glasgow Coma Scale (GCS), the CHOP Infant Coma Scale or the Infant Face Scale (IFS) and others, as well as different functional outcome scales, makes it hard to compare different groups of children or children and adults [3].

3.5.11.2 Specific Types of Head Injuries in Newborns and Infants

3.5.11.2.1 Birth Head Injuries

Birth head injuries result from the mechanical forces acting during labour and/or normal or assisted vaginal delivery. Malpresentation, cephalo-pelvic disproportion, large gestational weight of the foetus, delivery by forceps or vacuum extractor, and urgency of the delivery are the main risk factors; the method of assisted delivery is the most significant one. Birth head traumas include cerebral injuries (brain contusion, swelling, infarction, haemorrhage), intracranial blood collections (epidural, subdural and subarachnoid haemorrhage), skull fractures, and scalp injuries. Scalp injuries are included, being almost exclusive to the paediatric age and potentially resulting from any kind of head trauma.

3.5.11.2.1.1 Caput Succedaneum (Subcutaneous Haematoma)

Caput succedaneum (CS) is a diffuse, subcutaneous, extraperiosteal fluid collection consisting of serum and blood. It results from the tourniquet effect of a narrowed cervix against the scalp, and is often associated with either premature rupture of the membranes or oligohydramnios. CS extends across the midline and over the suture lines, usually involving several cranial bones. The portion of the head presenting first is that most often involved. CS appears as a superficial and soft swelling with poorly defined margins under the newborn scalp, crossing the sutures and causing head moulding. The skin may be discoloured because of the possible bleeding, and bruised. CS is rarely associated with skull or intracranial...
complications. It completely and spontaneously resolves by the first few days after the birth; thus, generally, no radiological investigations or treatment are indicated. The scalp regains its normal contours.

3.5.11.2.1.2 Cephalhaematoma
(Subperiosteal Haematoma)

Cephalhaematoma (CH) is the most frequent cranial injury in the newborn, occurring in 0.2–2.5% of live births. It caused by bleeding from the veins of the pericranium (small vessels crossing the pericranium and communicating with the diploic veins), which may be disrupted during the delivery, especially after a prolonged labour or when forceps or a vacuum extractor is used (friction injury separating the periosteum from the skull). As a result of the bleeding, the pericranium is elevated, with subsequent subperiosteal blood collection. CH is confined by suture lines because of the periosteal attachment and because the diploic veins of each bone of the infant skull are separate. CH presents as a well-circumscribed fluctuant mass enlarging after the birth to become firm and tense (it is evident by the second to third day of life). The parietal bone is most frequently involved. The scalp can be moved freely over the lesion and the skin is not discoloured. CH can be easily differentiated from CS or from a subgaleal haemorrhage because it does not cross the sutures. The absence of pulsations and of increased pressure with crying allows it to be differentiated from a cranial meningocele. CH can be associated with linear skull fractures (10–25% of cases) or with traumatic intracranial lesions (Fig. 3.5.55). CH reabsorbs completely within 2–4 weeks to 3–4 months in more than three-quarters of cases. Otherwise, it may persist and calcify. Calcification appears during the first weeks and, later, a curvilinear film of bone may form from the elevated pericranium, sometimes simulating a depressed skull fracture (Fig. 3.5.56). CT is required for a correct diagnosis. In the case of significant blood accumulation, CH may be complicated by jaundice, because of the hyperbilirubinaemia resulting from the blood reabsorption, and by anaemia, especially if needle aspiration of the collection has been carried out. Therefore, phototherapy and/or blood transfusion may be necessary. The percutaneous fluid aspiration should also be avoided because of the risk of infection and subsequent meningitis and/or osteomyelitis. Surgery is indicated only for cosmetic reasons to correct the focal skull deformity following calcification of the haematoma.

3.5.11.2.1.3 Subgaleal Haematoma
(Subaponeurotic Haemorrhage)

Subgaleal haematoma (SH) is a rare, but potentially fatal, birth head injury. It consists of bleeding in the potential space between the pericranium and the scalp galea aponeurosis. As this virtual space extends from the orbital ridges to the neck and laterally to the ears, a significant amount of blood can accumulate within. The bleeding usually results from the prolonged use of a vacuum extractor or forceps. The presence of coagulopathy makes the risk highly increased. SH presents as a fluctuating and soft mass gradually developing a few hours/days after the birth. The mass can extend over the whole calvarium, thus crossing the sutures, but is more often limited to the occipital region. The growth may be insidious, leading to conspicuous blood loss or even to mass effect. Periorbital and auricular skin ecchymosis may appear. Calcification is usually absent. Severe SH is noticed immediately after the delivery; in fact, it can even start with a haemorrhagic

Fig. 3.5.55a–c Perinatal head injuries. a Bilateral parietal cephalhaematoma. CT shows the subperiosteal fluid collections and the associated brain swelling and occipital contusions. b,c Antero-posterior and oblique skull X-ray views demonstrating subgaleal fluid collections and the associated diastases of the cranial sutures (arrows)
3.5.11.2.2 Skull Fractures

Skull fractures following head trauma occur more frequently in childhood than in adulthood because of the thinness of the cranial bones and the increased head/body size ratio in children. The incidence ranges from 25 to 40% among all children with head injury, and up to 60% when only newborns and infants are considered [1]. The linear fractures are the most common form, representing more than 70% of all the paediatric skull fractures. They prevalently occur in infants and very young children. The depressed fractures are most frequently observed in older children (15–25% of the total).

3.5.11.2.2.1 Growing Skull Fractures (Post-Traumatic Leptomeningeal Cysts)

Growing fractures (GFs) are (usually linear) skull fractures that tend to widen over time, resulting in bone erosion and arachnoid herniation. They represent a rare event, accounting for less than 1% of all skull fractures, and generally occur in children less than 3 years old. In fact, the quickly enlarging brain of young children contributes to the development of GFs. The pathogenic mechanism starts with a laceration of the dura mater beneath the fracture, followed by the separation and erosion of the bone edges because of the pulsations of the CSF spaces. If not stopped, the process goes ahead, producing a subcutaneous leptomeningeal cyst and further enlargement of the skull defect with secondary herniation of the brain tissue in the late phases of the evolution. GFs present as a palpable, soft and pulsatile scalp mass progressively enlarging over the fracture site and becoming evident within 3–6 months of the head injury (Fig. 3.5.57). Usually asymptomatic, they may produce headache, or even exert mass effect or cause neurological deficits, such as hemiparesis and seizures. Skull X-rays and CT demonstrate the progressive separation and erosion of the edges of the fracture. CT can also show an arachnoid cyst herniating through the bone opening and the subsequent displacement of the underlying brain tissue (Fig. 3.5.57). A focal dilatation of the underlying lateral ventricle is common as well. Cerebral contusions may occur. The treatment of GFs consists of surgical repair (Fig. 3.5.57). The key points of surgery are wide exposition of the fracture site and the underlying dura mater; excision of the leptomeningeal cyst and the possible associated glial scar; identification of the torn dural edges, usually retracted below the bone margins; watertight dural closure; and adequate osteosynthesis. In older children, the repair of the skull may be carried out by using a split bone flap, obtained from the contralateral or neighbouring regions.

3.5.11.2.2.2 “Ping-Pong Ball Fractures”

Depressed “ping-pong fractures” (PFs) are exclusively observed in newborns and infants because of the thinness and plasticity of their skull, which can be indented without any bone discontinuity. PFs appear as a palpable inward buckling of the skull, with variable diameter and deepness. The overlying skin is depressed according to the degree of bone indentation. This kind of fracture, indeed, is often diagnosed with a simple skin inspection (Fig. 3.5.58). The neuroimaging investigations are used to confirm the skull depression, generally without bone breaking, and to detect possible brain contusions or associated haemorrhages. A child with a PF is usually asymptomatic unless associated post-traumatic lesions are present. The surgical treatment is required to avoid the possible occurrence of late seizures and/or for cosmetic reasons. The operation typically consists of a short linear skin incision and of a single burr-hole placed close to the skull depression. The burr-hole allows a Penfield dissector or an elevator used as a lever to be introduced, to push the fracture back out. Sometimes, an obstetrical vacuum extractor or a breast milk extractor can be utilised to elevate the fracture. In newborns, as the skull grows, mild PFs can elevate spontaneously.
3.5.11.2.2.3 Occipital Osteodiastasis
Occipital osteodiastasis depends on the separation of the squamous and basal portions of the occipital bone, secondary to torsion or compression of the skull. The condition may result in tentorial laceration with venous bleeding, posterior fossa epidural haematoma, cerebellar or medullary compression. Before the introduction of CT, this type of traumatic lesion was only detected post-mortem.

Fig. 3.5.57a–i Parietal growing skull fracture. a Early skull X-ray examination and b CT showing the parietal linear skull fracture. c Later skull X-ray examination and d CT demonstrating the wide diastasis of the fracture with herniation of the underlying brain. e At the time of the surgical repair, the child showed an obvious focal swelling of the scalp due to the herniated cerebral tissue and cerebrospinal fluid. f After a large craniotomy encompassing the skull defect has been carried out, the damaged herniated cerebral tissue is excised, g the torn dura mater edges identified and repaired by means of a dural implant. h An acrylic cranioplasty is carried out to repair the skull defect. i Control post-operative CT demonstrating the correct reconstruction of the dural and bone defect together with minimal dilation of the homolateral cerebral ventricle.
3.5.11.2.3 Child Abuse

It is defined as “non-accidental” or “inflicted” traumatic injury. The estimated incidence is 15 per 1,000 children per year, even though the phenomenon is certainly under-reported. Ten percent of children younger than 10 years of age hospitalised for head injury and 25% of those less than 2 years of age are victims of child abuse. These figures are even higher when only patients with severe injuries are considered.

Terms such as “battered child” and “shaken baby” indicate specific aspects of child abuse. The battered child syndrome (BCS) involves children < 3 years of age with signs of chronic abuse, such as skin and skeletal injuries, burn injuries, and poor nutrition and hygiene. The patients are usually referred to the hospital for unrelated problems or for specific injuries that are inconsistent with the clinical picture. The neurological impairment may be significantly worse than the signs of external trauma. Physical and radiological examinations point out signs of recurrent traumas, such as metaphyseal fractures in infants, bilateral femur and/or humerus fractures at different stages of healing, other multiple skeletal fractures, face and head traumatism, retinal haemorrhages, subdural collections, or duodenal haematoma. The battered child often exhibits a strong attachment to the parent responsible for the injuries. The shaken baby syndrome (SBS) is a subset of BCS, resulting from vigorous shaking of the child [2]. The increased head/body size ratio and the weakness of the muscles of the neck of young children favour the violent angular accelerations and decelerations occurring during this type of trauma. Although signs of external trauma are infrequent, several specific clinical, autopic and biomechanical studies suggest the occurrence of a blunt head impact as being necessary to produce the related brain injuries. The term “shaken-impact syndrome”, indeed, is more properly used. The shaken babies are usually infants or young children. They are brought to the medical attention because of a neurological deterioration varying from irritability and lethargy to seizures, apnoea and coma. The occurrence of a (minor) accidental trauma or of a sudden symptom (e.g. seizure, breathlessness) is typically reported by the care-givers. The main associated findings are:

- Subdural and/or other haemorrhages: observed in up to 80% of the cases. Subdural haemorrhage is the principal cause of early death in children with SBS. It arises from the rupture of the parasagittal veins fol-
fallowing angular deceleration or, less frequently, from a satellite cortical contusion or from the rupture of the deep draining veins (tentorial and interhemispheric bleeding). Subarachnoid haemorrhage is the second most common haemorrhagic finding, followed by chronic subdural haematoma, extradural haematoma and cerebral haemorrhage. Diffuse axonal injury can be demonstrated, especially by late MRI.

- Retinal haemorrhages: found in 50–95% of the cases. They are considered as pathognomonic of SBS if associated with head trauma, multiple injuries and inconsistent history. Retinal haemorrhage may range from unilateral blood suffusion to clear bilateral haemorrhages up to retinal detachment. The hypotheses on its formation include extravasation of subdural or subarachnoid blood, vitreo-retinal traction and raised venous pressure. It has to be remembered that retinal haemorrhages are also demonstrated after accidental traumas or after vaginal delivery, as well as in association with several diseases.
- Cranial and extracranial contact injuries: scalp injuries and skull fractures are usually located in the parieto-occipital region and may show some of the characteristics reported in the previous paragraphs. Extracranial lesions classically include skeletal fractures (20–70% of the cases), multiple rib fractures, pulmonary compression, lung haemorrhage/contusion, skin/soft tissue injuries (finger marks, swelling, bruising, wounds).
- Central nervous system injuries: acute lesions include brain contusions or infarctions, and cervico-medullary junction injuries. A later characteristic finding, usually evident on CT 1–3 days after the trauma, is a unilateral or bilateral diffuse cerebral hypodensity with poor white/grey matter differentiation (“big black brain”). This condition, which probably results from hypoperfusion/hypoxia, evolves into marked supratentorial brain atrophy.

The management of the abused child does not differ from that of any other injured patient, especially as regards the acute stabilisation, the monitoring of intracranial pressure and the indication for neuroimaging and surgery. In cases of suspected inflicted injury, however, fundoscopic examination, careful examination of the entire body and complete skeleton X-rays have to be performed. Prognosis and outcome vary according to the severity of the trauma and the child’s conditions at presentation. Overall mortality as high as 70% is reported for children with GCS 3 and with bilateral big black brain. Survivors appear to be severely impaired at long-term follow-up. One of the major risk factors is the frequent development of post-traumatic epilepsy, which should be recognised and treated early to avoid further brain damage. A good outcome is found only in children with focal lesions (unilateral subdural haemorrhage, patchy areas of hypodensity, focal subarachnoid haemorrhage), even though they present some cognitive and/or behavioural impairment. The medico-legal implications of child abuse can be summarised as follows:

- The physicians coming in contact with a child suspected of being abused have to report on it by law.
- The determination of an inflicted injury is very hard to obtain. In fact, a spontaneous confession by the perpetrator(s) is uncommon, the information about the trauma history is usually poor and confusing, the physician could not have enough experience in this field, and the knowledge of injury biomechanics in children still has several gaps.
- The physician has the responsibility to inform the child’s family about the report of a suspected abuse. Such information should be given in a non-accusatory manner.
- The treating physician (often a neurosurgeon) may be asked to testify as an expert witness, providing information on the child’s clinical condition, but also as a fact witness, providing opinions that are relevant from a criminal point of view.

### 3.5.11.3 Medical Aspects

The rationale of medical management of head trauma is based on the concept of primary and secondary injury. While the primary injury can only be prevented, but not treated, the goal of medical management is to prevent and treat secondary injury by appropriate intervention.

#### 3.5.11.3.1 Pre-Hospital Management

The first priority in children with severe head injuries (i.e. GCS score of <8) is to perform rapid and complete resuscitation to maintain normal cardiovascular and blood gas parameters. The systematic approach includes the primary survey following the ABCDE approach of assessing Airway, Breathing, Circulation, Disability, and Exposure/Environment, according to PALS guidelines (Pediatric Advanced Life Support). A decreased level of consciousness and obstruction of the upper airway by the tongue can be associated with elevated ICP as a result of poor ventilation with increased PaCO\(_2\), and decreased PaO\(_2\), and therefore the initial management is to ensure an open airway and establish good ventilation. During paediatric resuscitation following head trauma, the cervical spine should always be immobilised. The airway should be protected in children with a GCS 8 or less, to avoid hypoxaemia, hypercarbia and aspiration. This often involves rapid sequence intubation (RSI), which is ideally performed following neuromuscular blockade and sedation with
Midazolam and fentanyl plus vecuronium or rocuronium for neuromuscular blockade. Although succinylcholine can theoretically increase ICP, its use remains widespread for RSI after trauma because of its rapid onset of action. Premedication with lidocaine (1.5 mg/kg intravenously), given 2 min before intubation, is recommended in all cases of RSI after head trauma to minimise the rise in ICP associated with laryngoscopy and intubation. Following intubation, an orogastric tube should be placed to decompress the stomach. Hypotension and hypoxia cause secondary brain injuries and worsen neurological outcome; thus, they must be identified and corrected as soon as possible with fluid resuscitation (20 ml/kg of isotonic crystalloid in boluses).

Assessment of disability and assessment of neurological response should be carried out by evaluating the patient’s response to stimuli following the "AVPU" score: A=Alert, V=Verbal, P=Painful, U=Unresponsive. A better evaluation of neurological impairment is performed using the Paediatric Glasgow Coma Scale for children < 6 years of age and the GCS for older children. Abnormal pupillary response may indicate increased ICP, brain stem herniation and compression of the third cranial nerve. The presence of hypertension, bradycardia, and irregular breathing (Cushing triad) deserves particular attention as a late sign of increased ICP. In general, therapy directed at the reduction of intracranial hypertension is not necessary in the absence of clear signs of cerebral herniation or progressive neurological impairment. Therefore, routine Mannitol administration or mild hyperventilation is usually not necessary and should only be used in patients with evidence of cerebral herniation or worsening neurological function. Once the child is intubated, it is safer to ensure some degree of sedation and neuromuscular blockade until a CT is obtained and the child is in the PICU. It is customary to give drugs such as midazolam and/or i.v. narcotics to prevent pain and anxiety even if the ICP is well controlled.

Children with traumatic brain injury are more likely to survive if treated in paediatric trauma centres. Therefore, it is strongly recommended that after on-site management brain-injured children should be transported directly to such centres, or failing that, a tertiary care hospital with paediatric trauma care capability.

3.5.11.3.2 In-Hospital Management

Once adequate ventilation and sedation are established, the core of the treatment is the control of intracranial hypertension, appropriate sedation, careful management of metabolic issues and fluid therapy. Although the routine use of sedation and neuromuscular blockade in severe paediatric traumatic brain injury is not supported by scientific evidence, their use may be necessary to prevent intracranial hypertension raised by coughing, bucking on the tube and suctioning manoeuvres. Intracranial pressure monitoring is indicated for children with a GCS less than 8, but it may also be employed for children in whom serial neurological examination is not feasible.

It is important to guarantee a correct cerebral flow, depending on cerebral perfusion pressure. Cerebral perfusion pressure (CPP = MAP – ICP) should be maintained at > 40 mmHg in infants, 50 mmHg in children and > 70 mmHg in adolescents. The control of the ICP in a normal or minimally elevated range (i.e. < 20 mmHg) will help prevent secondary brain damage and cerebral ischaemia; therefore, treatment for increased intracranial pressure should be initiated when the pressure rises more than 20–25 mmHg.

Besides providing appropriate basic care (sedation, proper patient positioning, careful management of fluids to avoid excess hydration and hyponatraemia, blood pressure support, temperature control to avoid hyperthermia), other therapy is generally required to maintain the ICP below 20–25 mmHg. Mannitol given at 0.25–1 mg/kg/dose in 20′–30′ every 4–8 h represents a keystone in the management of intracranial hypertension and cerebral oedema. The use of hypertonic saline (NaCl 3%) is supported by strong scientific studies and is advantageous when Mannitol may be deleterious in hypovolaemic patients. Paediatric guidelines currently recommend continuous infusion of 3% hypertonic saline. An effective dose range falls between 0.1 and 1 ml/kg of body weight per hour. Hypertonic saline such as in a bolus infusion may be an effective adjuvant or alternative to Mannitol in the treatment of intracranial hypertension.

Cerebrospinal fluid drainage via ventriculostomy represents another first-line option for refractory elevated intracranial pressure. Moderate hyperventilation in order to decrease the CBF and cerebral blood volume has usually been considered a useful mean to reduce ICP, but prophylactic hyperventilation should be avoided in children. The PaCO₂ must be kept at levels > 35 mmHg to prevent vasoconstriction and to maintain adequate cerebral perfusion. Mild hyperventilation should only be considered as a life-saving manoeuvre for suspected cerebral herniation or in children with intracranial hypertension refractory to sedation and analgesia, muscle paralysis, cerebrospinal drainage and hyperosmolar therapy. In this setting, the PaCO₂ should be kept at 25–30 mmHg. High-dose barbiturates may also be employed in the treatment of refractory increased intracranial pressure. Patients receiving this therapy require extremely close haemodynamic monitoring for hypotension.

Hyperthermia has been postulated to increase secondary mechanisms of brain injury in adults and should be avoided in paediatric patients. Hyperthermia on the other hand, may be beneficial, and when intracranial hyperten-
sion is refractory, it should be considered, despite the lack of evidence.

Decompression craniectomy may also be considered to improve refractory intracranial hypertension. This treatment should be considered as a therapeutic option in patients with diffuse brain swelling and intracranial hypertension refractory to intensive management. There is no evidence to recommend steroid therapy in children with traumatic brain injury.

Although research has not directly addressed outcomes in pediatric patients with traumatic brain injury, nutritional support should be strongly considered with a goal of 130–160% of resting metabolic expenditure. Routine prophylactic anti-epileptic medications are not recommended; nevertheless, administration of anticonvulsant therapy for 1 week is still taken into account for patients with severe brain injury and who present with intracranial haemorrhage.

**Selected Reading**

3.6 Developmental and Acquired Anomalies

3.6.1 Hydrocephalus in Adults

HANS AXEL TROST, CHRISTIANTO B. LUMENTA

3.6.1.1 Basics

Adult hydrocephalus is a syndrome that is not yet fully understood. For almost a century Dandy’s observations in dogs paved the way to hydrocephalus being referred to as obstructive or communicating. Our knowledge of hydrocephalus has developed stepwise, based on fundamental inventions in diagnostic procedures such as pneumoencephalography, cisternography, computed tomography (CT), and magnetic resonance imaging (MRI).

While childhood hydrocephalus acts on a developing brain with soft and growing borders, in adults space within the skull is fixed, and the relationship among brain tissue, cerebrospinal fluid (CSF), and blood changes physiologically as a reaction to changing brain volume caused by ischemic or traumatic damage, toxic or degenerative atrophy. The adult brain may be more vulnerable due to co-morbidities such as hypertonic small vessel disease, multi-infarction syndrome, white matter lesions, and gliotic fibrosis. Many degenerative states and diseases of the brain can result in hydrocephalus. Thus, adult hydrocephalus may not be a disease per se, but a multi-etiological clinical entity as a result of chronic changes in an aging or damaged brain.

Hydrocephalus is one of the few almost completely reversible causes of dementia and gait disturbance in the elderly. Adult hydrocephalus markedly impairs mobility of affected persons. Falls and other problems associated with gait disorders, and the enforced immobility that ensues, are a major source of preventable morbidity and mortality.

Adult hydrocephalus is usually characterized by enlarged ventricles, compared with normal or compressed external subarachnoid spaces. However, normal ventricular size is no guarantee that hydrocephalus will not occur. CSF pressure in adult hydrocephalus may be elevated, but can be within normal ranges or even low. Ventricular enlargement in the presence of “normal” CSF pressure seems to be related to periodic wave-like changes in CSF pressure.

In occlusive or obstructive hydrocephalus CSF flow is impaired, thus producing an increase in ventricular pressure and ventricular size. In communicating hydrocephalus the relationship between CSF production and CSF resorption is impaired. While CSF production is almost constant, CSF resorption seems to be subject to change, owing to many states, resulting in elevated resistance to CSF outflow.

Normal pressure hydrocephalus (NPH) is usually referred to as being first described by Hakim and Adams in 1965. NPH can be idiopathic (iNPH), typically beginning in the sixth decade of life or secondary (sNPH), which may be a result of subarachnoid hemorrhage, brain injury, meningitis, posterior fossa surgery or tumors, including carcinomatous meningitis at any age.

Synonyms are Hakim–Adams syndrome, low-pressure hydrocephalus, malresorptive hydrocephalus, aresorptive hydrocephalus, and adult-onset hydrocephalus.

3.6.1.2 Diagnostic Procedures

Proper diagnosis is both fundamental and difficult, for treatment is not without risk. Hydrocephalus due to pure atrophy (hydrocephalus ex vacuo) will not respond to a shunt. After the intervention of shunting procedures in NPH patients, many patients with dementia of other origin were shunted, resulting in severe complications. Therefore, the aim of diagnostic studies is to find the optimal surgical procedures.

There is no commonly accepted standard for diagnosis at the moment. Usually, NPH is diagnosed by a combination of clinical signs and radiological findings.

3.6.1.3 Clinical Signs

The most important clinical signs are the so-called Adams–Hakim Triad: gait disturbance (shuffling), which usually precedes the other symptoms; cognitive deficit; and urinary incontinence. As these are common symptoms of many age- and degeneration-related diseases of the brain, it is often not possible to differentiate hydrocephalus from senility, Alzheimer’s disease, and other
forms of dementia. The combination of NPH and other diseases is common. Co-morbidity may complicate diagnosis, but it is not a negative prognostic factor per se.

Gait disturbance is the most important sign and should preferably be the first one to appear. Gait disturbance is referred to as the stretching of the fibers of the pyramidal tract caused by ventricular enlargement. Reduced gait velocity, owing to a diminished and highly variable stride length, may be found in both Parkinson's disease and NPH. It may be distinguished by a broad-based gait pattern with outward rotated feet and diminished height of the steps, which is typical of NPH. External cues will only mildly improve gait in NPH as opposed to good effects being obtained in Parkinson's disease. Unsteadiness and multiple steps on turning is another typical pattern in NPH.

Differential diagnosis in cognitive deficits and urinary incontinence may be even more difficult. Many patients with NPH are at an age at which they suffer from diseases that may result in the same symptoms.

Dementia in NPH usually starts with memory impairment, followed by impaired wakefulness, bradyphrenia (mental slowness), and bradykinesia.

Urinary incontinence takes place often unwittingly and may be exacerbated by gait disturbance, preventing the patient from reaching a toilet in time. Fecal incontinence is rare.

Headache, dizziness, vertigo, and psychiatric disturbances may also be symptoms of NPH.

### 3.6.1.4 Radiological Findings

Computed tomography and MRI allow for the evaluation of ventricular enlargement and brain atrophy, but diagnosis should not be based on these procedures alone.

Typical signs of hydrocephalus are said to be symmetrical communicating quadri-ventricular enlargement and flow void in the aqueduct of Sylvius. Ventricular enlargement may be detected as rounding of the frontal horns, enlargement of temporal horns ≥2 mm on both sides and upward bulging of the corpus callosum in MRI. A discrepancy between an enlarged third and a normal fourth ventricle is often seen. Cortical sulci are usually compressed apically and in the interhemispheric fissure, whereas the Sylvian fissure may be enlarged. Ventricular enlargement is calculated by various indices, e.g., Evan's ratio >0.3. Evan's ratio means the ratio of distances between the frontal horns of the lateral ventricles to the maximum biparietal diameter measured on axial slices in CT or MRI at the level of the foramen of Monro. Periventricular lucency (low density on CT, high intensity on T2-weighted MRI) adjacent to the frontal and temporal horns is often said to be a sign of hydrocephalus as transcerebrospinal CSF absorption or bulk flow, but has no significant value. Neither cortical or subcortical atrophy nor signs of cerebrovascular disease per se does not preclude NPH. Multiple white matter lesions as result of cerebrovascular disease, on the other hand, may be a negative prognostic sign.

Magnetic resonance imaging cine flow studies show un-specific CSF flow phenomena in the aqueduct of Sylvius, which some authors believe to be of prognostic value for treatment. Most important in CT and MRI findings is the exclusion of severe brain atrophy. When clinical signs and radiological findings alone do not allow for diagnosis, CSF pressure and dynamics should be evaluated.

### 3.6.1.5 Spinal Tap

Withdrawal of CSF is most often used to further evaluate the patient.

Normal CSF pressure in NPH is 5–15 cm H₂O in a lying position. Higher values are usually found in hydrocephalus of other origins. Withdrawal of CSF (spinal tap) of 40–50 ml of CSF is performed via lumbar puncture. The patient is examined before and several hours after spinal tap. Improvement in walking ability and consciousness is thought to give proof of CSF absorption disturbance-related hydrocephalus. If the result of this test is not clear, either it can be repeated after some time (days), or a temporary spinal catheter may be inserted and CSF drained at 500–1,000 ml/72 h, thus simulating the effect of shunting. The effect of CSF drainage has to be evaluated clinically for at least 3 days in order to achieve reliable results.

### 3.6.1.6 Continuous CSF Pressure Monitoring

Invasive methods to give objective criteria for CSF pressure are continuous intracranial pressure (ICP) monitoring via ventricular drainage or intraparenchymal sensors. Epidural pressure recording is less invasive, but gives less reliable values, which is especially true of absolute pressure values. The pressure monitoring has to be recorded for at least 72 h to be able to compare ICP values and pressure curves for at least two nights, as the first night after anesthesia is often not representative. During day time there may be too many artifacts due to activities of daily life and nursing procedures. The records are evaluated for absolute values of ICP and for specific breath- and pulse-dependent changes in ICP. Sometimes, pressure peaks at >20 cm H₂O and typical wave forms can be recorded. The time span of B-waves is recorded and set in relation to the recorded time. As B-waves seem to be associated with REM phases during sleep, up to 20% of the time is regarded as normal; if they are present more than 50% of the time, hydrocephalus is presumed.
3.6.7 CSF Dynamics

If the use of these procedures does not result in a certain diagnosis, CSF dynamics may be examined. While continuous recording of CSF pressure is installed via either ventricular or lumbar drainage, artificial CSF is added or withdrawn by bolus injection or via continuous, preferably computer-assisted, intrathecal infusion.

The responses of CSF pressure owing to multiple bolus injections allow for estimation of correlation between pressure and volume (P/V). For better visualization this correlation is usually shown in semi-logarithmic form; the slope of the curve is called the pressure volume index (PVI). The PVI allows the elastance of the brain to be calculated.

Changes in CSF pressure caused by continuous added or withdrawn fluid allow for calculation of resistance to CSF ($R_{\text{out}}$). For correct interpretation of CSF dynamics via the lumbar route, spinal stenosis and aqueductal stenosis have to be precluded.

Elevated outflow resistance ($R_{\text{out}} > 10$ mmHg/ml/min, $R_{\text{out}} > 18$ mmHg/ml/min is said to be almost predictive), coupled with improvement in symptoms following drainage for 72 h, is considered useful in identifying those patients most likely to benefit from implantation of a permanent shunt.

3.6.8 Additional/Useful Diagnostic Procedures

Neuropsychological testing of cognitive and motor function are most helpful in differentiating between hydrocephalus and dementia of other origin. They allow for an early and reliable assessment of functional outcome after shunt treatment. This is especially worthwhile during the diagnostic process before and after CSF withdrawal either by spinal tap or by lumbar drainage.

Urological and gynecological examination is essential to disclose urinary incontinence owing to dysfunction of the bladder, prostate or pelvic floor.

Physical therapy and occupational therapy examination may be of help in the evaluation of gait disturbance and ataxia.

Radionuclide cisternography may show evidence of an incisural block, prolonged activity in the ventricles or a delay in resorption over convexity, but nowadays does not have enough diagnostic power to warrant this invasive and consuming method.

Cerebrospinal fluid studies have been thoroughly examined. There is no evidence of relevant diagnostic value, but comparisons of CSF before and after shunting may help to predict response to shunting. Further follow-up studies may indicate shunt failure.

Electroencephalography and evoked potentials are abandoned as diagnostic procedures in NPH.

3.6.9 Therapy

The management of hydrocephalus is fraught with complications. Approximately 53% of shunts fail and require further surgery within the first 2 years of surgery. Infection rates at most centers vary between 5 and 15% per procedure. Of all the medical devices that are implanted in the body, shunts for hydrocephalus probably have the highest failure rate.

3.6.9.1 Conservative Therapy

There is no useful conservative therapy at the moment. If spinal tap improves the patient's state for some time, it may be repeated, if necessary, to delay surgery.

Drugs to decrease CSF production (furosemide, acetazolamide) will not work for long enough without severe side effects.

3.6.9.2 Operative Therapy

Reducing CSF production by destroying the choroid plexus by surgical removal, radiation therapy, local chemical destruction or by immunotoxins associated with choroid-specific antibodies is rarely practiced. The resulting reduction is unsafe and temporary, because the choroid plexus is only one of several sites of CSF production.

Surgical procedures are aimed either at restoring CSF flow within the cranium or at lowering CSF outflow resistance by creating alternative routes for CSF drainage within the cranium or to other sites of the body where CSF can easily be absorbed.

Complications include overdrainage- and under-drainage-related problems, dislocation or disruption of the implanted devices, shunt infection and seizures. Infection is a major problem in shunt surgery. Perioperative single-shot antibiosis is commonly advocated. In at-risk patients antibacterial impregnation of shunt hardware may be warranted.

Mostly, a ventriculo-peritoneal shunt is used. Alternatives are ventriculo-atrial, ventriculo-pleural or lumbo-peritoneal shunting. Ventriculo-renal and ventriculo-gallbladder shunts are rarely used. Ventriculo-sinusoidal shunting seems to provide for the most physiological procedure, although the results are still preliminary. Some surgeons use endoscopic inner shunting procedures (e.g., third ventriculo-cisternostomy, aqueductoplasty) to avoid shunts or as a first procedure, although results are equivocal.
Typical problems of peritoneal shunts are infections within the peritoneal space, formation of pseudocysts because of omental encasement, mostly in cases of chronic infection, laceration of abdominal organs, and unintentional injury to the distal catheter during abdominal surgery. Atrial shunts are prone to more serious infections and injury to the endocardium, leading to sepsis, endocarditis, glomerulonephritis and renal failure. Formation of thrombi at the tip of the distal catheter may cause repeated, often unapparent pulmonary thrombosis, leading to pulmonary hypertonus and cardiac failure. Thrombosis of the jugular or subclavian veins, or even the superior cava vein, has been reported.

Pleural shunts require adequate absorption within the pleural space. This may be insufficient in patients with pneumonia, pleuritis, during artificial ventilation, and in diseases or other circumstances leading to pleural effusions. Because of the physiologically negative interpleural pressure, pleural shunts are especially prone to overdrainage.

If the shunt is implanted correctly, a remarkable improvement in symptoms will appear within a few days. The sooner NPH is diagnosed and treated, the better the results of shunting.

In many patients, improvement will last for several months to many years, until secondary worsening occurs. This often gives rise to repeated testing of shunt patency and further diagnostic procedures.

There is an ongoing debate as to which valve should be used. Conventional differential pressure valves provide ample drainage of CSF. However, they produce an unphysiological state of CSF pressure. In normal individuals, CSF pressure in the lying position is somewhere between 5 and 15 cm H$_2$O, and in the upright position between –5 and –10 cm H$_2$O. CSF is absorbed into the blood, usually during the night in the horizontal position. In shunted individuals with differential pressure valves, no further drainage is produced, and the CSF pressure is just opposite to that in individuals without shunts. Gravitational valves provide for almost physiological relations concerning CSF pressure and diurnal CSF flow. They almost prevent overdrainage-related complications, but seem to more often produce underdrainage (because they do not have a daily hydrodynamic flush during erection). Often, the ventricular size is not or only to a small degree reduced by gravitational valves, despite good clinical results. This makes radiological control of the shunt function more difficult as in differential pressure valves, where usually a significant reduction in ventricular size will be the result of normal shunt function. The results of the Dutch Normal-Pressure Hydrocephalus Study showed better clinical results with low-pressure valves, but an increase in overdrainage-related complications.

Externally adjustable valves are more expensive, but offer the chance to react to complications like overdrainage-related subdural collections by choosing a higher opening pressure and by dialing down in minimally responsive patients or in the case of secondary failure because of ongoing disease. Some of these externally adjustable valves may be checked by external magnetic instruments; others require radiological examination by X-rays. Artifacts, unintended changes in opening pressure or even destruction of mechanical parts by MRI procedures represent further problems associated with these valves. Some externally adjustable valves now have integrated brakes to prevent unintended changes in opening pressure by MRI or other magnetic influences.

Ventriculo-sinusoidal shunts avoid differential pressure depending on the position. They seem to provide for most physiological procedures, draining ventricular CSF into the venous sinuses of the cranium. Their very short tubes allow for a minimized risk of damage to the shunting hardware. On the other hand the long-term patency of shunts and the sinusoidal drainage site is uncertain and results are still preliminary.

Endoscopic third ventriculostomy (ETV) is an alternative to shunting that may allow patients with hydrocephalus to avoid shunt implantation or allow a patient with a non-functioning shunt to have it removed. It is usually not intended for patients with iNPH, but for adults with sNPH or aqueductal stenosis. An opening is made in the floor of the third ventricle just in front of the corpora mammillaria. The opening allows CSF to flow out of the ventricle to the subarachnoid space via a bypass. Care must be taken to avoid damage to the basilar artery and the oculomotor nerves. Primary complications are fever, bleeding and disequilibrium owing to damage to hypothalamic structures. If successful, ETV avoids implantation of a foreign body and the increased risk of shunt infection and malfunction. Overdrainage-related problems are avoided, as there is no major intracranial pressure difference. Often the ventricular size is not or only to a lesser degree reduced after ETV, although good clinical recovery is observed. Secondary closure of the ventriculostomy may occur. Diagnosis of the resulting recurrence of hydrocephalus is difficult and based on clinical signs and missing flow void at the former site of the ventriculostomy.
Selected Reading


Useful Links

1. Hydrocephalus Association www.hydroassoc.org
2. Hydrocephalus Database Project www.hydrocephalusdatabase.org
3. Arbeitsgemeinschaft Spina bifida und Hydrocephalus www.ASBH.de

3.6.2 Congenital Arachnoid Cysts

GIANPIERO TAMBU RINI, CONCEZIO DI ROCCO

3.6.2.1 Synonym

Congenital arachnoid cysts are also called leptomeningeal cysts. This term includes neither secondary “arachnoid” cysts (i.e., post-traumatic, post-infectious, etc.), lined with diseased arachnoidal membranes, nor glio-ependymal cysts, lined with glial tissue and epithelial cells.

3.6.2.2 Definition and Etiology

Congenital arachnoid cysts are developmental lesions that arise from the splitting or duplication of the arachnoid membrane (thus they are in fact intra-arachnoid cysts).

The etiology of these lesions has long been the subject of debate. The most accepted theory is that they develop from a minor aberration in the development of the arachnoid mater from around week 15 of gestation onward, when the cerebrospinal fluid (CSF) is generated to gradually replace the extracellular ground substance between the external and the internal arachnoid membrane (endomening). The malformative hypothesis is supported by the common location of arachnoid cysts at the level of normal arachnoid cisterns, their occasional occurrence in siblings, the presence of accompanying anomalies of the venous architecture (i.e., the absence of the Sylvian vein), and the association with other congenital anomalies (agenesis of the corpus callosum and Marfan syndrome).

A further unclarified subject is why arachnoid cysts tend to expand. Electron microscopy and ultracytochemical analysis have demonstrated increased Na+ and K+ pump activity within the cyst walls compared with normal arachnoid, supporting the theory of active CSF production by the cyst-lining membranes; the latter are morphologically similar to the subdural neuroepithelium and to the neuroepithelial lining of arachnoid granulations. On the other hand, cine-MRI and direct endoscopic views have shown evidence that some arachnoid cysts may enlarge by trapping CSF within them by a ball-valve mechanism. The pressure gradient for the movement of CSF into the arachnoid cyst would be ensured by transient increases in cerebrospinal fluid pressure, especially those increases brought about by cerebral artery systolic oscillations or by pulsations transmitted through the veins.

Specific problems in the definition of the pathogenesis concern intraventricular arachnoid cysts. For some authors, they represent a kind of “internal” meningocele;
for others, they derive from the arachnoid layer and are transported along with the vascular mesenchyme when it invaginates through the choroidal fissure.

### 3.6.2.3 Intracranial Arachnoid Cysts

#### 3.6.2.3.1 Incidence
Congenital arachnoid cysts have been reported to account for roughly 1% of atraumatic intracranial mass lesions. This relatively old figure is the result of a correlation between data obtained from the clinical experience in the pre-CT/MRI era (0.7–2% of space-occupying lesions), and those obtained from autopsy observations (0.1–0.5% of incidental autoptic findings); an increased frequency has been described in recent years. Intracranial arachnoid cysts are nearly always sporadic and single. They occur two or three times more often in males than in females and three to four times more often on the left side of the brain than on the right. The bilateral occurrence of more or less symmetrical cysts has been reported, although rarely, in normal as well as in neurologically impaired children. In the latter instance, especially in patients with bitemporal cysts, the differential diagnosis should be made with lesions resulting from perinatal hypoxia.

According to the information provided by large mixed series (i.e., including both children and adults), 6–90% of patients belong to the pediatric age group; it is recognized that the largest proportion of infantile cases occur during the first 2 years of life.

#### 3.6.2.3.2 Anatomical Distribution
The most common location for arachnoid cysts is within the middle cranial fossa, 30–50% of lesions being found there. Another 10% occur over the cerebral convexity, 9–15% in the suprasellar region, 5–10% in the quadrigeminal plate cistern, 10% in the cerebellopontine angle, and 10% in the midline posterior fossa. The anatomical classification and topographic distribution of the different types of arachnoid cysts are summarized in Table 3.6.1.

#### 3.6.2.4 Supratentorial Arachnoid Cysts

#### 3.6.2.4.1 Sylvian Fissure Cysts
Sylvian fissure cysts alone account for about half of adult and one-third of pediatric cases. Galassi and colleagues have classified Sylvian fissure cysts into three types, depending on their size and apparent communication (metrizamide CT study) with the normal CSF spaces (Fig. 3.6.1):

- Type I cysts are the mildest form, are small, biconvex or semicircular, and communicate freely with the adjacent cisterns.

- Type II cysts are medium-sized, have a more quadrangular appearance involving the anterior and middle portions of the temporal fossa with moderate mass effect; they may or may not communicate with the adjacent cisterns.

- Type III cysts are large, roundish or oval lesions that occupy the middle cranial fossa almost entirely, effecting constant and severe compression of the adjacent nervous structures and eventually causing ventricular displacement and midline shift; the communication with the subarachnoid spaces is absent or functionally inadequate.

Sylvian fissure cysts may manifest clinically at any age, but they become symptomatic more frequently in children and adolescents than in adults, and in most series infants and toddlers account for about a quarter of the cases.

The diagnosis is frequently incidental. In symptomatic patients, the symptoms are often non-specific, headache being the most common complaint. Among focal signs, mild proptosis and contralateral motor weakness may be noted in advanced cases. Seizures and signs of increased intracranial pressure (IICP) represent the clinical onset in about 20–35% of patients. When signs of IICP appear acutely they are usually the consequence of an abrupt increase in the cyst volume, because of subdural or intracystic bleeding.

Mental impairment is found in only 10% of the cases; however, developmental delay and behavioral abnormalities are common in children with large lesions and are nearly constant and severe in patients with bilateral cysts.

A localized bulging of the skull and/or asymmetrical macrocrania are characteristic features in half of the patients. CT in these cases reveals an outward bulging

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td></td>
</tr>
<tr>
<td>• Sylvian fissure</td>
<td>30–50</td>
</tr>
<tr>
<td>• Sellar region</td>
<td>9–15</td>
</tr>
<tr>
<td>• Cerebral convexity</td>
<td>4–15</td>
</tr>
<tr>
<td>• Interhemispherical fissure</td>
<td>5–8</td>
</tr>
<tr>
<td>• Quadrigeminal plate</td>
<td>5–10</td>
</tr>
<tr>
<td>Infratentorial</td>
<td></td>
</tr>
<tr>
<td>• Median</td>
<td>9–17</td>
</tr>
<tr>
<td>• Cerebellar hemisphere</td>
<td>5–11</td>
</tr>
<tr>
<td>• Cerebellopontine angle</td>
<td>4–10</td>
</tr>
<tr>
<td>• Retro-clival</td>
<td>0.5–3</td>
</tr>
</tbody>
</table>
3.6.2 Congenital Arachnoid Cysts

3.6.2.4.2 Sellar Region Cysts

Sellar region cysts represent the second most common among supratentorial intracranial arachnoid cysts. Affected males slightly outnumber females, with a male-to-female ratio of about 1.5/1. The cysts can be subdivided in two groups:

- Suprasellar cysts that develop above the diaphragma sellae
- Intrasellar cysts that are found within the sellar cavity.

and thinning of the temporal squama and anterior displacement of the lesser and greater wings of the sphenoid bone. Cysts appear as well-defined lesions between the dura and the distorted brain, with the same density of cerebrospinal fluid and without contrast enhancement. Cerebral ventricles are usually of normal size or minimally dilated. MRI shows lesions to have hypointensity on T1-weighted and hyperintensity on T2-weighted images. Scanning of the vascular structures is useful in order to define the arteries and veins in relation to the cyst wall. Cine-flow sequences have been recently employed as substitutes for metrizamide CT in order to define the presence or absence of communication between the cysts and the subarachnoid spaces. This may be particularly important in asymptomatic patients, as in patients with non-specific clinical symptoms. In this context, further information that might indicate the need for surgery may be provided by intracranial pressure (ICP) monitoring. Perfusion MRI sequences and SPECT studies have also been proposed; the latter may help to evaluate brain perfusion around the cyst walls.

There are essentially three surgical options, even in combination:

- Cyst marsupialization through open craniotomy
- Endoscopic cyst marsupialization
- Cyst shunting

Open cyst marsupialization is considered the preferable surgical procedure. Successful open fenestration rates vary from 75 to 100%; moreover, a substantial reduction in the earlier morbidity rates has been reported in recent series and surgical mortality has been reduced to almost nil. Two issues concerning open surgery should be pointed out:

- Total excision of the arachnoid cyst membranes is no longer considered worthwhile; large windows in a bipolar fashion are sufficient to allow CSF pulsations through the cyst cavity and reduce the risk of harming the adjacent cortex. A more focal cyst opening might also prevent CSF escape into the subdural space and the development of postoperative subdural hygromas.
- All vessels either traversing the cyst cavity or lying in the cyst membrane represent the normal vasculature and are therefore to be preserved.

Pure endoscopic cyst marsupialization has been proposed as an alternative to open fenestration in recent years. Endoscopy has also been used to assist open surgery in order to reduce the extension of the surgical approach. Alternating results of pure endoscopic techniques have been reported, with success rates ranging between 45 and 100%.

Cyst diversions are obviously safer, but are accompanied by a high incidence of additional surgical procedures (around 30%) and the stigma of lifelong shunt dependency.

Fig. 3.6.1 Examples of Type I, Type II, and Type III Sylvian fissure cysts according to the Galassi classification

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- Suprasellar cysts that develop above the diaphragma sellae
- Intrasellar cysts that are found within the sellar cavity.
The latter are far less common than the former and are exceptional in children.

The term sellar region cysts includes neither the “empty sella” syndrome, nor intrasellar and/or suprasellar arachnoid diverticula. Metrizamide CT or cine-MRI studies are helpful in the differential diagnosis, showing neither contrast entering nor relevant CSF flow inside true cysts.

Intrasellar arachnoid cysts are asymptomatic in about half of the cases. Headache is the most frequent complaint in symptomatic patients, and endocrinological disturbances are frequently associated with this. Similarly, suprasellar cysts most commonly manifest as headache; visual disturbances and neuroendocrine symptoms are common. Hydrocephalus, usually associated with this type of lesion, ensues when the foramina of Monro and/or the basal cisterns are obstructed because of the cyst’s enlargement. In large lesions, a posterior dislocation of the brain stem, with secondary compression of the Sylvian aqueduct, may contribute to the ventricular dilation. This kind of process is relatively slow; for this reason, signs of intracranial hypertension (papilledema, optic atrophy), although common, occur relatively late. Hypopituitarism is common, affecting more frequently growth hormone and corticotropin production. Delayed menarche in women may also be noted. A rare but typical manifestation of a suprasellar cyst is the “bobble-headed doll” syndrome, characterized by slow, rhythmic movements of the head in an antero-posterior direction.

During prenatal life, in the neonatal period, and in infancy, echoencephalography is a useful diagnostic tool, allowing the evolution of this kind of lesion to be followed during the first months of life. An MRI examination should be performed whenever technically feasible. It allows a multiplanar evaluation of the relationships between the cyst and the surrounding neural and ventricular structures, which is necessary for planning surgical treatment. MRI studies (or alternatively, contrast-enhanced CT) are also important for the differential diagnosis between suprasellar arachnoid cysts and other possible cystic lesions of the sellar region (i.e., Rathke’s cleft cyst, cystic craniopharyngiomas, epidermoid cysts, etc.).

The rapid advances in endoscopic technologies have significantly changed the management of sellar region cysts. The endoscopic transnasal approach is ideally suited for pure intrasellar cysts and has substituted the traditional microsurgical approach to these lesions. Suprasellar cysts have been managed by only opening the cyst roof (endoscopic transventricular ventriculo-cystostomy) compared with opening both the cyst roof and the cyst floor (ventriculo-cysto-cisternostomy); the latter technique, is actually considered safe and if compared with ventriculo-cystostomy is associated with a lower recurrence rate (5–10% vs 25–40%). Shunting procedures have been practically abandoned. Although relatively safe, they are associated with a surprisingly high percentage of re-operations. Microsurgical excision, fenestration or marsupialization have to be reserved for patients in whom the endoscopic management has failed or for patients with main extraventricular extension of the cyst walls (i.e., suprasellar arachnoid cysts involving the medial aspect of the temporal lobe).

It is important to remember that whatever the surgical treatment, endocrinological problems, if present, rarely resolve, medical substitution therapy being required in most cases. Visual symptoms and symptoms of intracranial hypertension, on the other hand, improve remarkably after surgery. Flow-sensitive MRI is needed to confirm a pulsation artifact in the follow-up period in order to confirm the presence of stable communication between the cyst and the CSF spaces.

3.6.2.4.3 Cerebral Convexity Cysts

They are relatively uncommon (4–15% of all intracranial arachnoid cysts); females are more frequently affected than males. We distinguish between two main varieties:

- Hemispherical cysts, huge fluid collections extending over most or all of the surface of one cerebral hemisphere
- Focal cysts, small lesions generally involving the cerebral convexity

Hemispheric cysts have been considered to be extreme extensions of Sylvian fissure cysts, differing because of a compressed rather than an enlarged Sylvian fissure and the absence of temporal lobe aplasia. They are most commonly discovered in infants presenting with macrocrania, bulging anterior fontanel, and cranial asymmetry. CT and MRI allow the differential diagnosis with chronic subdural fluid collections (subdural hygroma and hematoma) in most cases.

Localized bulging of the skull usually suggests a focal cyst. In children, typically, neurological signs are lacking, whereas adults frequently exhibit focal neurological deficits and/or seizure disorders. The differential diagnosis with low-grade neurolgial tumors is usually made using MRI.

Microsurgical cyst marsupialization is the treatment of choice. It is not necessary to remove the medial cystic wall, which is intimately connected with the underlying cerebral cortex. Shunt implantation is advised only in case of recurrences, although it has also been proposed as a primary procedure in infants with hemispheric cysts because of their immature absorptive ability, and because of the related high risk of failure of open surgical procedures. In such cases, programmable valves are useful for better control of the intracystic pressure and for favoring the development of natural CSF pathways.
3.6.2.4.4 Interhemispherial Fissure Cysts

Interhemispherial fissure cysts are rare, accounting for 5–8% of intracranial arachnoid cysts in all age groups. Two main varieties are recognized:

- Interhemispherial cysts, associated with a partial or complete agenesis of the corpus callosum
- Parasagittal cysts, which are not accompanied by defects in the formation of the corpus callosum

Macrocrania is the presenting sign in a large proportion of cases and symptoms of intracranial hypertension develop in about two-thirds of patients. Localized bulging of the skull is the second most common finding. Hydrocephalus is mild or absent in patients with parasagittal cysts, while it is relatively common in patients with interhemispherial cysts.

On MRI, interhemispherial fissure arachnoid cysts can be differentiated because of their typical wedge-shaped appearance in coronal sections, sharply delimited by the falx on one side. Primary agenesis of the corpus callosum and Type IC holoprosencephaly may have a similar MRI appearance; however, in interhemispherial cysts the occipital horns of the lateral ventricles can be easily identified, even though they are displaced by the cystic lesion, and the basal ganglia are normally separated.

Craniotomy with excision of the cystic linings is the treatment of choice. It allows the normalization of the intracranial pressure and brain expansion in the vast majority of affected patients. Because of the significantly high rate of related complications, shunting procedures should be considered only as a second choice in refractory cases.

3.6.2.4.5 Quadrigeminal Plate Region Cysts

Quadrigeminal plate cysts account for 5–10% of intracranial arachnoid cysts. Most are diagnosed in children, with a slightly higher incidence in girls than in boys.

Clinical manifestations depend on the direction of expansion of the cyst growth. The largest proportion of these cysts develop upward into the posterior part of the interhemispherial fissure or downward into the cistern of the superior cerebellar vermis, with the possibility, in selected cases, of both a supratentorial and infratentorial extension. Because of their critical position along CSF pathways, these cases are usually diagnosed in infancy because of the secondary obstructive hydrocephalus. Anomalies of pupillary reaction or eye movements owing to compression of the quadrigeminal plate or stretching of the trochlear nerve may be found; however, impairment of the upward conjugate gaze is relatively infrequent. When the direction of expansion is lateral in the cisterna ambiens, hydrocephalus is usually absent and focal signs can be found.

Sagittal median and coronal MRI sequences clearly show the relationship of the cysts with supratentorial and infratentorial ventricular and neural structures.

As for sellar region cysts, modern neuroendoscopy has significantly changed the management practice of this kind of lesion, once considered a technical challenge. In the case of small lesions (<1 cm) causing secondary triventricular hydrocephalus, third ventriculostomy should be considered as the only surgical treatment needed. In larger lesions, ventriculo-cystostomy should be performed, possibly combined with third ventriculostomy in patients with associated hydrocephalus. Although at the time of writing limited series of patients appear in the literature, they univocally come to the conclusion that the endoscopic management of quadrigeminal plate cysts is safe and successful in almost all cases.

3.6.2.5 Infratentorial Arachnoid Cysts

Posterior fossa arachnoid cysts are rather uncommon, representing approximately 15% of all intracranial cysts. They should be distinguished from other cystic malformations of the posterior fossa, namely the Dandy–Walker malformation, the Dandy–Walker variant, and the cystic evaginations of the tela choroidea (i.e., the persistent Blake's pouch). The main differentiating features of these different pathological conditions are summarized in Table 3.6.2.

Three varieties of posterior fossa arachnoid cysts are recognized:

- Midline cysts, which push the vermis anteriorly, while separating the two cerebellar hemispheres
- Hemispheric cysts, overlying and compressing one cerebellar hemisphere
- Cerebellopontine angle cysts, displacing both the cerebellum and the brain stem contralaterally

Clinical manifestations depend on the cyst location and the age of the patient. In pediatric patients with midline or hemispheric cysts, macrocrania and symptoms of intracranial hypertension are the most frequent signs at presentation, in most instances because of the common association with hydrocephalus. Nystagmus and cerebellar signs may be associated in patients with hemispheric cysts. In adults, the clinical picture of a cerebellar cyst is that of a slowly developing posterior fossa mass, which usually has an intermittent course, suggesting periodic volume fluctuations of the lesion. Symptoms of cerebellopontine angle (CPA) cysts include cochleo-vestibular dysfunction, cerebellar signs, and, less frequently, fifth and seventh cranial nerve deficits, as well as pyramidal signs. Papilledema is often observed.

Magnetic resonance imaging is the diagnostic investigation of choice for posterior fossa cysts; flow-sensitive
Developmental and Acquired Anomalies

We recognize two varieties of intraspinal arachnoid cysts, intradural and extradural. Intradural cysts are commonly found in the thoracic segment posterior or posterolateral to the spinal cord. The clinical presentation is quite variable. Local or radicular pain, dysesthesia, motor deficit, and in almost half of cases, bladder disturbances, are the most frequent complaints, and they usually appear and evolve over a period of months to years. A remittent course has been described and exacerbation of symptoms may occur with changes in posture. Only rarely are the presenting signs anomalies of the spine, such as scoliosis or kyphosis.

Magnetic resonance imaging is the diagnostic procedure of choice. Direct microsurgical excision of the cyst walls is currently considered the most appropriate type of surgical management for patients with hemispheric and CPA cysts. In patients with midline cysts, relatively high rates of recurrence and persistent postoperative hydrocephalus have been reported, leading some authors to reconsider cyst and/or ventricular shunting to be the preferable surgical option/s. The main disadvantage of this approach is the high rate of shunt malfunctions that have been reported, with a frequency ranging from 10 to 26% in this specific subset of patients. Neuroendoscopy has been recently introduced into the management of posterior fossa cysts. Successful endoscopic cyst marsupialization has been reported in limited series of patients.

### 3.6.2.6 Intraspinal Arachnoid Cysts

Congenital intraspinal arachnoid cysts are relatively rare. They should be differentiated from other congenital intraspinal cystic lesions, such as neuroepithelial, neurenteric, and teratoid cysts, and from post-inflammatory adhesions within the subarachnoid space.

The pathogenesis of true intraspinal arachnoid cysts is still debated. Most authors consider them to be the result of an abnormal derangement of the arachnoid trabeculae during the early embryogenic period. The prevalent location at the level of the cervical and thoracic segment has been explained with the persistence in these patients of the septum posticum, which subdivides the cervicothoracic subarachnoid space at the midline during fetal life. Other authors consider these cysts to originate from herniation of the arachnoid through a congenital defect of the dura mater.

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Magnetic resonance imaging is the diagnostic procedure of choice. Direct microsurgical excision of the cyst walls is followed by an immediate remission of symptoms in the vast majority of patients. Extradural cysts usually present as arachnoid diverticula at the entry points of nerve roots into the spinal subarachnoid space. More rarely, they are found on the midline at the point of fixation of the filum terminale. The latter are considered to result from a defective closure of the posterior neuropore. Although reported in children, extradural spinal arachnoid cysts are more frequently found in adolescents and young adults. They may remain silent for a long period before diagnosis; kyphoscoliosis is the most frequent presenting sign, occurring in about half of the patients. At the time of diagnosis, progressive limb weakness, thoracic and/or abdominal pain are common.

### Table 3.6.2 Main differentiating features of cystic malformations of the posterior cranial fossa and posterior fossa arachnoid cysts

<table>
<thead>
<tr>
<th></th>
<th>Dandy–Walker syndrome/variant (DWS/DWV)</th>
<th>Blake’s pouch cyst</th>
<th>Posterior fossa arachnoid cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relationship with the fourth ventricle</strong></td>
<td>Cystic dilatation of the fourth ventricle: borders of the fourth ventricle not recognizable in DWS; roof and lateral borders present in DWV</td>
<td>Fourth ventricle separated in normal position or moderately dislocated</td>
<td>Fourth ventricle separated, compressed, and dislocated</td>
</tr>
<tr>
<td><strong>Communication with the subarachnoid spaces</strong></td>
<td>Absent in DWS, present in DWV</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Associated hydrocephalus</strong></td>
<td>Present (distinguishing feature)</td>
<td>Absent</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Associated cerebellar anomalies</strong></td>
<td>Partial or complete agenesis of the vermis</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Associated cerebral anomalies</strong></td>
<td>50–70% of the cases</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>
A widening of the interpedicular space, an enlargement of the spinal canal, with scalloping of the vertebrae are the most frequent CT/MRI findings.

Management consists of complete excision of the cyst; laminotomy has to be preferred to laminectomy, especially in children and in multiple level lesions, in order to preserve spinal stability.

3.6.3 Chiari Malformations

Massimo Caldarelli, Concezio Di Rocco

3.6.3.1 Background

In the last decade of 19th century, the German pathologist Chiari described four congenital anomalies of the cerebellum and brain stem, regarded as manifestations, of increasing severity, of the same pathogenetic mechanism, that is, the pressure exerted from above on the hindbrain by congenital hydrocephalus.

The main anatomical feature of Chiari type 1 malformation is the caudal displacement of the cerebellar tonsils into the cervical canal to a variable extent. Chiari type 2 malformation is characterized by more severe cerebellar herniation, which also involves the inferior vermis and fourth ventricle; it is typically associated with myelomeningocele. Chiari type 3 associates the feature of a high cervical meningoencephalocele with hindbrain herniation. Finally, Chiari type 4 is characterized by severe cerebellar hypoplasia, with no hindbrain herniation.

After many years and an increasing amount of theoretical, clinical, and neuroradiological evidence, the understanding and awareness of these conditions have reached a new level. Currently, the four malformations are regarded as separate entities with different pathogenesis, clinical manifestations, and prognosis, and no longer as the progressive worsening of the same disease. From an anatomical point of view, grades 1 to 3 share different degrees of hindbrain herniation, as well as the possibility of secondary cavitation of the spinal cord, whereas grade 4 is characterized by cerebellar hypoplasia. A hypoplastic posterior cranial fossa is a common finding in grades 1 to 3, but not in Chiari type 4.

Clinical manifestations are distinct and peculiar to each form. For these reasons, the various Chiari malformations should be treated under separate headings.

3.6.3.2 Chiari 1 Malformation

Chiari type 1 malformation (CM-1) is characterized by an abnormal position (and shape) of the cerebellar tonsils, which herniate outside the cranial cavity, below the foramen magnum, into the cervical canal. This anatomical abnormality leads to occlusion of the subarachnoid spaces at the level of the foramen magnum, with the consequence of disordered CSF circulation in both the cranial and spinal compartments; in fact, besides posterior fossa alterations, CSF pressure derangement is responsible for the often associated syringomyelia. The proposed mechanisms for starting and progression of the malformation have been thoroughly investigated and debated in the literature. The various pathogenetic interpretations can be schematically subdivided into three categories:

- Hydrodynamic (based on a pressure gradient between the intracranial and spinal CSF spaces)
- Mechanical (which recognizes the block of CSF circulation at the level of the foramen magnum as the causative mechanism of Chiari 1 malformation)
- Maldevelopmental (which interprets the posterior fossa abnormalities as the local expression of a more generalized developmental disorder)

Although congenital CM-1 usually becomes symptomatic in early adulthood, recently, it has been recognized in children with the same frequency as in adults.

3.6.3.2.1 Clinical Manifestations

Occipital or cervical pain, often exacerbated by sneezing, coughing, or the Valsalva maneuver, is the most frequent complaint; other painful manifestations include shoulder, back or limb pain, without radicular distribution. Most common signs are motor or sensory deficits in the extremities (>70%), which are an expression of the associated spinal cavitation. Truncal and appendicular ataxia, expression of the cerebellar dysfunction, is the second most common sign (in 30–40%). Less frequently (in 15–25%), clumsiness, nystagmus, diplopia, dysphagia, and dysarthria are observed, due to lower cranial nerve deficits. Apneic spells are observed in up to 10% of cases, manifesting in infants or young children. A peculiar manifestation of CM-1 in children and adolescents is progressive scoliosis (in 30%).

3.6.3.2.2 Neuroimaging

Chiari malformation type 1 is best investigated by MRI. The leading aspects of this malformation are the following: herniation of one or both cerebellar tonsils below the foramen magnum (>5 mm); possible cervico-medullary kinking; absence of supratentorial anomalies (apart from sporadic cases of mild ventricular dilation); and the fourth ventricle in the usual location (Fig. 3.6.2). CM-1 may be associated with bony anomalies, like small posterior cranial fossa, platybasia, atlanto-occipital assimilation...
tion, basilar invagination, fusion of the cervical vertebrae (Klippel–Feil anomaly). Hydro/syringomyelia occurs in 50–60% of cases; it may be limited to one or two districts, or extended to the whole spinal cord (holocord). Typically, the spinal cavitation spares the C1 level.

Cine-mode MRI is a useful complement to the diagnosis as it demonstrates both the degree of neural crowding at the foramen magnum level, and the characteristics of CSF flow; likewise, postoperative study may provide some insights into the adequacy of surgical decompression.

3.6.3.2.3 Management

The aim of surgical treatment is the decompression of the posterior cranial fossa to restore CSF circulation in the basal cisterns and to relieve the impact of the neural structures at the level of cranio-cervical junction. Surgical treatment of the Chiari 1 malformation usually consists of a well-defined protocol that includes suboccipital craniectomy, C1 laminectomy, lysis of the arachnoid adhesions, tonsillar resection (either traditional tonsillectomy or subpial coagulation), and enlarging duraplasty. In the case of concomitant ventral compression (like, for example, in the case of platybasia, C1 assimilation, etc.), this should be resolved prior to undertaking dorsal decompression. Recently, some reports seem to indicate the possibility of achieving comparable results utilizing simple bony decompression without an enlarging duraplasty (or by performing a delamination of the outer dural layer). Intraoperative ultrasound can provide useful information in this regard, by demonstrating movements of the tonsils that are synchronous with respiration and the cardiac cycle, and the presence of adequate CSF flow from the fourth ventricle.

Further surgical options are represented by procedures aimed at relieving the associated spinal cord cavitation (plugging of the obex, placement of a syringo-subarachnoid or syringo-pleural shunt, and fourth ventricle stents). In this regard, Hida et al., comparing the results of the two major surgical procedures utilized for the treatment of CM-1 associated with syringomyelia, i.e., foramen magnum decompression and a syringo-subarachnoid shunt, demonstrated a decrease in the size of the syrinx in 94% of the patients undergoing suboccipital craniectomy, and in 100% of those undergoing syringo-subarachnoid shunting. With regard to the prognosis, patients with symptoms related to paroxysmal intracranial hypertension are those who will maximally benefit from decompression. Likewise, those presenting with cerebellar or foramen magnum syndrome have an elevated chance of recovery from their preoperative complaints, whereas those with central cord syndrome have the poorest prognosis.

When dealing with pediatric patients, the first problem is that of surgical indication. In fact, in many cases the diagnosis of CM-1 is accidental, following MRI performed to investigate non-specific clinical manifestations like headache, mental retardation or epilepsy. Most authors disagree on a preventive surgical treatment, and in fact agree that surgical indication should depend on the presence of symptoms and clinical signs unequivocally referable to the malformation, rather than on its mere neuroradiological demonstration.

With regard to surgical technique, some authors utilize the same armamentarium as in the adult population, i.e., suboccipital craniectomy, C1 laminectomy, dural grafting, and cerebellar tonsil resection in 40–60% of cases. A one-hundred percent improvement in symptoms, and a more than 90% improvement in signs is reported, as well as a decrease in syringomyelia in 80% of cases on postoperative MRI. In recent years, some authors raised criticism of this “classical” approach, which appears too heavy (namely, the intradural manipulation), especially in cases of moderate tonsillar herniation. In fact, some reports seem to indicate the possibility of achieving comparable results utilizing a less aggressive surgical treatment, i.e., suboccipital craniectomy (and C1 laminectomy) with or without delamination of the outer dural layer. Improvement or resolution of clinical manifestations is reported in more than 90% of children, and disappearance of the syringomyelic cavity in 80% of the cases. Tonsillectomy with dural opening or duraplasty should be reserved for patients who are unresponsive to this minimally invasive treatment.
3.6.3.3 Chiari 2 Malformation

The hindbrain abnormalities that characterize the Chiari type 2 malformation (CM-2) consist of a more impressive elongation and caudal displacement of the posterior cranial fossa structures into the cervical canal. In addition, multiple brain stem, cerebellar, and cerebral anomalies are observed, as well as calvarial and skull base abnormalities. Herniation of the cerebellar tonsils, inferior vermis, and the fourth ventricle with its choroid plexus into the upper cervical canal; cervico-medullary kinking; upward herniation of the superior vermis through the enlarged tentorial notch; kinking or forking of the aqueduct; “beaking” of the quadrigeminal plate (secondary to partial or complete fusion of the colliculi) are the leading features of posterior fossa malformation.

Concerning supratentorial abnormalities, the main alterations include hydrocephalus, polygyria, heterotopia, varying degrees (from partial to complete) of callosal agenesis, large massa intermedia. Hydrocephalus is present in up to 90% of cases; it is often asymmetrical, with prominent occipital horns (colpocephaly) and a small third ventricle.

Finally, skull abnormalities include a small posterior cranial fossa, scalloping of the petrous bone, shortening of the clivus, enlargement of the foramen magnum, and craniolacunia. Also, dural envelopes present some abnormalities, namely, tentorial hypoplasia and low tentorial attachment (with the torcula, in most cases, lying only slightly above, or at the level of the foramen magnum), and falx hypoplasia and fenestration. Besides cranial anomalies, cavitation of the spinal cord, mainly at the cervical level, is a distinguishing feature in 40–95% of cases. CM-2 is almost exclusively associated with myelomeningocele.

3.6.3.3.1 Clinical Manifestations

Vary according to the time of onset. When developing in early infancy the clinical picture is dominated by signs of brain stem compression. These include stridor secondary to vocal cord paralysis; central obstructive apnea; swallowing disturbances; breath-holding spells with possible loss of consciousness; hypotonia and tetraparesis; and opisthotonos. On occasion, and almost exclusively in infants and young children, the hindbrain dysfunction can present acutely, configuring a life-threatening syndrome characterized by stridor, apnea, swallowing disturbances with aspiration pneumonia, and opisthotonos, which can progress until the infant’s death, irrespective of any therapeutic procedure. It has been demonstrated that this potentially catastrophic syndrome is correlated neither with increased ICP nor with the site and extent of the spinal defect.

In older children or adolescents, and young adults, the clinical picture is dominated by spinal, cerebellar and ophthalmologic signs. These include: occipital and cervical pain; myelopathy with weakness of the upper extremities; ataxia; strabismus; nystagmus; defects of pursuit and optokinetic movements, and of convergence; and scoliosis.

3.6.3.3.2 Neuroimaging

Magnetic resonance imaging plays a major role in the diagnosis of CM-2. In fact, the various posterior fossa, supratentorial, and spinal anomalies are perfectly imaged with this technique (Fig. 3.6.3). CT maintains a role in the demonstration of skull base and calvarial abnormalities.

3.6.3.3.3 Management

As most patients are also affected by hydrocephalus, the placement of a CSF shunt, or the evaluation of the function of a shunt that has already been inserted, should be considered first, before undertaking posterior fossa decompression. In fact, symptoms and signs related to CM-2 can simply translate a condition of increased ICP secondary to an inadequately functioning CSF shunt.

Before undertaking surgical decompression of the posterior fossa, accurate planning of the operation is needed, because of the malformed anatomy of the region (low-lying torcula, cervico-medullary kink, and the fourth ventricle often at the cervical level, as well as the presence of anomalous dural sinuses). Dense arachnoidal adhesions and superficial hypervascularity can make arachnoid dissection very difficult and dangerous; nevertheless, the procedure has to be continued unless the floor of the fourth ventricle is discovered. Discrete subpial coagulation of the inferior vermis can help by keeping the fourth ventricle open in the subarachnoid spaces.

The effects of surgical decompression vary according to the preoperative status. While infants presenting only with stridor have a chance of complete recovery, those with stridor and apneic spells will survive in 75% of cases, but only 50% will make a complete recovery. Infants with stridor, apneic spells, dysphagia, and cyanotic spells have only a 40% chance of survival and minimal chance of functional recovery. These negative results may be attributed either to an extensive and irreversible damage of brain stem structures, or to an anatomical rearrangement of these structures that cannot benefit from any surgical procedure.

3.6.3.4 Chiari 3 Malformation

The exceedingly rare Chiari 3 malformation (CM-3) is anatomically characterized by the association of a high
cervical (or occipital) meningoencephalocele containing herniated cerebellar tissue with many of the abnormalities usually found in the second type, such as, a small posterior cranial fossa, caudal displacement of cerebellar tonsils and vermis, medullary kinking, tectal beaking, and obviously hydrocephalus. The largest published series refers to 9 neonates, of whom only 4 were treated surgically. CM-3 accounted for only 2 out of 312 cases of Chiari deformities observed at one pediatric neurosurgical department.

Besides clinical evidence of the encephalocele, the diagnosis mainly relies on neuroradiological findings. CT and MRI demonstrate a complex malformation characterized by an occipito-cervical meningoencephalocele, protruding through a bony defect involving the lower occipital squama and/or the posterior arch of the first cervical vertebrae; a small posterior cranial fossa with low tentorial attachment; scalloping of the clivus; massive herniation of the hypoplastic cerebellar structures into the malformation; beaking of the tectal plate; dysgenesis of the corpus callosum; more or less severe ventricular dilatation.

As for management, primary closure of the malformation is usually the treatment of choice, postponing to a later phase CSF shunting of the associated hydrocephalus. Moreover, affected neonates often require intensive care treatment for the associated severe respiratory distress.

Although CM-3 is not necessarily incompatible with life, its functional prognosis remains severe. In fact, nearly all the cases reported were invariably afflicted by various degrees of developmental delay, epilepsy, hypotonia and/or spasticity, upper and/or lower motoneuron deficits, as well as lower cranial nerve dysfunction. These severe clinical manifestations are usually attributed to the mechanical effects of distortion and traction exerted by the malformation on brain stem structures. On the other hand, they may also be interpreted as an expression of primary brain stem dysfunction, which would challenge the possibility of improvement by means of surgical treatment.

Selected Reading

3.6.4 Cranio-Vertebral Junction

Massimiliano Visocchi, Dario Romano

3.6.4.1 Definition, Embryology, Anatomy, Anomalies, Indications and Technical Notes for Posterior Arthrodesis

3.6.4.1.1 Introduction

The term cranio-vertebral junction (CVJ) refers to the occipital bone that surrounds the foramen magnum, the atlas and the axis vertebrae with their related ligaments and muscles. The medulla oblongata, the cervico-medullary junction and the upper cervical spinal cord, with their meningeal covers, are encompassed by this complex enclosure. Neural compression along the entire circumference, vascular compromise and abnormal cerebrospinal fluid (CSF) dynamics can occur secondary to bony abnormalities that affect the CVJ. The knowledge of the anatomy, the biomechanics and the embryology of this region is of paramount importance in understanding its functional problems and in planning the correct surgical strategy in candidates for surgical correction.

3.6.4.1.2 Embryology

A definite notochord forms between the ectoderm and the endoderm during the third week of gestation. At the cephalic end of the embryo, the ectoderm immediately overlying the notochord begins to thicken and differentiates into neural ectoderm, which forms the neural plate. A collection of mesenchymal cells begins to coalesce in three regions. The most medial becomes a solid mass, the paraxial mesoderm, which is just lateral to the notochord and on either side of it. This precursor of bone, skeletal muscle and skin begins to segment in the cranial and caudal directions [1].

During the fourth week of gestation, 42 somites are formed. There are 4 occipital somites, 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 8–10 coccygeal pairs. Each somite differentiates into an outer dermatome, an inner myotome and a medial sclerotome. The sclerotomes are ventral-medial in location and destined to form the vertebral bodies (Table 3.6.3). These bilateral ventral-medial cells migrate towards the midline and surround the notochord [2].

The superior half of one sclerotome (caudal) unites with the lower half of its neighbour (cranial) and thus forms the earliest manifestation of a vertebral body.

The neural arch of the proatlas splits into a rostral and caudal segment; the former is fused into the occipital bone to form the paired occipital condyles. The caudal portion of the proatlas neural arch is incorporated into the atlas and is represented by the paired rostral articulation facets of the atlas and the small portion of the lateral mass.

Table 3.6.3 Embryology and development of the cranio-vertebral junction

<table>
<thead>
<tr>
<th>1) Sclerotomes:</th>
<th>Division:</th>
<th>Subdivision:</th>
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<tr>
<td>• Occipital 1st</td>
<td>Hypocentrum</td>
<td>Ventral-rostral</td>
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<td>• Occipital 2nd</td>
<td>Centrum</td>
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<tr>
<td>• Occipital 3rd</td>
<td>Neural arch</td>
<td>Dorsal-caudal</td>
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<th>2) Sclerotomes:</th>
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<td>• 4th Proatlas:</td>
<td>Hypocentrum persist</td>
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<td>Centrum</td>
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<td>Neural arch</td>
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<th>3) Sclerotomes:</th>
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<th>4) Sclerotomes:</th>
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<td>• Spinal 2nd:</td>
<td>Hypocentrum</td>
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<th>Formations:</th>
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<tr>
<td>• Occipital bone</td>
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<tr>
<td>• Atlas anterior arch</td>
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<tr>
<td>• Dens</td>
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<tr>
<td>• Posterior inferior atlas arch</td>
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<th>Formations:</th>
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<tbody>
<tr>
<td>• Anterior tubercle clivus</td>
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<td>• Apical ligament, apex of dens</td>
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<td>• Occipital condyles, third condyle</td>
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<tr>
<td>• U-shaped foramen magnum</td>
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<tr>
<td>• Alar and cruciate ligaments</td>
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<tr>
<td>• Posterior arch of atlas (C1)</td>
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<td>• Lateral atlantal masses</td>
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<th>Formations:</th>
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<tr>
<td>• Disappears</td>
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<td>• Body of axis</td>
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<td>• Facets, posterior arch of axis</td>
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The hypocentrum of the proatlas is reduced to the vestigial condylus tertius or the thin ridge-like anterior prominence of the basicranium. The core of the proatlas centrum metamorphoses into the apical ligament of the dens. This apical ligament may contain notochordal tissue and can be regarded as a rudimentary intervertebral disc. The paired alar or check ligaments and the transverse ligament of the atlas are derived from the proatlas as unossified tissue [3].

3.6.4.1.3 Anatomy of Bone and Ligaments of the CVJ

3.6.4.1.3.1 Bone Anatomy of the CVJ

The posterior occipital bone surrounds the oval-shaped foramen magnum, which is wider posteriorly than anteriorly. The narrower anterior part sits above the odontoid process and is encroached on laterally by the occipital condyles.

The atlas consists of two thick lateral masses that are connected in front by a short anterior arch and at the back by a longer posterior arch. The medial aspect of the lateral mass has a small tubercle for the attachment of the transverse ligament. The transverse foramina transmit to the vertebral arteries after running across the paired grooves adjacent to the lateral masses (Fig. 3.6.4).

The axis is distinguished by the odontoid process (dens); on the front it is an articular facet. The transverse foramina are directed supero-laterally, thus permitting the lateral deviation of the vertebral arteries (Fig. 3.6.5).

3.6.4.1.3.2 Ligamentous Anatomy of the CVJ

The transverse atlantal ligament (1 cm thick) is the thickest, strongest spinal ligament. It is the major restraint for C1, anchoring it to the dens, and allowing C1 to rotate around the dens. The alar ligaments connect the occipital condyles and C1 lateral masses to the odontoid. The alar...
The secondary ligaments include the anterior and posterior atlanto-occipital membranes, the apical ligament, the tectorial membrane, the interspinous and supraspinous ligaments, and the capsular ligaments. The secondary ligaments at C1–C2 are weak and stretch relatively easily after the primary ligaments (transverse alar ligaments) are disrupted [4].

3.6.4.1.4 Anatomy of the Vertebral Artery
The vertebral artery (VA) can be divided into four segments:
- I: prevertebral
- II: vertebral from C6 to C2 (left segment)
- III: vertebral from C2 to C1 (S – kinking segment)
- IV: extra-vertebral – intracranial (Fig. 3.6.6)

Left VA (vertebral artery) arises off aortic arch in 4%.

Collateral arising from VA, the anterior meningeal: arises at the body of the C2 (axis), may feed chordomas or foramen magnum meningeomas, and may also act as collateral in vascular occlusion: posterior meningeal; medullary (bulbar); antero-posterior spinal; and PICA (largest branch) [4].

3.6.4.1.5 Developmental Anomalies
The failure of segmentation or fusion of different components of the bone structures of the CVJ, or hypoplasia and ankylosis accounts for the anatomical and functional anomalies of the region. The period between the fourth and seventh weeks of intrauterine life are most likely to result in a combination of several anomalies (Table 3.6.4) [3]. Among these anomalies, some deserve special consideration because of their more common occurrence.

3.6.4.1.5.1 Occipital Vertebra
Occipital vertebra occurs when the third occipital sclerotome fails to be incorporated into the two more rostral occipital sclerotomes. In the event of this occurring, the occipital condyles become attached to the vertebra. If the occipital vertebra contains a transverse process, it does not have a foramen to accommodate the vertebral artery.

3.6.4.1.5.2 Atlas Assimilation
Atlas assimilation, sometimes called occipital–atlantal fusion, is different from the occipital vertebra because the transverse process of the atlas harbours the bony foramen for the vertebral artery. In atlas assimilation, segmentation fails between the fourth occipital sclerotome and the first spinal sclerotome. Chiari type I malformation may be associated with this. A para-mesial invagination may exist, as well as reducible atlanto-axial dislocation or basilar invagination.

3.6.4.1.5.3 Os Odontoideum
Os odontoideum was in the past considered to be congenital and described as a failure of the fusion between the centrum component of C1 and that of C2. However, a congenital segmental failure would imply that the failed fusion would lie below the superior slopes of the C2 facets. Os odontoideum is considered to result from the failure of the centrum component of the atlanto-axial complex to fuse with the axis.

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Fig 3.6.6 a Lateral view of the relationships of the skull, the CVJ and the cervical spine with the vertebral artery. b Antero-posterior view of the cervical spine and vertebral arteries joining into the basilar artery. c Angio-MRI of posterior neck circulation with dominant left vertebral artery
**3.6.4.1.5.5 Basilar Impression**

Basilar impression is the elongation of the odontoid process probably related to a maldevelopmental depression of the basiocciput, often associated with Chiari type I malformation (Fig. 3.6.8) [6].

**3.6.4.1.6 Surgical Indications and Planning**

The surgical interest in CVJ anomalies is due to the involvement of the spinal cord, which may result from continuous compression or an impingement or distortion due to the instability of the region.

The factors that must be considered in planning the surgical management of the congenital or acquired disorders of the CVJ are:

- Reducibility
- The direction and manner of encroachment of the lesion in the cranio-vertebral circumference and its effect on the neural structures
- The aetiology of the lesion (whether it is bony, soft tissue, extracranial or intracranial, intramedullary or extramedullary)
- The potential growth attitude of the lesion.

The stability of the region after a surgical approach is crucial as well as the indication for the radical resection of chemotherapy- and radiotherapy-resistant tumours. Thus, reducible lesions require primary stabilisation, while irreducible lesions require decompression in the manner in which an encroachment has occurred, whether this be ventral, dorsal, or lateral. Stabilisation is of paramount importance if instability is present before treatment or after the surgical approach (Table 3.6.5) [7].

**3.6.4.1.7 Current Surgical Techniques**

Intraoperative traction and reduction of CVJ is mandatory. It is achieved by using a head holder and is assisted by fluoroscopy (Fig. 3.6.9).

With the patient in the prone position, after dissecting the superficial and deep planes (subperiosteal dissection) using bipolar scissors, preparing the occiput and the cervical spine, the stabilisation of the cranio-vertebral junction can be performed using two different techniques: wiring and screwing.

**3.6.4.1.7.1 Wiring Techniques**

The surgical stabilisation of the CVJ is carried out by applying a titanium, contoured loop, U-shaped rod. Occiput (C0) is fixed to two or three cervical laminae according to the local anatomical features (bone assimilation and the degree of bone removal) by using Songer titanium sublaminar wires.

For the fixation procedures, two burr-holes are placed into the occipital bone 0.5 cm cranially to the rim of the

**Table 3.6.4** Classification of disorders of the cranio-vertebral junction (CVJ)

<table>
<thead>
<tr>
<th>A. Congenital</th>
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<tbody>
<tr>
<td>1. Malformation of occipital bone</td>
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<tr>
<td>A. Manifestations of occipital vertebra (e.g., clivus segmentations, remnants around foramen magnum, proatlas remnants)</td>
</tr>
<tr>
<td>B. Basilar invagination</td>
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<tr>
<td>C. Condylar hypoplasia</td>
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<tr>
<td>D. Atlas assimilation</td>
</tr>
<tr>
<td>2. Malformations of the atlas</td>
</tr>
<tr>
<td>A. Atlas assimilation, atlanto-axial fusion, aplasia of the atlas arches</td>
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<tr>
<td>3. Malformations of the axis</td>
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<tr>
<td>A. Segmentation failure of C1–C2 or C2–C3; hypoplasia of the dens, occissure terminale</td>
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<th>B. Developmental and acquired</th>
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<tr>
<td>1. Traumatic</td>
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<tr>
<td>A. Acute ligamentous and bony injury to CVJ complex</td>
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<tr>
<td>B. Delayed manifestations of CVJ instability. Development of os odontoideum</td>
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<tr>
<td>2. Inflammation leading to instability and granulation masses (e.g. rheumatoid arthritis, regional ileitis, psoriasis, scleroderma, pseudogout, ankylosing spondylitis)</td>
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<tr>
<td>3. Infections (e.g. Grisel’s syndrome)</td>
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<tr>
<td>4. Metabolic (e.g. Morquio’s syndrome, Conradi’s syndrome, foetal warfarin syndrome, renal rickets)</td>
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<tr>
<td>5. Genetic transformations (e.g. Down’s syndrome, osteogenesis imperfecta, achondroplasia, Paget’s disease, neurofibromatosis)</td>
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<tr>
<td>6. Neoplastic</td>
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<tr>
<td>A. Benign (e.g., aneurismal bone cyst, osteoblastoma, osteochondroma, chondroma)</td>
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<tr>
<td>B. Malignant</td>
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<tr>
<td>1. Primary (e.g., chordoma, chondrosarcoma, plasmocytoma)</td>
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<td>2. Secondary (e.g., multiple myeloma, metastatic disease, naso-pharyngeal malignancy)</td>
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an odontoid trauma occurring between the ages of 1 and 4 years, with subsequent separation and distraction of the odontoid fragments. A hypertrophied rounded ossicle, a hypoplastic dens, as well as the hypertrophy of the anterior arch of the atlas lead to incompetence of the cruciate ligament and further abnormalities (Fig. 3.6.7) [5].

**3.6.4.1.5.4 Aplasia of Hypoplasia**

Aplasia or hypoplasia of the dens is an uncommon feature, but often it is described as an associated finding.
Os odontoideum in a Down's patient aged 9 with bulbo-cervical long tracts compression syndrome. a X-rays, b CT and c, 3D CT sagittal reconstructions showing irreducible listhesis of C1–C2, os odontoideum (encroached upon the anterior aspect of the body of C2), d C1 posterior bifid arch (small axial reconstruction)

Sagittal reconstructions of CVJ in impressio basilaris. a CT bone window. b T2-weighted MRI. c 3D CT. Note a the invagination of the odontoid into the foramen magnum, b the T2 hyperintensity consistent with a secondary bulbo-cervical contusion, c the maximum degree of the compression (arrows)
Developmental and Acquired Anomalies

foramen magnum and waxed for haemostasis. Bone graft is harvested from the iliac crest. For systemic diseases we prefer to include the occiput.

Without further fluoroscopy, a titanium, contoured loop, U-shaped rod is applied at the CVJ along with sublaminar titanium cables (Songer sublaminar wires for instrumentation and fusion). Such an option is considered “old-fashioned”, but still viable (Fig. 3.6.10) [5, 6].

3.6.4.1.7.2 Screwing Techniques

3.6.4.1.7.2.1 Magerl C1–C2 Transarticular Fusion

The screws are put into the transarticular space by bending the screw-holder by 45° in the sagittal plane, in order to entirely purchase the articulation and to reach the immediate stability of the complex; the implant can be “stand alone” or can be used along with further sublami-

Table 3.6.5 Menezes’ criteria

* Reducible:
  1. Immobilisation
  2. Posterior Fusion

* Irreducible:
  A. Ventral: Transoral Decompression:
     1. Stable
     2. Unstable:
        – Posterior Fusion
  B. Dorsal: Posterior Decompression:
     1. Stable
     2. Unstable:
        – Posterior Fusion

Fig. 3.6.9 a In the prone position the X-ray C-arm is fitted around the head of the patient. b Intraoperative reduction of CVJ instability can be obtained and shown on the screen. c The head holder (Mayfield) is crucial in obtaining preoperative reduction. d Preoperative skin mark for iliac crest bone harvesting
3.6.4 Cranio-Vertebral Junction

It needs continuous fluoroscopy. Accurate preoperative neuroradiological planning is mandatory in order to rule out anatomic anomalies of the vertebral arteries, which could result in potentially fatal bleeding complications. It is reported that mechanical rigidity is better after screw fixation of the CVJ than with use of the wiring techniques. This minimises the need for postoperative cervical orthosis, but exposes the patient to the risk of vascular (vertebral artery) and neurological (spinal cord and nerve roots) injury, as well as inadequate fixation [13]. CVJ screw fixation is technically quite demanding and requires operative precision and expertise when placing screws in the cervical vertebrae, mostly in children [14, 15].

3.6.4.1.7.2.2 C1–C2 Transpedicular Screwing Technique

Biomechanically, it is equivalent to the Magerl technique and requires clear intraoperative identification of the vertebral arteries and the C1 nerve roots (Fig. 3.6.12) [16]. Continuous fluoroscopy is necessary as well. This screwed implant needs two vertical titanium bars in order to connect C1 to C2.

3.6.4.1.7.2.3 The Anterior Screwing and Plating of the CVJ

This approach to the C1–C2 complex needs a transoral technique (Fig. 3.6.13). This surgical option is not widely used and is not advisable because of the high risk of infections owing to the submucosal position of the hardware beneath the incision line and the associated low degree of stability. It is not a “stand alone” implant as it requires continuous fluoroscopy and is not strong biomechanically [17, 18].

3.6.4.1.8 Postoperative Radiological Control

Usually, a complete postoperative radiological set is obtained before discharge and repeated every 3 months up to the complete bone fusion assessment, which requires no more than 6 months. X-rays are suggested monthly in order to check the stability of the construct. X-rays and CT provide information on the ongoing bone fusion process.

Fig. 3.6.10 a Grooved titanium rods; b Hartshill rectangle; c Ransford loop; d titanium frame. All these techniques include the occiput and the cervical spine. When the construct includes only C1 and C2 it is named Sonntag, Gallie or Brooks Fusion according to the type of bone fusion and the trajectory of the sublaminar wires.

Fig. 3.6.11 a X-ray examination of the classic Magerl fusion technique. The transarticular C1–C2 screws are evident along with the sublaminar wires. b Lateral and c posterior view of the trajectory of the screw, from the lateral masses of C2 to the anterior border of the anterior arch of C1. The Sonntag fusion with sublaminar cables surrounding the interlaminar bone graft (black) is also evident on both images.
3.6 Developmental and Acquired Anomalies


Fig. 3.6.12a,b The transpedicular C1–C1 screwing technique. a Lateral view: note the parallel route used for the screws. b Posterior view: note the light converging inclination of the surgical route used for the screws. Vertical titanium bars are fixed to the heads of the screws.

Fig. 3.6.13 The anterior transoral plating and screwing stabilisation. Left: the titanium plate; centre: the plastic model of the anterior aspect of the CVJ with plate and screws; right: X-ray lateral examination of the construct showing the position of the screws in the bodies of C1 and C2.

Selected Reading


process. MRI confirms the stable decompression of the neural tissue along with preservation of nerve roots and vascular structures (Fig. 3.6.14) [5, 6, 19, 20, 21].

Fig. 3.6.14  a Postoperative standard X-ray, b CT scout view and c CT bone window sagittal reconstruction show the complete reduction of the C1–C2 shift with normalisation of the alignment of the odontoid + os odontoideum and CVJ decompression. The C0–C3 hardware (titanium U-shaped rod suboccipitally and the C1–C2 sublaminar wires) and the external orthosis with the SOMI (sternal–occipital–mandibular immobilisation) brace are also evident.
3.6 Developmental and Acquired Anomalies

Cranio-Cervical Junction Anomalies in the Paediatric Population

DOMINIC N.P. THOMPSON

3.6.4.2.1 Introduction

The cranio-cervical junction (CCJ) is the most mobile element of the cranio-spinal axis, and is the site of a wide range of developmental and acquired anomalies, many of which commonly present in the paediatric population.

The aim of this chapter is not to attempt a comprehensive review of the many disease processes that affect the cranio-cervical region in childhood, but rather to propose a simplified approach to the classification, investigation and management of these disorders. Tumours of this region and the Chiari malformations will not be dealt with here.

3.6.4.2.2 Classification

There are numerous ways of classifying the disorders of this region. Most previous attempts at classification have been on the basis of presumed origin (congenital or acquired) or of pathology (developmental, traumatic, neoplastic, degenerative etc.). In the paediatric population in particular the spectrum of disorders is wide and many conditions either do not fit neatly into such subgroups or fit well into more than one. A more pragmatic approach, functionally based, which may additionally aid investigation and management, is proposed.

There are essentially three mechanical processes that may affect the CCJ: deformity, instability and compression. Whilst these may occur in isolation, clearly combinations regularly occur.

3.6.4.2.2.1 Rotational Deformity

Deformity at the CCJ may be the result of distorted normal anatomy, or may be the result of anomalous segmentation.

3.6.4.2.2.1.1 Rotational Deformity

The clinical presentation is one of torticollis. Torticollis comprises a combination of head tilt and rotation, the so-called “cock robin” deformity. There are numerous causes of torticollis in childhood (Table 3.6.6). Atlanto-axial rotatory fixation (AARF) and tight sternomastoid are particularly amenable to surgical intervention and need to be recognised. AARF is almost never encountered in the adult population. Children present with an acute, initially painful torticollis; this may be spontaneous or follow relatively minor trauma, operative procedures (e.g. ENT procedures during which excessive rotation has occurred) or following infections of the nasopharyngeal region (Grisel’s syndrome). Tight sternomastoid is more commonly painless, dates back to infancy, and there may be a history of birth trauma or unilateral swelling of the neck in the neonatal period, the so-called sternomastoid tumour.

Table 3.6.6 Torticollis in childhood – aetiology

<table>
<thead>
<tr>
<th>Muscular</th>
<th>Skeletal</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital muscular torticollis</td>
<td>Normal segmentation</td>
<td>Ophthalmoplegia</td>
</tr>
<tr>
<td></td>
<td>– AARF</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Sternomastoid imbalance</td>
<td>Abnormal segmentation</td>
<td>Brachial plexus lesions</td>
</tr>
<tr>
<td></td>
<td>– Disorders of fusion</td>
<td>Posterior fossa tumour</td>
</tr>
<tr>
<td></td>
<td>– Disorders of form</td>
<td></td>
</tr>
</tbody>
</table>

3.6.4.2.1.2 Segmentation Failure
Various patterns of segmentation anomaly affecting anywhere along the cranio-cervical axis are commonly encountered. Frequently, these occur in the context of more extensive cranio-vertebral anomalies, such as craniosynostosis and disorders of branchial arch development, where congenital ocular and ear deformities co-exist. Broadly speaking, two types of anomaly are found.

3.6.4.2.1.2.1 Anomalies of Fusion (Klippel–Feil Anomalies)
There is a failure of intervertebral disc development with the formation of block vertebrae (Fig. 3.6.15). Commonly affected levels are CO–C1 and C2/C3, although much more extensive involvement is well recognised. The triad of short neck, low posterior hairline and restricted neck movements is characteristic (Klippel-Feil syndrome).

3.6.4.2.1.2.2 Anomalies of Form
Hemivertebrae, butterfly vertebrae or ectopic ossification centres may produce a chaotic radiological appearance (Fig. 3.6.16). The asymmetry caused by these anomalies is more obvious and the risk of progressive deformity also greater than for anomalies of fusion.

3.6.4.2.2 Instability
The integrity and stability of the CCJ is maintained by osseous, ligamentous and muscular factors. Where these are compromised by congenital or acquired disorders, movement may exceed normal physiological limits and risk damage to the neuraxis. In infancy and childhood a greater range of movement is permitted by virtue of greater ligamentous laxity and immature joints. Conditions particularly prone to CCJ instability include Down’s syndrome, Morquio’s syndrome and spondylo-epiphyseal dysplasia. The site of instability may be:
- Occipito-atlantal
- Atlanto-axial
- A combination

3.6.4.2.3 Compression
Assessing the effects of, or the potential for, compression of the cervico-medullary junction is fundamental to the evaluation and management of these disorders. The mode of compression can be described as stenotic or telescopic.

3.6.4.2.3.1 Stenotic
There is circumferential narrowing of the spinal canal that may occur as a result of soft tissue infiltration (by glycosaminoglycans in the mucopolysaccharidoses) or bone growth (e.g. achondroplasia; Fig. 3.6.17).

3.6.4.2.3.2 “Telescopic”
There are a number of disorders characterised by bone softening, conditions that include Hadju-Cheney syn-

drome, osteogenesis imperfecta and rickets in which the skull base infolds resulting in basilar impression or invagination (Fig. 3.6.18). The result is the gradual displacement and compression of the cervico-medullary junction.
3.6.4.2.3 Symptoms and Signs
The symptoms and signs that accompany disorders at the CCJ are extremely variable. In the infant and in young children focal neurological signs are commonly not detected. The clinical history is important as apparently subtle changes reported by the parents may have significance. The presenting features can be divided into spinal, bulbar, postural and syndromic.

3.6.4.2.3.1 Neurological – Spinal
Neck pain and headache, commonly occipital in location and occasionally labelled "migraine", accompanies instability and neuraxial compression at the CCJ. Sensory disturbance, limb weakness, gait deterioration (falls, unsteadiness) and clumsiness are some of the presenting complaints that occur in children, but sometimes their significance is overlooked, particularly in the very young.

3.6.4.2.3.2 Neurological – Bulbar
Sleep apnoea, gaze palsy, aspiration pneumonia and swallowing difficulties are not uncommon, for example, in cases associated with hindbrain herniation or basilar compression.

3.6.4.2.3.3 Postural
Head tilt, scoliosis and neck stiffness typically accompany deformity at the CCJ. The clinical history is often sufficient to distinguish between many of the causes of torticollis listed in Table 3.6.6.

3.6.4.2.3.4 Syndromic
Children with syndromes, particularly the bone dysplasias, e.g. spondylo-epiphyseal dysplasia and mucopolysaccharidoses, may present because of their known propensity to develop problems at the CCJ and are thus picked up as a result of "surveillance imaging". Some understanding of the natural history of these conditions is thus required to guide investigation and management.

3.6.4.2.4 Investigation
The correct imaging modality with which to study CCJ disorders very much depends on the question being asked. It is here that the functional classification can be of assistance (Table 3.6.7).
3.6.4 Cranio-Vertebral Junction

### Deformity
Rotational deformities and segmentation anomalies are best demonstrated with high-resolution CT (Fig. 3.6.19). 3D reformating may add to the understanding of particularly complex anomalies. Where AARF is suspected, scanning needs to be performed with the patient looking to first to one side and then the other. In normal children there is a large range of rotational movement at C1/C2. The diagnosis of AARF requires the rotational deformity between C1 and C2 to remain unchanged in each direction of movement. In other causes of torticollis, e.g. dystonia and muscular torticollis, some movement at C1/C2 will be seen as a result of turning the head.

Occipitalisation of the atlas, a common anomaly of segmentation and the most frequent bony abnormality to accompany Chiari 1 malformation is best demonstrated using CT.

The head tilt or rotation that characterises these anomalies makes the interpretation of plain X-rays extremely difficult; their role in this instance is very limited.

### Instability
Whilst instability can be inferred from static imaging, a dynamic investigation such as flexion and extension plain radiographs is required to determine the extent of movement, the site of instability (occipito-atlantal or atlantoaxial) and in particular the reducibility of the deformity (Fig. 3.6.20). For complex congenital anomalies, flexion/extension CT can be helpful; however, plain X-rays generally permit a greater range of movement than can be

<table>
<thead>
<tr>
<th>Deformity</th>
<th>Instability</th>
<th>Compression</th>
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<tr>
<td>High-resolution CT</td>
<td>Flexion/extension</td>
<td>MRI</td>
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</table>

### Table 3.6.7 Investigation of cranio-cervical junction anomalies in children

**Fig. 3.6.19** 3D CT image of atlanto-axial rotatory fixation

**Fig. 3.6.20a,b** Reducible atlanto-axial instability. a Flexion; b extension
obtained on CT. As these tests require the patient to be awake, plain radiographs are often quicker and easier to obtain in children. The atlanto-dental interval is commonly used as a measure of instability, although this needs to be interpreted with caution. The films need to be of good quality and any rotation avoided. If the child is in pain, frightened or uncooperative, the information yielded from the investigation may be compromised. Children have a greater range of normal movement than adults. An atlanto-dental interval of up to 4 mm is normal. The posterior atlanto-dental interval (PADI), corresponding to the depth of the spinal canal at this level, is thought by some to be a more useful measure of the severity of instability. In infants, immature ossification of the bones of the CCJ can make interpretation extremely difficult; in such circumstances, MRI can provide better visualisation of the effects of the cartilaginous elements of C1 and C2 on the neuraxis.

3.6.4.2.4.3 Compression
Magnetic resonance imaging is the modality of choice for assessing the extent and effects of this group of disorders on the neuraxis. Effacement of the subarachnoid spaces (e.g. achondroplasia), distortion of the neuraxis (e.g. osteogenesis imperfecta) and signal change or syrinx formation within the cervico-medullary junction (e.g. associated with hindbrain herniation) are readily demonstrated. The compressive effects of soft tissue, for example, infiltration of glycosaminoglycans in the mucopolysaccharidoses, that are not easily appreciated on CT, are readily demonstrated by MRI.

3.6.4.2.5 Descriptive Terms
3.6.4.2.5.1 Os Odontoideum
The odontoid is separated from the rest of the axis vertebra (Fig. 3.6.21). Previously considered a primary, congenital abnormality, there is now good evidence to suggest that the os odontoideum might be the result of a fracture to the odontoid at an early, cartilaginous stage of development, because of excessive movement and resulting in non-union. The os can therefore be regarded as a consequence rather than a cause of instability. It is commonly seen in Down’s syndrome and implies significant instability as the transverse ligament is rendered incompetent. Os odontoideum needs to be distinguished from ossiculum terminale; usually much smaller, this is a bony nodule within the apical ligament and is not associated with instability.

3.6.4.2.5.2 Basilar Invagination and Impression
The skull base infolds into the posterior fossa with compression of the structures therein. Basilar invagination is used to describe a congenital anomaly of occipital bone development. Segmentation anomalies such as occipitotlantal assimilation often co-exist and there is a strong association with hindbrain herniation. Basilar impression refers to a similar infolding of the skull base, but occurring secondary to bone softening conditions such as osteogenesis imperfecta and Hadju-Cheney syndrome.

3.6.4.2.5.3 Translocation
Translocation is an upward displacement of the odontoid process relative to the foramen magnum and C1 ring. It may be seen in conjunction with basilar invagination, but also occurs due to destructive processes or malformations of the lateral masses of C1 (e.g. rheumatoid arthritis) or occipital condyles.

3.6.4.2.5.4 Platybasia
Platybasia is a flattening of the skull base in which the clivus has a more horizontal disposition than usual. It is sometimes seen in association with developmental anomalies of the CCJ, but is a term more frequently used in comparative anatomy.

3.6.4.2.6 Treatment
The surgical approaches to the CCJ are similar for both adults and children, and these have been described elsewhere in this book (see Sect. 3.2.6.4) and will not be expanded further here.

There are, however, certain factors that need to be accounted for in the paediatric population.

3.6.4.2.6.1 The Potential for Growth
This is particularly relevant to infants. Ongoing growth in each of the bony elements of the CCJ may significantly modify the course of the disease, resulting in either improvement or progression. Many congenital malformations of this region are asymptomatic at the time of presentation, cautious clinical and radiological surveillance (occasionally utilising moulded orthoses to maintain alignment), allowing the bones to mature and the anat-
omy to “evolve” is often the better strategy for the long term than early intervention. Early intervention, for example, posterior fusion, may lead to later deformity or compression because of ongoing anterior growth.

### 3.6.4.2.6.2 The Limitations of Instrumentation

Instrumental fixation at the CCJ is being increasingly used in the paediatric population as this results in a more immediate, biomechanically stronger construct; however, young age and poor bone quality (for example, in some congenital dysplasias) are factors that preclude instrumentation. In such cases, autologous bone graft secured with sublaminar cables is needed. Calvarial graft is readily available and its intrinsic curve contours nicely to the occipito-cervical lordosis.

### 3.6.4.2.6.3 The Perceived Natural History of the Condition

The surgery of the cranio-cervical region is not without significant risk. Some understanding of the natural history of the underlying disease process is essential before embarking upon treatment, particularly in asymptomatic or minimally symptomatic children. For example, in Down’s syndrome, the inherent ligamentous laxity results in excessive atlanto-axial mobility in up to one-third of cases; however, as few as 1% develop symptoms or signs related to this. Careful clinical appraisal and the presence of additional bony anomalies may help in the selection of children for surgery. By contrast, in Morquio’s disease, progressive compromise of the cervico-medullary junction by a combination of soft tissue infiltration and instability is a more predictable feature of the disease, mandating much closer surveillance and a lower threshold for intervention in this group.

The algorithm proposed already for evaluation and investigation based upon the three biomechanical processes, namely, deformity, instability and compression, can be extended to incorporate treatment.

### 3.6.4.2.7 Deformity

Establishing an accurate diagnosis is essential before considering intervention. Many aetiologies of torticollis do not require treatment, or treatment is directed towards the underlying cause (e.g. medical therapy for dystonia, division of the sternomastoid muscle for fibrotic contracture of the sternomastoid muscle). Conditions that may present to the neurosurgeon include the following.

#### 3.6.4.2.7.1 Atlanto-Axial Rotatory Fixation

Having established the diagnosis (see above), the aim of treatment is to realign the CCJ and maintain the reduction. A proportion of cases will spontaneously reduce, or will reduce after analgesia and muscle relaxation. Cases that persist can be successfully manipulated and reduced under general anaesthetic. If the history is short (less than 1 month) postoperative immobilisation in a hard collar is usually sufficient; for longer standing cases the risk of recurrence is high and more rigid immobilisation in a halo-body orthosis following reduction is recommended. Open surgical reduction and internal fixation are reserved for cases that fail to reduce or recur after successful closed reduction.

### 3.6.4.2.7.2 Segmentation Anomalies

It is unusual for these to require intervention in the paediatric age group. In practice, the spinal canal is in fact often wider than usual in this group and instability or neuraxial compression is rare. Criteria for intervention include progressive deformity, pain or neurological compromise.

### 3.6.4.2.8 Instability

Where instability is reducible, normal cranio-vertebral alignment is established and internal fixation is performed. Limiting the extent of the fusion is important; in most cases fusing the atlanto-axial segment is all that is required. Where there is coexistent occipito-atlantal instability, or in the very young child in whom the C1 ring is incomplete or still cartilaginous, the occiput needs to be incorporated. In cases of mobile atlanto-axial subluxation the cervico-medullary junction is extremely vulnerable, and this is particularly so during surgical positioning of the anaesthetised child. Prior immobilisation in a halo-body orthosis affords the opportunity of making adjustments to optimise alignment before embarking upon surgery and permits much safer manoeuvring under anaesthetic.

Where atlanto-axial instability is irreducible, traction may be considered, although this can be difficult in the young child. Os odontoideum is commonly associated with irreducibility because of the interposition of the transverse ligament between the posterior arch of C1 and the base of the odontoid. In cases of persisting ventral compression, a transoral decompression will be required before posterior fixation.

### 3.6.4.2.9 Compression

Decompressive surgery is indicated in the presence of clinical symptoms or radiological changes such as signal change within the spinal cord. In achondroplasia, bony thickening at the rim of the foramen magnum is the primary abnormality and foramen magnum decompression without dural opening is usually sufficient. The bone is thick, the foramen magnum circumferentially narrowed and the vertebral arteries are closer to the midline and thus at risk of damage. Bony removal is performed using
3.6 Developmental and Acquired Anomalies

3.6.4.2.10 Summary
There is a wide spectrum of disorders, both congenital and acquired, that may affect the CCJ in childhood. A logical, yet simplified approach identifying the relevant underlying biomechanical processes will ensure appropriate investigation and guide subsequent management. An understanding of the natural history is often difficult, but should be sought wherever possible to enable the clinician to ascertain not only the need for, but also the timing of, any intervention.

Selected Reading
2. Brokmeyer DL Advanced Pediatric Craniocervical Surgery Theime Medical Pub 2005

the high-speed drill, removing bone until a shell of inner cortex remains, which is removed as the final part of the procedure. Exposing the dura earlier in the procedure results in the dura prolapsing into the decompression, thus compromising further bony removal. Good outcomes are reported following decompression.

In the mucopolysaccharidoses, for example, Maroteaux–Lamy and Hurler’s disease, compression is more extensive and requires more intensive decompressions. In the absence of significant deformity or pre-existing instability, decompression alone without stabilisation is all that is required.

In cases of telescopic compression due to translocation or basilar invagination, again, preoperative traction should be considered. Where ventral compression persists, an anterior, transoral approach followed by posterior decompression and fusion is necessary. The use of the transoral approach in children is well described and provides a much safer option than to decompress posteriorly in the face of significant ventral pathology. Good preoperative imaging, perioperative immobilisation and familiarity with the approach are essential.
3.7 Movement Rehabilitation for Trauma and Vascular Patients: Traumatic Brain Injury and Stroke

DEJAN B. POPOVIC

3.7.1 Introduction

Traumatic brain injury (TBI) occurs when a sudden trauma causes damage to the brain. TBI can result when the head suddenly and violently hits an object, or when an object pierces the skull and enters brain tissue. Symptoms of a TBI can be mild, moderate, or severe, depending on the extent of the damage to the brain [4, 12].

A stroke or cerebrovascular accident (CVA) occurs when the blood supply to a part of the brain is suddenly interrupted by occlusion (ischemia), by hemorrhage, or other causes. Ischemia is a reduction of blood flow most commonly because of an obstruction. Hemorrhagic stroke occurs when a blood vessel in the brain bursts, spilling blood into the spaces surrounding the brain cells or when a cerebral aneurysm ruptures. A small proportion of strokes are watershed strokes caused by hypoperfusion or other vascular problems including vasculitis.

3.7.2 Symptoms

A person with a mild TBI may remain conscious or may experience a loss of consciousness for a short time. Symptoms of mild TBI include headache, confusion, lightheadedness, dizziness, blurred vision or tired eyes, ringing in the ears, a bad taste in the mouth, fatigue or lethargy, a change in sleep patterns, behavioral or mood changes, and trouble with memory, concentration, attention, or thinking. A person with a moderate or severe TBI also has a headache that gets worse or does not go away, repeated vomiting or nausea, convulsions or seizures, an inability to wake up, dilation of one or both pupils of the eyes, slurred speech, weakness or numbness in the extremities, loss of coordination, and increased confusion, restlessness, or agitation.

A stroke is a medical emergency. Most strokes occur when a blood clot blocks one of the arteries (blood vessels) that carry blood to the brain. This type of stroke is called an ischemic stroke. Transient ischemic attack (TIA) is a short-term stroke that lasts for less than 24 h. The oxygen supply to the brain is restored quickly, and symptoms of the stroke disappear completely. A transient stroke needs prompt medical attention, as it is a warning of a serious risk of a major stroke. Cerebral thrombosis occurs when a blood clot (thrombus) forms in an artery (blood vessel) supplying blood to the brain. The clot interrupts the blood supply and brain cells are starved of oxygen. Cerebral hemorrhage occurs when a blood vessel bursts inside the brain and bleeds (hemorrhages). With a hemorrhage, extra damage is done to the brain tissue by the blood that seeps into it. The immediate and long-term results lead to marked morbidity and mortality.

3.7.3 Immediate Treatment

Anyone suffering a TBI should receive medical attention as soon as possible. Medical personnel should try to stabilize an individual with TBI and focus on preventing further injury. In the first few days after a stroke, treatment involves ensuring that the patient is well hydrated and nourished.

Rehabilitation is the process by which patients undergo treatment to help them return to normal life as much as possible by regaining and relearning the skills of everyday living. It is multidisciplinary in the fact that it involves a team with different skills working together to help the patient. These include nursing staff and physiotherapy, occupational therapy, speech and language therapy specialists, and usually a physician trained in rehabilitation medicine. Some teams may also include psychologists, social workers, and pharmacists.

Physical therapy (PT) and occupational therapy (OT) are essential components of the rehabilitation process. OT involves exercise and training to help the stroke patient relearn everyday activities, sometimes called the activities of daily living (ADL), such as eating, drinking, and swallowing, dressing, bathing, cooking, reading and writing, and toileting. Speech and language therapy are appropriate for patients with problems understanding speech or written words, or problems forming speech.

Patients may have particular problems, such as an inability to swallow or a swallow that is not safe, such as when swallowed material may pass into the lungs and
cause aspiration pneumonia. The swallow function may improve with time, but in the interim a nasogastric tube may be passed, which enables liquid food to be given directly into the stomach. If after a week the swallow function is still not safe, then a PEG tube is passed and this can remain indefinitely.

Rehabilitation can last anything from a few days up to several months. Return of function is mostly seen in the first few days and weeks and then falls off. It is unusual that there is complete recovery, but not impossible. Most patients will improve to some extent.

### 3.7.4 Prognosis

Approximately half of severely head-injured patients will need surgery to remove or repair hematomas or contusions. Common disabilities include problems with cognition, sensory processing, communication, and behavior or mental health. More serious head injuries may result in stupor, an unresponsive state, but one in which an individual can be roused briefly by a strong stimulus, such as sharp pain; coma; vegetative state; and a persistent vegetative state, in which an individual stays in a vegetative state for more than a month.

Stroke typically affects the entire body. Some of the disabilities that can result from stroke include paralysis, cognitive deficits, speech problems, emotional difficulties, pressure sores, pneumonia, continence problems, daily living problems, and pain. If the stroke is severe enough, coma or death can result. Depression is common in post-stroke patients.

### 3.7.5 Restoration of the Functions of the Upper Extremities

Conventional therapies in humans with upper limbs disability (ULD) comprise pharmacological means, physical therapy, and integrated behavioral and physical therapy. An effective method of rehabilitation is constraint-induced movement therapy (CIMT) [11, 17, 18]. Clinical studies showed that CIMT is effective in improving limb use in the real-world environment. The therapy involves constraining the movements of the less affected arm with a sling for 90% of waking hours for 2 weeks, while intensively training the arm that is more severely affected. The common therapeutic factor is the forced induction of a concentrated, repetitive use of the latter limb. The neuroimaging and studies that applied transcranial magnetic stimulation (TMS) showed that CIMT produces a massive use-dependent cortical reorganization. CIMT has been shown to be effective in patients who, before intervention, have rudimentary movement in the fingers and the wrist. Authors showed a substantial improvement in the performance time and in the quality of movement (Actual Amount of Use Test, Motor Activity Log, Wolf Motor Function Test, and Arm Motor Ability Test).

Repetitive movement therapy leads to improvements for patients with milder initial impairments [16]. In contrast, and counter to the motor skills theory, a treatment approach that encouraged patients to practice outside the therapy session was not advantageous.

Robot-induced therapy provided evidence that extensive exercise is beneficial [8, 19]. A robot designed to provide interactive, goal-directed motor activity for clinical neurological applications was used to test whether the externally driven impaired limb influences motor recovery. In a randomized, blinded study in 20 stroke patients, the conventional therapy was supplemented by either robot-aided therapy or sham robot-aided therapy. Impairment and disability declined in both groups between hospital admission and discharge; yet, a robot-treated group showed a greater degree of improvement in all measures of motor recovery, and the change in motor status measured in the proximal upper limb musculature. In the follow-up study of 56 stroke patients, randomly assigned to receive standard post-stroke multidisciplinary rehabilitation, and either robotic training (at least 25 h) or exposure to the robotic device without training, the outcomes (upper extremity component of the Fugl–Meyer Motor Assessment, the Motor Status score, the Motor Power score, and Functional Independence Measurement) showed that the robot-aided group with training demonstrated improvement, but this did not generalize to the untrained wrist and hand.

Electrical stimulation [2, 12] at levels where only the afferent pathways are activated contributes to the recovery of the sensory–motor impairment [5]. The effects of whole-hand electrical stimulation via a wired mesh glove upon the residual motor control of the upper extremity have been investigated. Functional motor capacity of the paretic extremity when exposed to a low-intensity, low-frequency (1.7 Hz) transcutaneous electric nerve stimulation (Low-TES) was studied a relatively short time after the stroke (6–12 months) in 46 patients. Results showed that motor function increased significantly in the treatment group, compared with controls. The Low-TES did not decrease either pain or spasticity.

Therapeutic electrical stimulation (TES) was evaluated in several clinical studies. Improvement in the upper limb of chronic stroke patients who underwent different techniques of stimulation of wrist extensors (EMG triggered TES, Low-TES, proprioceptive neuromuscular facilitation) for 3 months was investigated. The comparison of the Fugl–Meyer (FM) post-stroke motor recovery test
and grip strength assessment at the start, after completion of treatment, after 3 months, and after 9 months show the benefits of TES. In a single blinded, randomized, controlled multi-center trial 100 stroke patients were included in either a group that received an additional treatment of sensory-motor stimulation or a control group for 6 weeks. The Brunnstrom–Fugl–Meyer test, the Action Research Arm test, and the Barthel Index before, midway, and after the intervention period, and at follow-up 6 and 12 months after the stroke showed that the TES group improved their motor performance more than the controls throughout the study period, but differences were significant only at follow-up. Results of the Action Research Arm test and the Barthel Index revealed no effect at the level of disability. In a blinded, randomized study, 60 patients were divided in two equal groups (40 sessions over 8 weeks). The best results were obtained in patients with some residual motor function at the beginning. Forty-six stroke patients were randomly assigned to receive either neuromuscular stimulation or placebo. The treatment group received surface neuromuscular stimulation to produce wrist and finger extension exercises. The control group received placebo stimulation over the paretic forearm (1 h per day, 15 sessions). Outcomes were assessed in a blinded manner with the upper extremity component of the Fugl–Meyer Motor Assessment and the self-care component of the Functional Independence Measure at pre-treatment, post-treatment, and at 4 and 12 weeks after treatment. Parametric analyses revealed significantly greater gains in the Fugl–Meyer scores for the treatment group after treatment, at 4 weeks after treatment, and at 12 weeks after treatment. Functional Independence Measure scores were not different between the groups at any of the time points.

The EMG-triggered neuromuscular stimulation enhances upper extremity motor function and promotes functional recovery of acute stroke patients [1, 6]. Patients received two 30-min sessions per day of wrist-strengthening exercises with EMG stimulation (experimental) or without (control) for the duration of their rehabilitation stay. Upper extremity Fugl–Meyer motor assessment and the feeding, grooming, and upper body dressing items of the Functional Independence Measure (FIM) were assessed in one; the Box and Block and grasp strength were evaluated in the other. Patients treated with EMG-triggered stimulation exhibited significantly greater gains than did the controls.

Functional electrical therapy (FET) consists of a combination of electrical stimulation that augments the exercise, which consists of performing functional movements [13]. In an early study clinicians analyzed functioning of the upper extremities after two-channel electrical stimulation that augmented elbow extension and fingers/wrist extension (three weekly sessions of 30 min). The movement quality improved in all 8 patients after 2 months. The improvement was substantial in 5 patients; yet, in the remaining 3 the improvement was significant only for elbow extension. In recent studies in acute and sub-acute stroke patients, the recovery of reaching and grasping was assessed by the Upper Extremity Function Test, co-ordination, spasticity, range of movement, and a questionnaire assessing the amount and quality of use. The improvements were significantly better ($p < 0.05$) in the FET group than in the control group, which received only conventional physical therapy.

The first phase of restoring the walking function is the provision for standing. Today, the most promising approach is the use of balance trainers. One of the effective devices and methods is the Balance Trainer® (Fig. 3.7.1). This standing trainer allows safe standing as well as stability training in the trunk. Persons with restricted movement who cannot stand safely and independently are held safely at the pelvic region, and they can practice balance. This system combines the effectiveness of the classic standing training with stability training in the hip and in the upper part of the body.

![Fig. 3.7.1 Balance Trainer®](image)
The use of a treadmill is becoming a common practice in the rehabilitation of the walking function [7, 10]. Treadmill walking involves the use of body weight support during gait training on a motorized treadmill. The rationale for this approach was that while partial weight support removes some of the biomechanical and equilibrium constraints of full weight-bearing, walking movements may be facilitated on the treadmill by the activation of central pattern mechanisms. These carry-over effects were proven for hemiplegics. Nine hemiplegic individuals who were non-ambulatory were trained on a treadmill for 15 min in 25 sessions using partial weight support. The hemiplegic individuals exhibited gains in functional and motor abilities, as well as in velocity and cadence, after the treatment. In a controlled study with 100 patients, the effect of training on balance, motor tasks, and gait velocity indicated the advantage of combining partial weight support with treadmill training over treadmill training alone. In recent years, treadmill equipment has become more readily available in many physical therapy departments. Many hemiplegic individuals are able to train on a treadmill without the use of partial weight support early on in the rehabilitation process, provided the initial speed of the treadmill is as low as 0.2–0.4 km/h.

Use of the treadmill is made easier by means of robots that provide body support and generate locomotor-like cyclic movements (e.g., Locomat®; Hokoma, Volketswil, Switzerland). Locomat generates movements of the hip and knee joints, thus making treadmill walking simple and effective [3, 20]. An alternative that results in different yet equally valuable training of cyclic activity is the Advanced Gait Trainer® [9]. The Advanced Gait Trainer (Fig. 3.7.2) provides movement of the feet, while the body is partly supported and controlled by the mechanism.

Electrical stimulation has been tested in hemiplegics for augmentation of the walking function. In most cases, the assistance only dealt with the drop-foot problem, although other methods were tested (e.g., stimulation of the iliopsoas muscle with percutaneous electrodes). In parallel, the development of walking systems for paraplegic individuals led to technology that is appropriate for activation or inhibition of sensory-motor systems. The implementation of the same technology in post-TBI and stroke patients was tested. In general, electrical stimulation with the presently available interfaces is a suitable technique for augmentation of functions of the paretic extremities. Electrical stimulation activates both afferent and efferent pathways, thus resulting in direct or reflex motor responses, and a strong input into the central nervous system.

The FET for walking is a protocol that combines voluntary intensive exercise; yet, also uses electrical stimulation that is timed to activate several muscle groups in a pattern that mimics the activation of healthy individuals [14]. The role of this stimulation is to provide augmentation of the muscle activation of paretic muscles, and augmentation of the sensory flow toward the upper motor neuron. The basis for the FET follows the recent finding that the stimulation of the central nervous system in paraplegics triggers descending signals and activates the half-centers, called the central pattern generator.

Many trauma and vascular patients do not recover their functions. These individuals may benefit from simple mechanical splints that might provide better posture and, possibly, limited movement. The technology that is slowly finding a place in everyday life uses functional electrical stimulation [15]. Functional electrical stimulation can be applied via surface electrodes; yet, the ultimate solution is the use of implantable technology that maximizes the
comfort and minimizes the complexity of use (e.g., Acti-gait®; Neurodan, Aalborg, Denmark; Fig. 3.7.3).

Recent opinion summarized from many clinical studies is that intensive, task-related exercise early after the onset of injury/disease is the most effective method of promoting the sensory-motor recovery. This treatment ensures the best use of the plasticity of the central nervous system and prevents the development of compensatory mechanisms and patterns of non-use, which lead to disability.

Selected Reading

The spinal column is an axial organ consisting of about 33 vertebrae (7 cervical, 12 thoracic, 5 lumbar vertebrae articulating with the fused sacrum [5 vertebrae] and the caudal coccyx [usually 4 vertebrae]). The smallest motion unit of the spine is a segment which consists of the intervertebral disc and the two adjacent vertebral bodies with articulating facet joints. Thus these anatomical features of the spine are adapted to its two major functions, which are:
1. To provide axial stability allowing a certain degree of mobility and
2. To protect the spinal column and the origin of spinal nerves

4.1.1.1 Spinal Column

Following the four major segments on lateral view (cervical, thoracic, lumbar and sacral) the spinal column has four curvatures, which provide flexibility and support the spine. The anatomical features are adapted to the specific requirements of the spinal segments. However, principal features are the anterior component, the vertebral body, which is connected to a posterior arch via the pedicles. In addition the superior and inferior articular processes form a diarthrodial articulation. The transverse processes insert on the lateral aspect near the intersection of the pedicle and the lamina and the spinous process connects both laminae in the posterior midline. The characteristics of the segments of the spine are listed below. The craniocervical junction with the unique anatomy of C1 and C2 has some specific anatomical features and some vertebrae have to be considered as transitional vertebrae, e.g. C7 at the cervicothoracic junction and T11 and T12 at the thoracolumbar junction.

\textit{Upper cervical spine (C1 and C2)}

- Atlas C1
  - Has no vertebral body.
  - Consists of an anterior ring and posterior arch.
  - Bilaterally concave superior articular surfaces articulate with the occiput (C0).
- Bilaterally inferior articular surfaces articulate with C2 with an approximately 20° angle on the AP view.
- At the posterior midline the two parts of the arch form a vestigial spinous process (posterior tubercle).
- On the posterior lateral arch, behind the posterior aspect of the superior articular surface a sharp rim marks the sulcus arteriosus were the V3 segment of the vertebral artery runs before entering the subarachnoid space via the atlanto-occipital membrane.
- The anterior ring has an anterior prominence (anterior tubercle).
- On the inner anterior ring is a synovial-lined articular surface allowing the rotation of C1 around the odontoid of C2.
- The transverse ligament inserts on the medial aspect (tubercle) of the lateral mass and prevents anterior subluxation of C1 while permitting normal atlantoaxial rotation.

\textit{Axis C2}

- The odontoid process is the most prominent feature of C2 and constitutes the superior projection from the vertebral body articulating with the anterior ring of C1 anteriorly and transverse ligament posteriorly.
- Each part of that joint around the odontoid process has its own synovial cavity [1].
- The odontoid tip has three rough bony prominences for the insertion of the apical ligament and the alar ligaments which connect the odontoid to the skull base.
- The apical ligament connects the odontoid tip with the anterior rim of the foramen magnum, while the alar ligaments connect it to the occipital condyle. The ligaments are extremely important for the biomechanical stability of the craniocervical junction.
- The transverse foramen is located anterolateral to the pedicle and is partially covered by the superior facet medially. It consists of an angulated canal that deviates the vertebral artery 45° laterally before entering the transverse foramen of C1 [2].
- The pedicle is the largest of the entire C-spine [3].
Basics

**Diameter** gradually decreases from superior to inferior.

**Has a vestigial medial crest** (remnants of the spinous processes), an intermediate crest (vestigial articular processes) and a lateral crest (location of the transverse processes at a more primitive stage) on the dorsal surface.

**The sacral hiatus** is at the level of S5 (rare at S4 level too), due to the absence of the lamina and spinous process, and contains the filum terminale, which itself contains fatty and fibrous tissue that serves as an anchor for the caudal spinal cord.

**Coccyx**

- A triangular remnant of the tail that contains three or four fused bones.
- Articulates with the sacral cornua and has no load bearing.
- Serves as an insertion for gluteal and pelvic muscles.

**Intervertebral discs**

- Present from C2/C3 to L5/S1.
- Each disc consists of a soft nucleus pulposus surrounded by a peripheral ring of fibrous tissue, the annulus fibrosus.
- The fibres of the annulus are organised in concentric rings, running obliquely from one vertebra to another, providing stability but allowing a certain degree of adjacent segment mobility.
- Fibrous fibres are anchored in the cartilaginous surfaces of the vertebral end plates and blend with the anterior and posterior longitudinal ligaments.
- The nucleus pulposus consists of a loose network of fibres and proteoglycans which receives nutrition via diffusion.
- The high water content of the nucleus pulposus decreases with age and during daily activity and in the vertical position a moisture re-expansion occurs.

**Spinal ligaments**

- Anterior longitudinal ligament (ALL):
  - Runs from the sacrum to the anterior tubercle of C1 on the ventral surface of the vertebrae.
  - The part between C1 and the anterior basion is the anterior atlanto-occipital membrane.
  - Strength through longitudinally arranged interdigitating collagen fibres.
  - Strength increases in the craniocaudal direction and it prevents hyperextension and overdistraction.
- Posterior longitudinal ligament (PLL):
  - Runs on the posterior side of the vertebral bodies from C2 to the sacrum.
  - The rostral extension is the tectorial membrane and therefore stabilises CVJ.

**Lower cervical spine (C3–C7)**

- Vertebrae have a thin lateral mass containing a foramen transversarium on each side, which serves as a bony canal for the vertebral artery running from C6 to C1.
- Articular facets are oriented coronally and have an inclination of 45° in craniocaudal direction in the horizontal plane.
- Vertebrae contain bilateral small bicornuate transverse processes.
- Small and thin laminae with a wider base.
- Spinous processes are almost horizontal and bifid except for C7.
- Small pedicles.

**Thoracic spine**

- The vertebral bodies have an intermediate size between small cervical and large lumbar vertebral bodies.
- The vertebral body contains an articular facet for the rib as the costovertebral joint and the ribs articulate with the transverse processes at the costotransverse joint.
- Articular facets are oriented coronally from T1 to T10 and turning sagittally between T10 and T12.
- Transverse processes are shorter and at more caudal levels.
- Laminae are thicker than in the cervical spine.
- Spinous processes are longer and directed inferiorly in the midthoracic level and are more horizontal in the lower thoracic spine.
- Pedicles are short and high, and their width progressively increases from T1 to T12.

**Lumbar spine**

- Largest vertebral bodies in the spinal cord with a wedge shape (high: anterior > posterior) forming the lumbar lordosis.
- Articular facets are oriented sagittally.
- Transverse processes emerge on the lateral surface of the posterior arch close to the intersection of the pedicle and the superior articular facet.
- A mammillary process is located at the posterior transverse process at the intersection with the inferior articular facet.
- Laminae are wider and shorter than in the thoracic spine.
- Pedicles are thick and oval shaped.

**Sacrum**

- Composed of four or five fused vertebrae resembling a triangle.
- Articulates laterally with the iliac bone and superiorly with L5 creating an angle of 130–160°.
- Forms the posterior wall of the pelvis.
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4.1.1 Anatomy

– Consists of two layers (the anterior or deep layer contacts the vertebral bodies and the discs, while the posterior or superficial layer is close to the dura) embedding the venous plexus [4].
– Permits more deformation than the ALL.
– Ligamentotaxis is the phenomenon whereby in patients with burst fractures and an intact PLL retropulsed bony fragments are reduced into the vertebral boundaries by distraction without pushing them back.
– Limits hyperflexion and prevents disc protrusion into the spinal canal.
– Thickness decreases in craniocaudal direction.

• Ligamentum flavum
  – Extends from the midportion of the anterior superior lamina to the upper edge of the inferior lamina.
  – Reaches from lateral (superior articular process) to medial (inner posterior part of the lamina).
  – Prevents hyperflexion.
• Interspinous ligament and supraspinous ligament
  – Attach at adjacent spinous processes and prevent excessive flexion.

4.1.1.2 Spinal Cord

In adults the spinal cord extends from the foramen magnum, were the medulla oblongata transits into the spinal cord and turns into the conus medullaris at the level of the L1/L2 disc interspace. A fibrous band, called filum terminale, continues distally down to the insertion in the coccyx. The length of the spinal cord is between 42 and 45 cm [5]. Even if an ascendance of the conus in the neonatal period has been considered for a long time, it was shown recently that the conus level at birth was also in L1/L2. The ascendance of the conus to L1/L2 was demonstrated by ultrasound [6] by the 40th postmenstrual week and by MRI [7] in newborns.

4.1.1.2.1 Specific Anatomy of the Spinal Cord

The shape of the cords resembles a cylinder. Anteroposterior diameter is less than the distance from both lateral edges.

• Ventral median fissure: an anterior median sulcus in which the anterior spinal artery runs
• Posterior median fissure: less pronounced than the anterior sulcus
• Dorsolateral sulcus: demarcates the area of the dorsal root entry zone (DREZ)
• Anterolateral sulcus: demarcates the origin of the ventral roots

The cord consists of the central grey matter (butterfly shaped) and the peripheral white matter. The anterior and posterior median sulcus ‘divides’ the cord into two halves. The central canal runs in the midline within the grey matter. Each side of the cord is divided into three columns, the dorsal, the lateral and the anterior column, which are formed by several funiculi and tracts running either from central to distal or vice versa as ascending or descending tracts. In the cervical cord an additional sulcus divides the posterior column into the fasciculus gracilis (medial) and the fasciculus cuneatus (lateral).

4.1.1.2.1.1 Grey Matter

The anterior half of the grey matter contains cell bodies for the ventral roots, while the posterior half extends dorsally reaching the surface of the cord close to the DREZ.

4.1.1.2.1.2 White Matter

The white matter is composed of ascending and descending tracts. An anterior commissure is located adjacent to the anterior median sulcus. Sensory input to the spinal cord is via the dorsal roots. All impulses are forwarded according to the origin of the impulse on the contralateral side. Fibres containing pain and temperature sensation ascend as the lateral spinothalamic tract up to the thalamus, and fibres involved in transmitting tactile sensation (light touch) ascend as the ventral spinothalamic tract also reaching the thalamus. Myelinated fibres ascend in the fasciculus gracilis and cuneatus in the dorsal column towards the medulla. Impulses are projected by third-order neurons to the thalamus after decussation in the medial lemniscus. The ventral spino-cerebellar tract enters the cerebellum via the superior cerebellar peduncle and the dorsal spino-cerebellar tract via the inferior cerebellar peduncle.

The major descending tract is the corticospinal tract (pyramidal tract). Fibres originating in the central region course downwards in the corona radiata via the posterior limb of the internal capsule. In the region of the pyramids 90% of fibres decussate to the contralateral side and descend as the lateral corticospinal tract, while the remaining 10% of fibres continue to descend uncrossed forming the anterior corticospinal tract.

4.1.1.2.2 Vascularisation of the Spinal Cord

• Posterior spinal arteries (PSA): paired, run medially to the DREZ and supply the posterior one third of the cord.
• Anterior spinal artery (ASA): emerges as two arteries that join at the level of the medulla. ASA runs in the anterior median fissure and supplies the anterior two thirds of the cord.
• Anterior and posterior radicular arteries run through the intervertebral foramen and anastomose with the
ASA more in the distal cord and are prominent on the left side.

According to the level of the cord different radicular arteries contribute to the vascular supply. Radicular arteries accompany nerve roots at many levels, but the overall contribution of radicular arteries to the blood flow of the spinal cord is low and limited.

- **Upper region C1–T3:**
  - C1–C4: supplied by anterior and posterior spinal arteries
  - C5–C6: supplied by vertebral artery branches and thyrocervical trunk
  - C7–T3: supplied by the costocervical trunk
- **Middle region (T4–T8):** only supplied by one single thoracic radicular artery at T7 from the aorta and therefore very vulnerable to low flow (‘watershed zone’)
- **Lower region (T9–sacrum):**
  - Supplied mainly by the single left great radicular artery of Adamkiewicz (75% T10–T12), which constitutes the main supply for the conus medularis.
  - Branches from the aorta and the iliac arteries to the thoracolumbar spine.
- A leptomeningeal perimedullary network is an anastomosis between the posterior and anterior system most prominent at the conus level.
- Blood flow is centripetal from the posterior system towards the posterior column and posterior horns.
- Blood flow is centrifugal from the anterior system towards the anterior and central grey matter and the anterior and lateral funiculi.

The venous drainage varies considerably and usually an anterior spinal vein and two posterior veins drain rostrally towards the head.

### 4.1.1.3 Meninges and Nerve Roots

#### 4.1.1.3.1 Meninges

The whole spinal cord and the emerging nerve roots are protected by the spinal dura mater. Thus the cranial dura continues at the craniocervical junction and forms a tube around the cord and cauda equina down to the sacrum. A thick fibrous membrane and collagen bundles guarantee its strength. At the lateral border of the dorsal spinal root ganglion the dura continues as a dural sheath of the spinal nerve root and far more laterally it merges into the epineurium of the segmental nerve. The dura is innervated from branches arising from the proximal spinal nerve.

Close to the dura the next inner layer is the arachnoidea, leaving only a small subdural space. The space between the pia and arachnoidea is filled with cerebrospinal fluid (CSF). The pia lies on the spinal cord and nerve roots and surrounds the vessels. In contrast to the brain, in the spinal cord there are no perivascular spaces (‘Virchow-Robin spaces’).

Dentate ligaments extend from the lateral surface of the cord and attach to the dura to support the spinal cord during flexion and extension. Each dentate ligament consists of a collagenous core which is continuous with the subpial connective tissue and is attached at intervals to the dura. Pia–arachnoid cells coat the surface of the dentate ligaments [8]. The ligaments are stronger in the cervical region and they decrease in strength as the spinal cord descends. Anterior and posterior motion is constrained to a limited degree by these ligaments [9]. The insertion of the dentate ligaments is between the DREZ and the anterior roots and may serve as a landmark for the corticospinal tract posteriorly and the spinothalamic tract anteriorly [5].

#### 4.1.1.3.2 Nerve Roots

Spinal nerve roots exit the spinal canal via the intervertebral foramen. Usually 31 paired nerve roots emerge from the spinal cord and consist of anterior and posterior fibres. No posterior ganglion is found in the first cervical and first sacral roots lacking a corresponding sensory dermatome. The anterior fibres emerge about 1–3 mm from the midline and the posterior fibres enter the cord via the DREZ in the posterolateral sulcus. All cervical nerve roots are above the vertebral body while C8 is located between C7 and T1. The following roots are below the respective vertebral body. Cervical and lumbar roots leave the canal at an oblique angle, while thoracic roots exit almost horizontally.

All spinal ganglia and nerve roots receive segmental vessels from the vertebral artery, subclavian artery and aorta depending on the level of exit from the spinal cord. After entering the vertebral foramen all these segmental vessels branch into radicular, dural and medullary vessels.

- Dural branches: supply the spinal dura and the dura around nerve roots
- Radicular branches: penetrate the dura and irrigate the anterior and posterior nerve roots
- Medullary branches: ascend and descend intradurally and supply the anterior and lateral funiculi

### 4.1.2 Pathophysiology

Pathophysiology and causes of spinal disorders vary and one has to consider the affected level of the spine and the time course of clinical symptoms to establish a correct di-
agnosis and to design appropriate treatment algorithms. The transition between the rigid thoracic and the mobile lumbar curves make this region particularly susceptible to traumatic injuries. The following section covers the pathophysiology of common degenerative disorders of the spine. Aetiology and management of degenerative diseases is discussed in Sect. 4.3.

### 4.1.2.1 Degenerative Disc Disease

Degenerative disc disease (DDD) is associated with vascular, biochemical and anatomical changes in the disc. Clinical signs and symptoms result from compression of neural structures at the cervical, thoracic and lumbar levels.

- Characteristic pattern of incidence with the most frequent changes occurring in the midcervical, thoracolumbar and lower lumbar regions, which reflects the mechanical stress caused by spinal movement and axial loading.
- Three anatomical parts are involved in the degenerative process:
  1. Nucleus pulposus: high percentage of proteoglycans and high water content
  2. Annulus fibrosus: consists of lamellae of collagen resisting tensile forces deriving from the enclosed nucleus
  3. Cartilaginous end plates: attach the disc to the end plates of vertebral bodies
- Disc nutrition occurs via small vessels in the cartilage end plates and the periphery of the annulus. Nutrition supply changes with age. Progressive aging leads to a decreased water content in the nucleus and annulus and end plates calcify while a reduction of vessels leads to an almost avascular disc. The consequences of these degenerative changes are a disorganised nucleus pulposus with dehydration and circumferential and radial tears. A myxomatous degeneration of the annular lamellae occurs with fissure formation.

As compared with a shock absorber the intervertebral disc attenuates axial loading due to deformation and bulging of the nucleus which is restricted by the annulus and end plates. The biomechanical cause of disc herniation may be the result of a combination of complex movements involving compression, lateral flexion and rotation [10].

### 4.1.2.2 Spinal Stenosis

#### 4.1.2.2.1 Central Stenosis

Central stenosis is a narrowing of the AP dimension of the spinal canal. Spinal stenosis can be congenital or acquired but is most often superimposed on acquired forms. The clinical symptom of lumbar spinal stenosis is neurogenic claudication while cervical stenosis is often associated with cervical myelopathy. The reduced diameter of the central spinal canal can cause either direct compression of nerve roots or compromise blood supply to the cord or cauda equina.

In the lumbar spine DDD with reduction of the intervertebral disc space frequently associated with disc bulging or calcification leads to facet joint hypertrophy and thickening of the ligamentum flavum causing stenosis of the spinal canal. Occasionally degenerative spondylolisthesis is associated. It is most frequent in L4/L5 followed by L3/L4 but can occur in multiple segments.

#### 4.1.2.2.2 Foramen Stenosis or Lateral Recess Stenosis

Before entering the neural foramen the nerve root can be compromised in the so-called lateral recess. The borders of the recess are the vertebral body anteriorly, the pedicle laterally and the superior articular facet posteriorly. Compression is due to hypertrophy of the superior articular facet leading to nerve root impingement.

### 4.1.3 Clinical Symptomatology

#### 4.1.3.1 Radiculopathy

- Nerve root impingement with typical pain radiation and/or motor or sensory impairment leading to nerve root dysfunction.
- Weakness of the index muscle mainly innervated by that nerve, diminished reflexes of the same muscle and dermatomal sensory disturbance are typical findings.
- The most common distribution of radiculopathy is the lumbar spine followed by the cervical spine. Radiculopathy is less common in the thoracic spine.
- Pain usually exacerbated with coughing, sneezing or during defaecation.

#### 4.1.3.2 Myelopathy

- Compression or stretching of the spinal cord can cause myelopathy, which is more common in the cervical rather than the thoracic spine.
- Pure cervical myelopathy is found in less than 60% of patients, which means about 41% of patients present with myelopathy and radiculopathy.
- Hyperreflexia and positive Babinski sign are common.
- Sensory deficits include impaired sensory level, dermatomal sensory disturbance in the arms, glove-dis-
distribution sensory loss in the hands and posterior column dysfunction.

- Motor deficits with arm weakness and wasting of hand muscles are encountered (31%) or paraparesis can occur (21%). However, hemi- or tetraparesis are less frequent.
- Spasticity is present in more than 50% of cases and in the series by Lunsford et al. 49% of patients had sphincter disturbance [11].
- Usually symptoms get worse either in a stepwise progression or gradually progress.

### 4.1.3.3 Cauda Equina Syndrome

- Compression of either the conus medullaris or the cauda equina.
- Causes can be either traumatic, neoplastic, infectious or degenerative.
- Massive midline disc rupture with compression of the neural structures may suddenly lead to symptoms with motor, sensory and bladder dysfunction. It can be superimposed on a pre-existing degenerative condition as for instance spinal stenosis.
- Any other space-occupying condition within the spinal canal can lead to a cauda equina syndrome (CES) if a compressive effect occurs.
- Very common finding in the CES is a sphincter disturbance with urinary retention, urinary and/or faecal incontinence and diminished anal sphincter tone.
- The most common deficit is saddle anaesthesia in the distribution around the anus, lower genitals, perineum and over the buttocks.
- The motor weakness usually involves more than one root, is bilateral and can progress to paraplegia.
- Absence of Achilles reflex has been noted.
- Sexual dysfunction is usually not noted during the acute stage of the CES but can persist afterwards.

### 4.1.3.4 Low Back Pain

- Low back pain (LBP) is a very common finding in the general population and in the majority of cases no specific underlying cause can be diagnosed.
- It has to be distinguished from radicular pain.
- During initial assessment it is important to exclude serious pathology by inquiring into the patient's history and by careful clinical examination.
- In the absence of clinical findings that may indicate nerve root or cauda compression, imaging studies are usually not necessary within the first weeks.
- Symptomatic treatment with rest and non-prescription pain medication usually helps to relieve discomfort. However, bed rest longer than a few days may be more harmful than helpful and daily activity should be modified.
- Prognosis of most cases is usually good even with little or no medical intervention.

### 4.1.3.5 Failed Back Syndrome

- Describes a condition where there is a failure of satisfactory improvement after surgical treatment for either a herniated disc or decompressive surgery to treat spinal stenosis.
- The majority of patients with the ‘failed back syndrome’ had pending legal or Workers’ Compensation claims, or were at psychological risk for surgery [12].

### 4.1.4 General Methods of Clinical Examination

The initial assessment of patients presenting with spinal column or cord problems consists of history and physical examination. It is important to identify serious underlying pathological conditions such as fracture, tumour, infection or cauda equina syndrome, which may need immediate further work-up.

#### 4.1.4.1 Inspection and Palpation

Examination should start with a careful inspection with regard to the patients pose, habitus (athletic, pyknic), scars (previous surgery), lumps (abscess, tumour, muscle spasm), sinuses and hairy patch (open or closed dysrhythmism). Asymmetry of shoulder height, trunk balance and loin crease should be excluded. Scoliosis (lateral curvature with rotational deformity of vertebral bodies), lateral deviation of the spine, kyphosis and lordosis, round back and gibbosity should be noted. Leg length discrepancy (check level of iliac crests) should be excluded. The ability to move and the degree of active and passive movement of the spine by bending back and forward and lateral bending give a hint about the severity of complaints. If the patient consistently stands with one knee bent in spite of equal leg lengths, this may indicate nerve root tension, as knee flexion relieves the pull on the nerve root(s).

With palpation one assesses tenderness (may be bony, intervertebral or paravertebral) and it may reveal bony prominences or steps. Look for spinous processes.
4.1.4.2 Specific Neurological Investigation

4.1.4.2.1 Nerve Root Tension Signs
- Lasègue's sign: Straight leg raising test differentiates sciatica (L5 and S1, L4 less so) from hip pain due to other pathology. Test is positive if pain or peristhesias in the distribution of pain occurring at less than 60°. Ankle dorsiflexion usually augments pain.
- Crossed straight leg sign: Contralateral (painless) leg raising causes pain in the ipsilateral painful leg.
- Reverse straight leg raising test: Backward leg lifting if the patient is in prone position causes pain and indicates upper lumbar root compression (L2–L4).
- Trendelenburg sign: Ipsilateral tilting of the pelvis if a standing patient lifts up one leg due to weakness of the contralateral thigh adductors (L5).

4.1.4.2.2 Motor Testing
The muscle is the unit of action that causes movement. In general strength should be almost equal on each side, proximal and distal in upper and lower extremities.

4.1.4.2.2.1 Inspection
Major muscle groups of the upper and lower extremities should appear symmetrically developed when compared with their counterparts on the other side of the body. They should also be appropriately developed, after making allowances for the patient's age, sex and activity level. Palpation should not elicit pain. Palpation of the muscles gives a sense of underlying mass. Look for asymmetries. Spontaneous muscle movement while the extremity is at rest is called fasciculation.

4.1.4.2.2.2 Muscle Tone
When a muscle group is relaxed, the examiner should be able to easily manipulate the joint through its normal range of motion. This movement should feel fluid. Test clonus by sudden and sustained flexion to the ankle.

4.1.4.2.2.3 Muscle Strength
The use of the Medical Research Council (MRC) rating scale (0–5) for muscle strength provides the most reliable assessment for muscle strength:
- 0/5 No movement
- 1/5 Barest flicker of movement of the muscle, though not enough to move the structure to which it is attached
- 2/5 Voluntary movement which is not sufficient to overcome the force of gravity
- 3/5 Voluntary movement capable of overcoming gravity, but not any applied resistance
- 4/5 Voluntary movement capable of overcoming 'some' resistance
- 5/5 Normal strength

4.1.4.2.3 Sensory Testing
Test each modality alternating with the patient having both eyes closed. Compare each side with each other.

4.1.4.2.3.1 Spinothalamics
These nerves detect pain, temperature and crude touch.
- Crude pain testing: Use a sharp disposable instrument (e.g. broken tongue depressor, needle) and alternate that with a blunt instrument and ask the patient to describe his/her feeling.

4.1.4.2.3.2 Dorsal Columns
These nerves detect position (a.k.a. proprioception), vibratory sensation and light touch.
- Proprioception testing: Grasp either side of the great toe. Orient the patient as to up and down. Flex the toe (pull it upwards) while telling the patient what you are doing. Then extend the toe (pull it downwards) while again informing them of which direction you are moving it.
- Vibratory sensation: Use a tuning fork and start at the toes.
- Testing two-point discrimination: Patients should normally be able to distinguish simultaneous touch with two objects which are separated by at least 5 mm.

Sensation might be diminished in a certain distribution pattern according to the dermatomes. According to the patient's complaints and symptoms the assessment should focus on either upper or lower extremities.

4.1.4.2.4 Reflex Testing
Reflex testing incorporates an assessment of the function and interplay of both sensory and motor pathways. However, assessment remains subjective and interpretation should be limited to absent, normal and increased.

Assessment should include biceps (C5, C6; musculo-cutaneous nerve), brachioradialis (C5, C6; radial nerve) and triceps (C7, C8; radial nerve) reflexes for the upper extremities, and patellar (L3, L4; femoral nerve) and Achilles (S1, S2; sciatic nerve) reflexes for lower extremities. Additional reflexes, which can provide information about lesion level throughout the spine, are the abdominal reflexes (T7–T12), the cremasteric reflex (L1) and the anal sphincter reflex (S4 and S5).
- Pathological reflexes: The Babinski response is a test used to assess upper motor neuron dysfunction. It is positive if dorsiflexion of the great toe occurs after scratching the lateral foot.

4.1.4.2.5 Gait Testing
A lot of information about neurological (and other) disorders can be gained from simply watching a patient
standing and walking. Observe the patient while walking into your office and during getting up and down from the examination table. Instability of walking is called ataxia, which can be cause by compression of the dorsal columns.

4.1.4.2.6 Coordination Testing
Test the ability to repeatedly run the heel from the opposite knee down to the shin to the big toe.

4.1.4.2.7 Urinary and Faecal Incontinence
In the setting of cauda equina syndrome, for example, multiple sacral and lumbar roots become compressed bilaterally (e.g. by posteriorly herniated disc material or a tumour). When this occurs, the patient is unable to urinate, as the lower motor neurons carried in these sacral nerve roots no longer function. Thus there is no way to send an impulse to the bladder instructing it to contract. Nor will the patient be aware that their bladder is full. There will also be loss of anal sphincter tone, which can be appreciated on rectal examination. The ability to detect pin pricks in the perineal area (a.k.a. saddle distribution) is also diminished.

References

4.1.5 Radiology: Fundamentals of Spinal Neuroimaging

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4.1.5.1 Introduction
Evaluation of spinal disorders may require the use of several different imaging modalities depending on the nature of the disorder. Plain x-rays are usually the first tool required, but complementary techniques are often needed, such as computed tomography (CT), magnetic resonance imaging (MRI), myelography, discography or spinal angiography.

Back pain, with or without neurological symptoms, is the most frequent situation that requires a radiological study, but it is not the only one. The American College of Radiology (ACR) has developed a specific list of recommendations, based on numerous studies, to use the different techniques of imaging in the spine depending on the nature of the problem. For example, uncomplicated back pain usually does not require imaging evaluation, but elderly patients, a previous history of trauma, osteoporosis, cancer or risk of infection will require a neuroimaging study. Plain x-rays may be done initially, but MRI is a better tool if neurological symptoms (radiculopathy, myelopathy, cauda equina syndrome, etc.) or signs of infection are present. CT scanning should be performed if any bony structure alteration is suspected. Intravenous contrast is useful mainly in postoperative spine, tumoral lesions, infection or inflammation (myelitis).

Once the decision about the proper technique is taken, it is important to decide the timing of the study (emergent or non-emergent/elective). It will always depend on the clinical status of the patients. An emergent study will
be needed if surgery or radiation therapy must be done immediately, but generally studies of spine can be scheduled in an elective way.

Not all the different techniques are always available in hospitals. That is the reason why it is necessary to know what information each one of them gives and in what situations they are essential.

Conventional plain x-rays continue to be a useful tool, despite the great advance in medical neuroimaging. It is easily accessible, fast and cheap. It does not require complex postprocessing, and the images obtained are easily interpretable. Radiography gives us great information after trauma and in degenerative diseases, showing or excluding pathology, and permitting to intuit the severity of some pathological findings.

Computed tomography and MRI give complementary information to evaluate the column; as we said before, CT is better to study details of cortical bone and MRI is more appropriate to evaluate soft tissues (discs, ligaments, nerves, muscles, fat, CSF and the spinal cord). But both techniques also have some disadvantages. CT uses ionising radiations, produces some artefacts of imaging when there are metallic materials in the region studied, and it is unable to differentiate some tissues in the spine. MRI is not always possible for all the patients; those with ferromagnetic material (some orthopaedic prostheses and screws), pacemakers and some catheters should not go into the machine; people with claustrophobia may not tolerate the study (even with medication); and unstable patients may require some medical support incompatible with the magnetic fields of the machine.

4.1.5.2 Special Characteristics of the Images

Computed tomography uses ionising radiation to generate images resulting from x-ray absorption of each specific tissue examined. CT produces cross-sectional displays and is very useful for examining the spine. It generates images of the body with a very wide range of grey scale.

There are various scales used for CT. The Hounsfield scale (HU) is the most used and it ranges from −1,000 HU to +1,000 HU. Water value is zero, fat is approximately −80 and bone is higher than +60. CT is an excellent technique to distinguish bone from water, fat or soft tissues, but one of its major problems is to differentiate between soft tissues.

In the spine, CT perfectly shows the vertebral bodies containing trabecular bone and how they are surrounded by hyperdense cortical bone. In contrast, MRI shows cortical bone as an area of low signal intensity (black) in all its sequences, so the cortical bone cannot be distinguished from ligaments (also black in all sequences) or CSF on T1-weighted images (T1-WI) [1].

Myelography and myelo-CT have been important techniques of imaging used to diagnose spinal diseases for many years. They are practised after the injection of iodated contrast into the thecal sac. The great advances in neuroimaging with MRI have left the use of these techniques to very limited cases, mainly patients excluded to MRI because of claustrophobia or pacemakers. Other indications could be the demonstration of CSF leaks, or in case of non-diagnostic MRI [2].

In MRI all the tissues play an active role in the process of generating images. Medical MRI relies on the relaxation properties of excited hydrogen nuclei in water and lipids. The hydrogen nuclei produce a useful signal which allows the making up of a diagnostic image of the body.

In order to obtain selectively image voxels (volume picture elements) of the subject, orthogonal magnetic gradients are applied. Although it is relatively common to apply gradients in the principal axes of a patient, MRI allows completely flexible orientations for images. Magnetic gradients are generated by three orthogonal coils, oriented in the x, y and z directions of the scanner. The scanners used in medicine have a typical magnetic field strength from 0.2 to 3 teslas.

The signal intensity of a normal vertebra varies with age. Haematopoietic (red) marrow is hypointense in T1-WI, and becomes hyperintense with conversion from red to yellow bone marrow (8–12 years).

Intervertebral discs also change their signal intensity with age. In children and young adults discs are hyperintense on T2-WI, but with the progressive lost of water become hypointense on T2-WI. The disc degeneration, desiccation and shape changes normally appear after the second decade of life. MRI is also able to distinguish the nucleus pulposus from the annulus fibrosus. The nucleus appears hyperintense on T2-WI, and the annulus fibrosus is seen in the peripheral region with lower signal intensity on T2-WI [3].

On CT, intervertebral discs are homogenous and have a density similar to soft tissues (50–100 HU). Unlike MRI, CT is not able to differentiate the internal architecture of the disc.

4.1.5.3 Guidelines and Technical Standards

4.1.5.3.1 Plain X-rays of the Spine

Radiography of the spine is a useful procedure to initially evaluate the vertebrae, disc spaces, neural foramina and paravertebral soft tissues. The goal of these radiographic examinations is to identify or exclude anatomical abnormalities or disease processes of the spine.

Plain x-rays of the spine have some general indications: pain or limitation of motion, spinal trauma (symptomatic or at risk patients), surgical planning, suspected
malignancy, congenital anomalies and alignment abnormalities (including scoliosis and kyphosis). The examinations should be performed with the minimum radiation necessary to produce diagnostic images [2].

A complete examination of cervical spine should include from the craniocervical junction to the superior end plate of T1. A standard examination includes anteroposterior (AP) and lateral views. Additional evaluation may be needed in some circumstances: bilateral oblique views (to evaluate the neural foramina), flexion–extension lateral views (when assessment of cervical instability is necessary) and open mouth projections.

In thoracic and lumbar spine, a standard examination includes AP and lateral views, and additional projections are both oblique views and flexion–extension lateral views. In lumbar spine it is very important to evaluate neural foramina and facet joints in case of trauma or degenerative disease.

To evaluate patients with scoliosis, erect PA (or AP) views of the entire thoracolumbar spine should be obtained. The erect view should include the iliac crests.

If other previous studies of spine are available, they should be compared. Correlation with CT, MRI or nuclear medicine studies should also be performed when appropriate.

4.1.5.3.2 Computed Tomography of the Spine
Computed tomography provides very good depiction of bone detail. Primary indications for CT of the spine include the study of traumatic, neoplastic, inflammatory and infectious lesions, as well as congenital, deposition and degenerative conditions [2, 4].

Computed tomography of the spine is very important in acute spinal trauma. It may be utilised when radiographs of a spinal segment (cervical, thoracic or lumbar) are abnormal, equivocal or non-diagnostic after a traumatic event. CT can also be utilised for evaluating vertebral compression fractures (acute or chronic) [5].

Computed tomography is an alternative to study conditions such as lumbar stenosis or degenerative disc disease when MRI is contraindicated (e.g. cardiac pacemaker or other implants that are not MR compatible). CT has shown its utility in the evaluation of postoperative patients with bone graft placement for fusion and/or with metallic spinal instrumentation.

Computed tomography protocols require close attention and development by the supervising physician, according to specified indications. It may be performed with a sequential single-slice technique or with single or multidetector helical protocol. Certain clinical indications require the use of intravenous, intrathecal, epidural, perineural or intra-articular contrast agents.

The evaluation of the craniocervical junction and cervical spine requires thin sections for precise diagnosis; the effective slice thickness should be no greater than 3 mm. Also in thoracic and lumbar spine, an effective slice thickness should be less than 3 mm. Diagnostic reformations can be made from these images, obtaining images also in coronal and sagittal planes. For evaluating spine fusion, 1- to 2-mm contiguous slices of the suspected spinal segment will be necessary.

Radiologists, medical physicists, radiological technologists and all supervising physicians have the responsibility to minimise the radiation dose to each patient, while maintaining the necessary diagnostic image quality. This is the concept known as ‘As Low As Reasonably Achievable’ (ALARA) [6, 7].

4.1.5.3.3 Magnetic Resonance Imaging of the Spine
Spinal MRI is one of the most sensitive diagnostic tests to detect anatomical abnormalities of the spine and adjacent structures. It allows direct visualisation of the spinal cord, nerve roots and discs, and is the only modality to evaluate the internal structure of the cord. It is very important to remember that MRI does not use ionising radiation, which is particularly advantageous in the lumbar area where gonadal exposure may occur.

There are many indications for spinal MRI, and we include here those we consider more important [2]:

1. Degenerative disc disease in the lumbar, thoracic and cervical spine
2. Injury of spinal cord, vertebral column, ligaments, and intraspinal and paraspinal soft tissues following trauma
3. Extraluminal soft tissue and bony neoplasms, evaluating nature and extent
4. Intraspinal extramedullary masses
5. Intramedullary tumours
6. Demyelinating and inflammatory diseases of spinal cord
7. Spinal vascular malformations and/or the cause of occult subarachnoid haemorrhage
8. Congenital spinal abnormalities
9. Postoperative intraspinal fluid collections
10. Postoperative intraspinal soft tissue changes
11. Spinal infection, including disc space infection, vertebral osteomyelitis and epidural abscess
12. Preprocedure assessment for vertebroplasty and kyphoplasty

There are a minimum recommended pulse sequences to evaluate the spine in degenerative diseases (pain, radiculopathy or suspected stenosis): in cervical/thoracic spine, sagittal T1- and T2-WI and axial T2-WI must be done. In lumbar spine, sagittal T1- and T2-WI and axial T1- and T2-WI are needed.

When evaluating spinal bone marrow for tumour,
they refer to signal intensity changes in vertebral body

Modic changes are a commonly observed in MRI, and
generative changes of bone marrow, end plates and discs.

ments and soft tissues of the spine.

adults [9]. The degenerative changes arise in bones, liga-
tebrae column is one of the main causes of disability in

The pain produced by degenerative changes in the ver-

1960s by Djindjian and Di Chiro, and nowadays it plays

nerve root compression [13].

The imaging protocol should be designed to cover
the area of clinical interest. In cervical spine, sagittal and
axial images should include from the atlanto-occipital
joints through the C7–T1 intervertebral disc at least. In
thoracic spine, if the entire thoracic spine needs to be
studied, C7–L1 should be imaged in the sagittal plane,
and axial images at each vertebral level. In lumbar spine,
the entire lumbar spine should be studied on the sagit-
tal images (T12–S1), and axial images of at least the low-
est three lumbar discs (L3/L4, L4/L5 and L5/S1). Axial
images through other discs can be obtained as needed.
Sagittal imaging should include the entire lumbar spine,
including parasagittal imaging of all of the neural foram-
ina on both sides.

Remember that, before applying for an MR study, cor-
rect patient selection must be done; individuals who may
be at risk from exposure to the MR environment should
be excluded (patients with a pacemaker, patients with
anxiety or claustrophobia, etc).

4.1.5.3.4 Spinal Angiography

The medullar angiogram was developed in the early
1960s by Djindjian and Di Chiro, and nowadays it plays
an important role in the diagnosis and treatment of arte-
riovenous diseases of spine.

In the cervical region the study must include both ver-
tebrae arteries and cervical arteries. In the thoracic region,
tercostal arteries must be studied by selective catheteri-
sation. The lumbosacral region includes the study of lum-
bar and internal iliac arteries.

4.1.5.4 Imaging in Spinal Disease

4.1.5.4.1 Degenerative Spinal Disease

The pain produced by degenerative changes in the ver-
tebrae column is one of the main causes of disability in
adults [9]. The degenerative changes arise in bones, liga-
ments and soft tissues of the spine.

Magnetic resonance imaging evaluates quite well de-
generative changes of bone marrow, end plates and discs.
Modic changes are a commonly observed in MRI, and
they refer to signal intensity changes in vertebral body

marrow adjacent to the end plates of degenerative discs.
Modic changes take three main forms [10]:

1. Type I change shows a decreased signal on T1-WI and
increased signal on T2-WI. It represents bone marrow
oedema and it is associated with an acute process.

2. Type II is the most common type and consists of in-
creased signal on T1-WI and isointense or slightly hy-
perintense signal on T2-WI. It represents fatty degener-
ation of subchondral marrow and is associated with a
chronic process.

3. Type III consists of a decreased signal on both T1-WI
and T2-WI. It represents extensive bony sclerosis.

Intervertebral disc degeneration begins at the end of
adolescence, with dehydration, lost of height and pro-
gressive protrusion. A degenerated disc in MRI appears
hypointense on T2-WI images while CT is only able to
show diminution of its height. The rupture of the annulus
fibrosus produces the bulge of material disc towards the
vertebral channel, beyond the vertebral body margins.

A diffuse posterior disc bulging is defined as a broad
and symmetrical extension of the disc material into the
spinal canal. Herniation is a focal or asymmetrical exten-
sion of disc material into the spinal canal and/or the neu-
ral foramen (posteroentral, posterolateral or lateral her-
niation) [11]. Protrusion and extrusion are subcategories
of herniation (protrusions are more broadly based against
the parent disc, while in extrusions the base is often nar-
rower than the extruded disc fragment) [12].

Myelo-CT may show the compression of thecal sac in
degenerative disc disease, but MRI is the diagnostic mo-
dality of choice to evaluate disc herniations, with high
sensitivity for demonstrating the presence of thecal sac or
nerve root compression [13].

4.1.5.4.2 Spinal Infection

A pyogenic osteomyelitis is a bacterial infection of verte-
bral body and intervertebral disc. *Staphylococcus aureus*
is the most common pathogen and it affects initially the
discs, unlike tuberculosis, which usually begins in the
vertebral body.

The imaging findings we can see are narrowing of the
disc space, loss of cortical end plate, alteration of struc-
ture of bone marrow and vertebral collapse.

Radiography is frequently negative until 2–8 weeks af-
after onset of symptoms. CT may show alteration of cortical
bone in vertebrea or affection of paraspinal soft tissues.

Magnetic resonance imaging is better than CT in de-
lineating the extent and stage of the spinal infection, and
it provides the precise information to decide if surgery
is needed. MRI perfectly shows the narrowing of inter-
vertebral disc (hypointense on T1-WI and hyperintense
on T2-WI), the alteration of vertebral bone marrow (hy-
pointense on T1-WI and hyperintense on T2-WI, STIR
and fat-saturated T2 sequences) and the formation of paraspinal or epidural abscesses (with rim enhancement) [14, 15].

4.1.5.4.3 Spinal Neoplasms
The most important information needed to make a correct differential diagnosis of an intraspinal mass is its precise anatomical location (intramedullary, extramedullary, intradural or extradural) [16, 17]. This information is essential for planning the treatment of the patient, and MRI is particularly good for this task (frequently supplemented with intravenous administration of gadolinium).

Some extradural neoplasms are bony metastases, haemangioma, osteoid osteoma, osteoblastoma, chordoma, plasmacytoma, multiple myeloma and others.

Spinal metastases are the most common extradural masses, and usually appear as multifocal lytic or blastic lesions of the vertebral body. MRI is the best method of investigating and defining spinal metastatic disease because it demonstrates the presence and extent of bony involvement and evaluates the paravertebral and epidural extension, with the degree of neural compromise.

Intradural and extramedullary tumours may be meningioma, nerve sheath tumours (schwannoma, neurofibroma) and CSF-disseminated metastases. Spinal meningiomas have identical histology to intracranial ones, and appear isointense on T1- and T2-WI. They enhance after administration of intravenous gadolinium and a dural tail may be seen. Schwannomas and neurofibromas both originate from Schwann cells, but have different aspect and histology. Schwannomas are well-circumscribed round or dumbbell shaped, with a normal size of a few millimetres and have intense enhancement with gadolinium. Neurofibromas are frequently bulky multilevel masses, poorly defined and with a variable enhancement pattern.

The main intramedullary neoplasms are gliomas, either ependymoma or astrocytoma. Ependymomas arise from ependymal cells in the central canal of spinal cord. They are isointense on T1-WI, hyperintense on T2-WI and enhance homogenously. A subtype frequently found in conus medullaris is myxopapillary ependymoma, which is histologically benign and has a good prognosis. Astrocytomas are infiltrating masses which usually affect multiple segments and expand the spinal cord. They are isointense on T1-WI, hyperintense on T2-WI and strongly enhance with contrast.

4.1.5.4.4 Spinal Trauma
Conventional radiography, CT and MRI may be used in the diagnosis of acute spinal trauma. The first technique should be radiography (plain x-ray), and if it shows pathological findings or if there is any doubt CT or MRI must be done [18].

Bony lesions are better diagnosed with CT because we can perfectly see any alteration in cortical bone with thin axial images and also obtain complementary information with three-dimensional reconstructions. MRI is a better tool for assessing the integrity of the ligaments, spinal cord and soft tissues after trauma. MRI may help determine the stability of the vertebral column and decide if surgery is needed. Epidural haematomas and intrinsic cord damage are particularly well depicted by MRI.

After a spinal trauma, the first goal should be evaluation of deformations in vertebral bodies. The four vertical lines of spine must be studied (anterior border of vertebral body, posterior border of body, the posterior line of neural canal and the line across the tip of spinous processes). A simple change in one of them indicates the presence of lesions in bones, discs or ligaments. Lateral radiography of spine and CT are good tools for this initial evaluation.

Lesions of intervertebral discs usually appear as narrowing of the disc space, and MRI may show signal intensity alteration on T1- and T2-WI.

As we said before, MRI has been demonstrated to be the best technique to diagnose spinal cord pathology after trauma [19]. We can see lesions such as contusions (with oedema and/or haemorrhage), post-traumatic syringomyelia or even spinal cord herniation. Contusions are usually hypointense on T1-WI and hyperintense on T2-WI, and typically expand the spinal cord.

Post-traumatic compressions of the cord (by bone fragment, disc herniation or epidural haematomas) are also well recognised by MRI. But in cases of spinal fracture it is strongly recommended to carry out a CT scan to localise bone fragments in the neural canal, which could be decisive to clarify if surgery is needed or not.

Do not forget that spinal trauma with isolated ligament lesions may be very dangerous, because they can affect the stability of the column. MRI is the best modality to see these structures, which appear hypointense on T1- and T2-WI in normal conditions.

4.1.5.4.5 Spinal Vascular Lesions
Spinal cord vascular malformations are a wide group of vessel disorders that affect the spinal cord parenchyma either directly or indirectly. There are spinal arteriovenous malformations (AVMs), dural arteriovenous fistulas (dAVFs), spinal haemangiomas, cavernous angiomas and aneurysms. MRI and angiography have provided further insight into the anatomy and pathophysiology of these lesions.

In 1992, Anson and Spetzler classified spinal cord vascular malformations into the following four categories:
1. **Type 1: dural arteriovenous fistula.** It is the most common type (80%). The fistula presents within the dura and has intradural distended draining veins. Patients become symptomatic when the AVF creates venous congestion and hypertension, resulting in hypoperfusion of the spinal cord. On MRI we can see flow voids and areas of cord with hyperintense signal on T2-WI.

2. **Type 2: intramedullary glomus AVM.** It is a compacted group of arterial and venous vessels (nidus) inside a short segment of the spinal cord. The localisation is frequently cervicodorsal. MRI shows T2 hyperintensity in cord (oedema, gliosis or ischaemia) or mixed signal produced by haemorrhage.

3. **Type 3: juvenile AVM (intramedullary-extramedullary).** There are direct arterial/venous communications without capillary bed involving the cord. They are extensive lesions with abnormal vessels that can be both intramedullary and extramedullary in location. These lesions are typically found in young adults and children. MRI shows T2 hyperintensity in cord (oedema, gliosis or ischaemia).

4. **Type 4: intradural-extra/perimedullary fistula.** It is localised on the surface of the cord. There is a direct arterial/venous communication between spinal artery to spinal vein without an interposed capillary bed.

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4.2 Spinal Tumours

4.2.1 Pathological Anatomy

GERHARD MARQUARDT, RÜDIGER GERLACH, AND VOLKER SEIFERT

According to their topographical relationship to dura mater and spinal cord, spinal tumours are generally classified as extradural, intradural extramedullary, and intradural intramedullary.

Extradural tumours, accounting for approximately 65% of all spinal tumours, are further subdivided into primary and secondary lesions. Primary tumours of the spine comprise benign lesions, such as osteochondromas, osteoid osteomas, osteoblastomas, haemangiomas, giant cell tumours, eosinophilic granulomas and aneurysmal bone cysts, and malignant lesions, including tumours such as osteosarcomas, Ewing’s sarcoma, multiple myelomas, solitary plasmocytomas, chordomas and chondrosarcomas. Since these primary lesions of the bone are less common than secondary tumours of the spine and in addition are rarely encountered in neurosurgical patients, they shall be mentioned here only in brief, and the appropriate orthopaedic textbooks and publications must be consulted for further information.

Secondary extradural tumours are approximately 40-fold more common than primary lesions. The spine is the most common site of skeletal metastases, and metastases from various primary cancers are the most frequent type of both extradural and malignant lesions affecting the spine. Although spinal metastases may arise virtually from any carcinoma, the most frequent spinal metastases (60%) are caused by breast, lung or prostate cancer.

Intradural extramedullary tumours account for approximately 30% of all spinal tumours, and meningiomas and neurinomas (schwannomas) constitute the vast majority of these lesions with about 45% of each. The remaining 10% consist of a great variety of different entities such as dysembryogenic tumours (dermoids and epidermoids), metastases, lipomas or arachnoidal cysts. Anatomically the ependymoma of the filum terminale is also an intradural extramedullary tumour.

Intradural intramedullary tumours are rare lesions comprising about 5% of all spinal tumours in adults. They are mainly of glial origin and are ependymomas and astrocytomas of both benign and malignant histopathology. Whereas ependymomas are the most common intramedullary tumours in adults, astrocytomas are more common in children and adolescents. Moreover vascular lesions such as haemangioblastomas or cavernomas are found. Tumours such as primary glioblastoma multiforme or intramedullary metastases are exceptionally rare.

4.2.2 Epidemiology

Seventy to 85% of all patients with a known carcinoma will develop skeletal metastases of which 30–70% will entail spinal involvement. About one third of the patients will harbour multiple lesions at non-contiguous levels. It is estimated that 5–10% of cancer patients develop symptomatic spinal metastases. Approximately 85% of these are caused by cancers originating from breast, lung, prostate, thyroid gland and kidney.

The incidence of spinal meningiomas is estimated to vary from 0.5 to 2 per 100,000 people annually. The real incidence, however, is most probably higher as many tumours may remain asymptomatic during lifetime owing to their low speed of growth. Spinal meningiomas are tumours of the elderly with their greatest incidence between the sixth and eighth decades. There is a clear female preponderance with a female to male ratio of about 4:1.

Spinal neurinomas feature roughly the same incidence as spinal meningiomas in Western populations but in Asian populations the ratio of spinal neurinomas to spinal meningiomas is estimated to be 4:1. Younger individuals are favoured, and the mean age at presentation is 40 years. Men and women are affected equally. Spinal neurofibromas are encountered mainly in patients with neurofibromatosis.

Intramedullary tumours are rare lesions. Spinal ependymomas most commonly occur in the fourth decade, and sex distribution is equal in most of the published series. It seems, however, that myxopapillary tumours have a slight male predominance with a female to male ratio of 1:1.7. Spinal astrocytomas represent 30–40% of all intramedullary tumours in adults and 70% in childhood. Spinal haemangioblastomas account for approximately 4% of intramedullary tumours. They are characteristic of von Hippel–Lindau syndrome, an autosomal dominant hereditary disorder. Ten per cent of these patients harbour multiple lesions.
**4.2.3 Clinical Symptomatology**

Small benign spinal tumours may be completely asymptomatic for a long time. They may be discovered by chance during a neuroradiological work-up done for other reasons and then have to be considered as an incidental finding. Sooner or later, however, as the tumour grows, it normally will compress adjacent neural and vascular structures leading to symptoms and signs that are directly attributable to the tumour itself. The clinical symptomatology of spinal tumours is dependent, on the one hand, on the topographical relationship of the lesion to spinal cord and spinal roots and, more importantly, on the other hand, on the location of the lesion in the craniocaudal direction determining the level of neurological impairment.

Most of the patients harbouring a spinal tumour will complain of a diffuse dull pain that is constantly increasing and localised to the spine. Most probably this pain is due to a regional impediment of venous outflow caused by the compressive effect of the tumour resulting in swelling of the spinal cord. In particular, with intramedullary tumours the pain may be worse at night or upon awakening and is relieved during physical activity.

As an extradural or intradural extramedullary tumour gains contact with nerve roots, pain of a burning or fulgurant character may develop irradiating radicularity into the arm, zonalarly into the trunk or radicularity into the leg, depending on the actual location of the tumour in the cranio-caudal direction. Quite frequently this radicular pain is accompanied by painful dysesthesias such as prickling sensations and formication. On further tumour growth the compressive effect on the nerve root may increase and beyond the above-mentioned irritating symptoms neurological deficits by means of hypeaesthesia and paresis in the distribution area of the respective nerve root may develop similar to degenerative disorders of the spine.

Apart from unspecific and radicular symptoms and signs the most striking feature of spinal tumours, however, is medullar involvement with functional disturbance of its long tracts. With regard to sensibility the patients will experience an abnormal sensation below the level of the lesion with hypeaesthesia, decreased touch, pain and/or temperature sensation, and disturbance of proprioception. Whereas extramedullary tumours of extradural and intradural localisation most often are characterised by ascending symptoms, intradural intramedullary lesions feature descending symptoms. Additionally patients do not infrequently exhibit a sensory dissociation in terms of a Brown–Séquard syndrome. Involvement of the posterior column of the spinal cord entails ataxia that may be pronounced in such a way that the patient is unable to walk despite absence of paresis.

Increase of the mass effect of the tumour onto the spinal cord will lead to hyperreflexia with a positive Babinski sign, increased muscle tone below the level of the lesion, clonus and spasticity. The most striking medullary sign, however, is motor weakness that will manifest as paraparesis in cases of a thoracic or lumbar lesion and as tetraparesis in the event of a cervical tumour. Motor function is usually assessed according to the muscle strength grading as outlined before in Sect. 4.1.4.2.2.3. Thereby a motor grade of not less than 4 is a precondition for gait function. As a late finding of palsy, muscle atrophy might become apparent.

Later symptoms and signs of medullar involvement are also associated with vegetative dysfunction. Bladder and bowel disturbances are seldom missed, with urinary and faecal incontinence or retention as most common signs.

It is noteworthy that there is no strict positive correlative between the clinical symptomatology and the size and expansion of a tumour within the spinal canal. It is not unusual to see a patient presenting with only mild symptoms and signs but who harbours a huge meningioma that takes up nearly the entire spinal canal resulting in a marked compression of the spinal cord that is displaced laterally and deformed in a shell-like manner. And vice versa there is a considerable number of patients who present with a spinal metastasis exerting apparently only moderate compression onto the cord but who exhibit neurologically a pronounced paraparesis. Of significance in this context is the speed with which the spinal tumour grows. Patients with benign spinal lesions such as meningiomas, neurinomas or certain intramedullary tumours most often experience symptoms that are slowly progressive over months or even years until the correct diagnosis is made due to the slowly increasing compressive effect of the tumour onto the neural structures. By contrast fast-growing tumours, such as most of the malignant lesions, will entail symptoms and signs that rapidly evolve within days or at most a few weeks.

A particular case is given in the event of a sudden loss of neurological function. This might be due to a haemorrhage within the tumour leading to abrupt interruption of the tracts of the spinal cord, as may happen for instance in ependymomas or cavernomas. The more frequent occurrence, however, and even observed in slow-growing lesions, is the development of an ischemia or infarction within the spinal cord. Functional prognosis is questionable in such a case.

**4.2.4 General Principles of Surgery on Spinal Tumours**

Surgical resection of spinal tumours is performed with the patient under general anaesthesia. Because of its
rapid onset and emergence continuous total intravenous anaesthesia (TIVA) is preferred. During maintenance of narcosis muscle relaxants should be avoided since they would interfere with intraoperative neurophysiological monitoring (IOM).

To monitor function of the sensory and motor pathways during the course of surgery, IOM with recordings of motor-evoked potentials (MEPs) and somatosensory-evoked potentials (SSEPs) has proved to be a valuable real-time tool. Even though surgery for extradural tumours might be performed without such a measure, it is indispensable to our point of view in cases of intradural and above all intramedullary lesions. Additionally D-wave recordings allow for prediction of postoperative motor status.

Even though there is no scientific proof of its effectiveness, many neurosurgeons administer corticosteroids intraoperatively (e. g. 40 mg dexamethasone i. v.) in order to decrease spinal cord compromise due to vasogenic oedema caused by the tumour and by the operative manipulation of the spinal cord itself. Postoperative application of corticosteroids (e. g. 3 × 4 mg dexamethasone p. o.) should be limited to a couple of days, however, since prolonged use of steroids may be associated with hyperglycaemia, immunosuppression and, above all, gastric ulceration. Thus, all patients treated in such a manner should receive gastric protection with high-dose antacids.

Since the majority of spinal tumours are approached from behind, the patient commonly is placed in a prone position. In order to prevent damage due to pressure special care must be taken during positioning of the patient to pad thoroughly all those parts of the body that are prone to pressure, eyes, nose, elbows, knees, etc.

Using a dorsal approach to the spinal column, a laminectomy is usually performed after radiographic confirmation of the correct spinal level (Fig. 4.2.1). In smaller sized lesions that are localised more laterally it may be sufficient to restrict the approach to a hemilaminectomy or even partial hemilaminectomy. In any case the bony defect must be fashioned in an adequate size to visualise healthy tissue above and below the tumour. If a multilevel approach is necessary to achieve this goal, and this particularly applies to the lumbar and cervical region, a laminotomy should be performed instead of a laminectomy to avoid postoperative instability and kyphosis. In doing so a complex consisting of laminae, spinous processes and interspinous and supraspinous ligaments is removed temporarily and reinserted after tumour removal fixing it with miniplates or sutures (Fig. 4.2.2a–c).

In the event of an extradural tumour, removal is started after adequate exposure of the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affected spinal level, and resection is performed piecemeal. Care must be taken not to exert undue pressure onto the affect...
of nerve roots and spinal cord resulting in neurological compromise with pain and paresis as the most common presenting complaints. Pain related to spinal metastases is beyond that caused by stretching of the abundantly nerved periosteum and by invasion of the paravertebral soft tissue. Additionally acute exacerbation of pain may originate from pathological fracture of the affected vertebral body as may acute tetra-/paraparesis. Due to improved survival of cancer patients the incidence of spinal metastases is expected to increase. This is of considerable importance with regard to quality of life since, despite increasing clinical awareness, loss of gait function continues to occur in over half of the affected patients. As a consequence the most important benefits which may result from treatment of these lesions are abatement of pain and maintenance or restoration of gait function.

In the diagnostic work-up of patients harbouring spinal metastases usually several radiological imaging modalities are implemented. In contrast to other spinal tumours, plain x-ray studies of the spine constitute an important part in this connection. They offer a good overview and thus provide essential information of the extent of metastatic spread to the spine permitting secondary conclusions about the state of the underlying disease. They are helpful in the detection of pathological fractures and normally allow for differentiation between osteolytic and osteoblastic tumours. Further they are of utmost value regarding the assessment of spinal malalignment, instability and the degree of axis deviation. CT scans are useful to demonstrate the displacement of the contents of the spinal canal and the extension of paravertebral invasion. More vital, though, are CT scans obtained in the bone window since they show the degree of bony destruction and provide essential information of the structure of bone and pedicles, data that are indispensable if spinal stabilisation is considered. The most important imaging modality, however, is MRI permitting display of the entire spine in the sagittal, coronal and axial plane. Hence it reveals, apart from the actually symptomatic site, all other spinal levels involved and gives essential information about the extension of contiguous and non-contiguous tumour spread. Furthermore the precise size of the metastasis and its intraspinal and paravertebral expansion are appreciated most reliably. It provides moreover best visualisation of spinal cord compression and, as no other imaging modality does, the potential presence of intramedullary signal changes in terms of a myelopathy.

The concept of treatment for extradural spinal metastases has undergone considerable changes during the last two decades, and significant advances regarding all treatment options available, i.e. radiation, chemotherapy and surgery, have been achieved. However, even though these advances have prolonged the survival of the cancer patient, treatment for spinal metastases is still virtually

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**Fig. 4.2.2a–c** Multilevel laminotomy. a Temporarily removed complex consisting of laminae, spinous processes, and interspinous and supraspinous ligaments. b Reinsertion and fixation after tumour removal. c Postoperative x-ray
always of a palliative character. If surgery is required this measure only can be regarded as a single part within the framework of a multidisciplinary oncological approach, and a shared decision involving all disciplines concerned is mandatory to offer what is considered best for the individual patient.

Bearing in mind the most important goals of surgery performed for spinal metastases, i.e. abatement of pain, preservation or restoration of gait function, and maintenance of an independent status as long as possible where the patient is not hospitalised, surgery is indicated whenever this aspired clinical status is jeopardised. This means that surgery is indicated in the event of compression of neural tissue, instability and progressive deformity. In a final stage of the underlying disease, surgery may also be requested for nursing reasons. And surgery may be indicated in case of a pathological fracture where kyphoplasty or vertebroplasty is considered to be improper to restore stability and to relieve pain. Whenever operative measures are necessitated they should be carried out before irradiation, however, since surgery performed after irradiation has a considerably higher rate of complications.

One issue in this connection, however, is scarcely covered in the pertaining literature and is still a matter of dissent, and that is the question of when to perform surgery. Should it be performed directly after admission of the patient as an emergency case, or is it sufficient to schedule surgery the next day(s) after appropriate preparation of the patient (deferred urgency)? In our opinion timing of surgery depends above all on the acuteness of neurological compromise. In the event of rapid neurological deterioration or spinal instability with imminent paresis, our strategy is to perform surgery directly after admission, i.e. without delay, irrespective of time of day, and even during night duty. Emphasising our point of view we are aware, though, that such an attitude is not supported by all surgeons. There are not few who, as a matter of principle, do not perform surgery during the night and schedule it the next day(s), a proceeding we would favour exclusively in subacute or chronic cases with slowly evolving paresis.

If surgical measures are indicated the most straightforward method should be chosen. In the event of metastatic involvement of the occipitocervical junction with impending or already verifiable horizontal or subaxial instability this is dorsal craniocervical stabilisation. For this the use of the Ransford loop has proved to be of outstanding value. Due to the instability of the spine, dislocation is imminent and consequently the utmost care must be taken during handling and preparation of the patient in order not to evoke or worsen a neurological deficit. Hence IOM should be implemented from the very beginning, and general anaesthesia should be induced using fibre optic bronchoscopy. Once the patient is intubated, skeletal traction is applied. Then the patient is positioned in a semi-sitting or prone position. Via a midline approach, the occipital bone and laminae of the upper and middle cervical spine are exposed. Using bilateral sublaminar wires the device is fixed to the cervical spine whereas the cranial part of the loop is anchored within the occipital bone using screws (Fig. 4.2.3a). This proceeding results in a solid occipitocervical fixation. Alternatively craniocervical stabilisation can be carried out with lateral mass screws (Cervifix system) (Fig. 4.2.3b). In the event of pure atlantoaxial instability, C1/C2 fixation is done with sublaminar wiring that is augmented with bone (Brooks technique, Gallie technique), methylacrylate and/or transarticular screws (Magerl technique).

In the middle and lower cervical spine (C3–C7, Fig. 4.2.4a) the anterior approach with anterior decompression and reconstruction is the most effective way to resolve neural compression and spinal instability. For this the patient is placed in a supine position. After fluoroscopic identification of the involved level a transverse skin incision is performed just above this level and the platys-
Spinal Tumours

The spine is approached by use of fluoroscopy. In most of the cases the affected vertebra is easily identifiable due to bulging, discoloration and reduced consistency. The longus colli muscle is detached and retracted laterally with a self-retaining spatula. To facilitate resection of the vertebral body the adjacent vertebral discs are excised first. Then the vertebral body is resected with drill, curettes and removers. In doing so, care must be taken in the lateral direction to avoid injury to the vertebral artery which may be en-circled by tumour, a circumstance in which complete tumour resection may turn out to be unfeasible. To warrant appropriate decompression of spinal cord and nerve roots the posterior longitudinal ligament should be removed as well in order to visualise the dura. Upon completion of resection, stabilisation is carried out with vertebral body replacement by use of a cage that appropriately bridges the gap and that is secured by additional ventral plating (Fig. 4.2.4b).

In the thoracic and lumbar region the mainstay of operative treatment for spinal metastasis has been for a long time posterior decompression with laminectomy, a procedure that is still applied in numerous facilities providing care of these patients. The popularity of such a proceeding is based on the facts that it is an easy, straightforward and quickly performable procedure that in addition bears only low risks for the patient and does not require complex reconstructive measures of the spinal column. And indeed, in most of the cases short-term outcome is favourable with relief of pain and retrieval or restoration of gait function. The efficacy of this kind of surgery is largely lost, however, with regard to the medium-term outcome of the patients. The reasons for this unfortunate experience are found in the answer to the question: What actually can be achieved with laminectomy? As a matter of course it is feasible to obtain tissue to make a diagnosis. But since the major part of the tumour lies mostly ventral to the spinal cord a significant mass reduction is not feasible without retraction of the cord. This, however, is unjustified as it bears the significant risk of substantial neurological worsening. Hence, decompression is only possible dorsally and laterally. As a consequence the spinal cord can shift dorsally resulting in reduction of the pressure exerted onto the cord by the ventral tumour. This explains the short-term amelioration of neurological dysfunction attained with laminectomy. Since such a measure does not have any impact on the bulk of the tumour, though, it will continue to grow leading expeditiously to increasing compression of the cord and relapse of neurological deficit. Such a course may be protracted, of course, by concomitant treatment with radiation and/or chemotherapy. However, there are several clinical studies that could show that in a considerable number of patients mere posterior decompression did not yield better clinical results than radiation therapy alone. Another fact against mere dorsal decompression has to be mentioned. A laminectomy is indispensably associated with the removal of healthy dorsal elements of the spine that provide for its stability. Consequently mere
laminectomy may cause or worsen spinal instability that might be followed by deformity resulting in more pain and neurological deficit. Since this is a mechanical issue it will not be attenuated by any concomitant therapy but requires mechanical measures. Taking into account all the above considerations it becomes obvious that mere posterior decompression does not yield a long-lasting positive effect. As a result many neurosurgeons nowadays perform posterior decompression in combination with internal dorsal fixation by use of pedicle screws. Such a measure provides far better clinical results with regard to neurological recovery and pain control, and several clinical studies have demonstrated the superiority of such a strategy.

A more radical concept of treatment for extradural spinal metastases that has emerged in recent years is circumferential spinal cord decompression. The purpose of this kind of procedure is to perform a 360° decompression of the spinal cord and to relieve it from all surrounding compressive tumour tissue. In numerous cases this goal can be achieved merely from behind. Using a posterolateral transpedicular approach or costotransversectomy, dorsal decompression, vertebral body resection and vertebral body replacement with a tailored cage device are followed by immediate dorsal stabilisation. In other cases, however, a combination of a dorsal and an anterior approach to the spine is required to achieve this goal. Whereas some neurosurgeons perform the anterior procedure in terms of a transthoracic or retroperitoneal approach independently we prefer to seek assistance of a well-versed thoracic or abdominal surgeon in these circumstances. It must be emphasised that patients harbouring spinal metastases originating from kidney or thyroid gland should undergo preoperative embolisation of these hypervascular tumours in order to minimise intraoperative blood loss (Fig. 4.2.5). In the majority of cases it is posterior decompression and stabilisation that is performed first. Upon completion of this step of surgical treatment the patient is turned and surgery proceeds from anterior. After adequate exposure of the affected vertebral body it is resected, and the dura is freed from all compressive parts of the tumour. Ventral stabilisation is carried out by use of an expandable cage. Instead of a one-stage procedure it is also possible to perform a two-stage procedure if considered advantageous (Fig. 4.2.6).

Fig. 4.2.5a,b Spinal metastasis originating from kidney. a Spinal angiogram. b Angiogram after embolisation of the hypervascular tumour

Accounting for approximately 45% each, meningiomas and neurinomas are the most common intradural extramedullary tumours. As a result they are of particular relevance to the neurosurgeon and, thus, shall be treated here exclusively as most important representatives of this kind of tumour. In fact ependymomas of the filum terminale also form part of the group of intradural extramedullary tumours, but shall be treated together with intramedullary ependymomas for didactic reasons and considerations of coherency (see Sect. 4.2.7).
Spinal meningiomas are usually slow-growing, benign tumours. Even though malignant transformation may occur, high-grade meningiomas are rather rare. Owing to the slow speed with which the tumours grow, spinal meningiomas can quite frequently reach a considerable size before they become symptomatic and a correct diagnosis is made.

Spinal meningiomas are supposed to arise from arachnoidal cells and may develop all along the spinal axis. The most common localisation, however, is the thoracic spine where 60–80% of all spinal meningiomas are found. As meningeal tumours they have a dural attachment that is ventrolateral in about 40% of all cases, ventral in 7.5%, and lateral, dorsolateral or purely dorsal in the remainder. As a matter of course the very localization of dural attachment has a great impact on surgical strategy. Usually spinal meningiomas are fleshy, purple, soft, hypervascular tumours that are not or only slightly adherent to the spinal cord (Fig. 4.2.7a). Some tumours, however, have a rather whitish aspect and then most commonly are less vascular, hard and even calcified. This kind of spinal meningioma most commonly features significant adherence to the spinal cord. It also may break through the dura resulting in extradural tumour extension, a condition that is found in about 5% of all patients.

The method of choice for diagnosis of spinal meningiomas is MRI. It provides among others things exact information about the spinal level involved, the size of the tumour, its localisation within the spinal canal, its dural attachment, the extent of spinal cord compression and further information about the spinal cord itself (e.g. potential presence of myelopathy). Usually spinal meningiomas are isointense to the spinal cord on T1- and T2-weighted images but show a most often homogenous enhancement with Gd-DTPA (gadolinium, Fig. 4.2.7b, c). As meningeal tumours they have a broad contact to the dura with tapering edges known as the dural tail. This sign may help to differentiate spinal meningiomas from spinal neurinomas, the most important differential diagnosis. However, even though these two tumour entities can usually be distinguished it is noteworthy that an absolutely reliable differentiation is still not possible with imaging techniques.

The aim of surgery is decompression of the spinal cord and gross total resection of the tumour without damaging the cord and evoking (additional) neurological deficit. In the vast majority of cases this surgical goal can be achieved using a dorsal approach. Usually a laminectomy is performed exposing the dura of the affected spinal level(s). The dura is opened longitudinally in the midline, and its margins are tacked laterally. After visualisation of the tumour the arachnoid is opened directly over it. Cottonoids are placed over the spinal cord to protect it from inadvertent injury as well as at the superior and inferior edges of the tumour in order to minimise the amount of blood seeping into the subarachnoid space. Then the surface of the tumour is cauterised with bipolar forceps. Detachment of the tumour is started if its dural attachment is dorsal, lateral or ventrolateral. In doing so tumour feeding vessels are occluded and dissected resulting in improved haemostasis. If the attachment of the tumour is ventral, however, its detachment is not possible this way without substantial displacement of the spinal cord that would be harmful to function. In these cases it is necessary that
4.2.6 Intradural Extramedullary Spinal Tumours

the dorsal approach is extended more laterally in order to gain a more oblique approach to the tumour and its dural attachment to avoid undue spinal cord manipulation. Generally spinal meningiomas are entered and debulked internally meaning a piecemeal resection. As the centre of the tumour is removed it collapses somewhat and more space is gained to mobilise the tumour. Concerning tumours localised dorsally or laterally to the spinal cord the tumour–spinal cord interface can be dissected free completely and the tumour removed entirely. Regarding tumours localised ventrally or ventrolaterally, gentle traction is applied to the tumour, and as spinal meningiomas are usually not tightly adherent to the spinal cord it is possible most often to pull them out under the spinal cord continuing piecemeal resection. If, regardless of its spatial relationship to the spinal cord, the tumour is hard and calcified, however, featuring significant adherence to the spinal cord, gross total resection of the tumour may prove to be unfeasible without incurring the substantial risk of spinal cord injury. In these cases decompression of the spinal cord is performed as far as justifiable, and a small layer of tumour adherent to the cord is left behind. Upon completion of the tumour removal, its dural attachment usually is scraped off and cauterised meaning a Simpson grade II resection. Complete excision of the dural attachment and insertion of a dural patch with watertight sutures resulting in a Simpson grade I resection is feasible in only a few cases.

Outcome after removal of spinal meningiomas is generally good. Complications are few and mainly encompass CSF leakage and wound infection.

Spinal neurinomas are also slow-growing, usually benign tumours and may reach a considerable size, too. They mostly emerge as single lesions, but are multiple in patients with neurofibromatosis and then, not infrequently, may show malignant transformation. Neurinomas are solid, sometimes cystic, roundish, yellowish, well-circumscribed tumours (Fig. 4.2.8a) that arise from the nerve root, mostly from its posterior portion. Due to their origin spinal neurinomas are localised juxta- medullary. Neurinomas may also grow, however, through the intervertebral foramen thus forming an intra-extradural dumbbell-shaped tumour, an entity that is distinct from purely intraspinal lesions. Neurinomas are found with an equal distribution all along the spinal axis. The method of choice for diagnosis of spinal neurinomas is MRI in which they appear as roundish lesions showing with moderate gadolinium enhancement (Fig. 4.2.8b). In cystic lesions, the centre is hypointense (Fig. 4.2.8c); in cases of dumbbell-shaped tumours, the respective intervertebral foramen is enlarged.

The goal of surgery is decompression of the spinal cord and complete resection of the tumour which in the event of purely intraspinal neurinomas is usually less demanding than resection of a meningioma. Since spinal neurinomas typically are located laterally to the spinal cord most often a limited surgical approach by means of a hemilaminectomy or even partial hemilaminectomy is sufficient to expose it entirely. The opening of dura and arachnoid follows the same surgical principles as outlined above. The most striking feature of spinal neurinomas on visualisation of the tumour is that it ‘swims’ within the spinal canal, i.e. that it has no attachment to dura or arachnoid and can easily be moved to and fro. Typically one fascicle of the affected nerve root enters into the tumour above and leaves the tumour below. Resection of the tumour consists of sharp dissection of this fascicle and thus the tumour most often can be resected in toto (Fig. 4.2.8d). If the lesion is larger and can not be pulled out without exerting pressure onto the spinal cord, the tumour is divided sharply and removed in several portions. In the event of a dumbbell-shaped tumour (Fig. 4.2.9) the surgical approach naturally has to be adapted to the size and extension of the tumour. For this the bony resection has to be extended more laterally in order to unroof the intervertebral foramen, and in the thoracic region resection of the head of the rib may be required for adequate exposure. Most often it is feasible to remove dumbbell-shaped tumours entirely in one procedure from behind. In very rare cases, however, with extreme lateral extension of cervical tumours, e.g. some 5 cm from the lateral
experience that in the majority of patients with dumbbell-shaped tumours severing of the affected nerve root interestingly does not evoke a new postoperative deficit. In some patients, however, and this mainly applies to dumbbell-shaped tumours of the cervical region, sacrifice of the affected nerve root is associated with postoperative loss of radicular function.

dural margin, it is advisable to restrict bony resection in order to prevent postoperative instability. In these cases it is advantageous to confine tumour resection to the mass within the foramen and to remove the residual tumour by means of a second-stage procedure using an anterior approach a couple of days later.

Outcome after removal of purely intraspinal neurinomas is excellent. Moreover it is a common neurosurgical

Fig. 4.2.8a–d  Spinal neurinoma. a Intraoperative aspect. b, c T2-weighted sagittal (b) and T1-weighted gadolinium-enhanced axial (c) MR images. d Tumour resected in toto
Intramedullary Tumours

Ependymomas are the most common intramedullary tumours in adults. They arise from the ependymal cells of the central canal and appear as two different histological variants, epithelial type and myxopapillary type. Owing to their origin, intramedullary ependymomas develop centrally within the spinal cord, extend most often more dorsally, and thus may even reach the surface of the spinal cord. They may grow anywhere within the spinal cord but the most frequent tumour location is the cervical and upper thoracic spinal cord. Due to their slow growth they may attain a considerable size and not uncommonly spread over several spinal segments. The tumour has a purple to grey aspect and is frequently associated with a cyst that is most often localised above its solid part; a cyst at the caudal pole of the tumour is less common (Fig. 4.2.10). Diagnosis is made by use of MRI in which ependymomas appear as well-circumscribed intramedullary solid tumours that are hypointense on T1-weighted and hyperintense on T2-weighted images showing a somewhat heterogeneous gadolinium-enhancement coupled with a non-enhancing cyst. Since ependymomas are not very invasive and just displace the cord as they grow, they are amenable to surgical resection.

The goal of surgery is gross total resection of the tumour. Since for the most part a multilevel approach is necessary a laminotomy should be performed in cases of cervical tumours. After adequate exposure of the dura it is opened in the midline, and the surface of the spinal cord is inspected. In cases in which the tumour is present on the surface the pia is opened directly over it, otherwise the spinal cord is incised in the midline between both posterior columns. Using gentle retraction dissection proceeds into the depth giving sight of the tumour.
The spinal cord is split longitudinally along the entire extension of the tumour, and with it cystic formations if present help to identify the cranial and caudal margins of the tumour. The tumour is then debulked internally, and in doing so some neurosurgeons prefer to use an ultrasonic aspiration device. As the centre of the tumour is removed, the most vital subsequent surgical step is to define the tumour–spinal cord interface. Once an appropriate dissection plane between tumour and normal parenchyma of the spinal cord has been determined, resection proceeds with gentle dissection along this plane. The blood supply of the tumour comes from anterior, and the vessels are cauterised and cut during further resection of the tumour. In cases with a well-defined tumour margin complete removal of the tumour will most probably be achieved. When surgical resection is completed, dura and muscles are closed in the usual fashion. If the tumour–spinal cord interface is not obvious or is ill-defined, however, resection should stop leaving behind a thin layer of tumour tissue so as to avoid neurological injury. In these cases insertion of a dural patch should be considered in order to enlarge the space for the spinal cord.

Even though ependymomas of the filum terminale are virtually extramedullary tumours they shall be treated here as well. Their predominant clinical symptom is pain irradiating into the legs, and it is a not uncommon that, assuming a degenerative disorder of the spine, neuroradiological imaging of the lower lumbar spine is performed in order to confirm the tentative diagnosis of lumbar disc herniation. However, the tumour as the underlying cause of the complaints may be overlooked on CT or MRI without contrast-medium and radiological results can be adjudged as negative. Thus patients occasionally are wrongly labelled as psychosomatic or even hypochondriac cases until the correct diagnosis is made, sometimes not until additional signs have developed after some years. Ependymomas of the filum terminale mostly belong to the myxopapillary type of ependymomas and may reach a remarkable size involving multiple spinal segments. On conventional roentgenograms the spinal canal occasionally is widened and the posterior parts of the vertebral bodies are eroded owing to the slow growth of the tumour. On MRI the tumour, surrounded by flattened and compressed fibres of the cauda equina, features the same characteristics as described above showing a heterogeneous gadolinium enhancement (Fig. 4.2.11a).

Performing surgery the aim is gross total resection of the tumour, and since the lumbar spine belongs to the most mobile parts of the spinal column a laminotomy is recommended to avoid postoperative instability and kyphosis. The dura is exposed along the entire longitudinal extension of the tumour and opened in the midline which immediately gives a view of the brownish-red to purple tumour. The arachnoid over the tumour is incised as far as the cranial and caudal margins of the tumour are visualised, and the filum terminale merging into the tumour is identified. The filum terminale has the appearance of a solid, whitish cord that is encircled by a dense network of meandering vessels. It is usually localised strictly in the midline and is somewhat thicker than the
surrounding fibres of the cauda equina. If there is difficulty in identifying the filum terminale reliably, intraoperative stimulation of the assumed structure is extremely helpful in differentiating it from nerve roots by means of absent muscular responses. In most cases resection of the tumour is carried out by transection of the filum at the upper and the lower pole of the tumour allowing for in toto removal after dissection of adhesions to the nerve roots of the cauda equina (Fig. 4.2.11b). In complex cases, however, the tumour capsule adheres to the nerve roots to such an extent that such an approach is unfeasible. In these cases the tumour is debulked internally, the capsule is removed as far as justifiable, and if in doubt a small layer of tumour tissue adherent to the nerve roots that cannot be dissected without sizeable risk is left behind in order not to add to the patient’s neurological deficit. The same applies to tumours with ill-defined tumour margins that have invaded into the conus medullare.

Since tumour cells may spread through the CSF, a neuroradiological work-up of the whole spinal axis and the brain using MRI is indispensable whenever the diagnosis of an ependymoma is confirmed histopathologically.

While ependymomas are the most common intramedullary tumours in adults, astrocytomas are more prevalent in children and adolescents with the cervical spine as their most common localisation. The vast majority of spinal cord astrocytomas are of benign histology and appear as diffusely infiltrating fibrillary or pilocytic types, while 10% of spinal astrocytomas are high-grade lesions. Diagnosis is made with MRI. Whereas pilocytic astrocytomas show a dense enhancement with gadolinium and are often accompanied by large cysts, fibrillary astrocytomas mostly appear as a focal, non-enhancing distension of the spinal cord (Fig. 4.2.12).

Since pilocytic astrocytomas mostly feature a well-defined tumour margin they are amenable to surgical resection following the same operative principles as described above. In contrast fibrillary astrocytomas are ill-defined, whitish enlargements of the spinal cord, and owing to the diffusely infiltrating character of the tumour its margins intermingle with functioning spinal cord tissue. Thus resection of the tumour without severe neurological damage is not possible, and consequently surgery has to be restricted to mere biopsy and a dural patch graft.

If symptomatic vascular lesions such as haemangioblastomas or cavernomas are resected these tumours can be cured. It is noteworthy that a considerable number of patients with von Hippel-Lindau disease harbour asymptomatic tumours. In these cases of incidental findings no operation is indicated and the tumour is kept under observation.

4.2.8 Prognosis

With regard to extradural spinal tumours it should not be forgotten that occurrence of spinal metastasis is the expression of a systemic spread of the underlying disease. As a consequence prognosis quoad vitam depends main-
ly on site and type of the primary cancer, on the extent of metastatic spread to the diverse organ systems, and on the response to different adjuvant therapy modalities administered. However, it can also be demonstrated that an intact walking ability is an important positive factor for survival, and that paralysed patients have a significantly worse prognosis. Hence, recovery of neurological function with retrieval of gait function is of significant importance with regard to life expectancy. The variable mostly used as a prognostic factor to predict functional outcome is the initial degree of paresis. The clinical results of numerous studies, both surgical and radio-oncological, demonstrate that pretreatment ambulatory function is one of the main determinants for post-treatment gait function, and that the more severe the initial palsy the less likely is recovery. From these series it is evident that patients who are ambulatory before surgery mostly maintain their walking ability, with quoted favourable results ranging between 75% and 100%. In patients who are not able to walk before surgery the reported retrieval of gait function shows a large variability ranging from 16.5% to 83%. Other variables used as prognostic factors are the speed of onset of paresis and its duration before the initiation of treatment. Various studies showed that the faster pareses occur and the longer they persist before commencement of therapy the less likely is recovery. Whereas an individual functional prognosis cannot be made by utilisation of the aforementioned prognostic variables, recent results suggest that this might be possible by determination of S100b serum levels provided that neither melanoma nor thyroid cancer is the primary tumour. Patients with a paraplegia lasting longer than 24 h virtually never experience a meaningful recovery of function.

Concerning intradural extramedullary tumours outcome after removal of spinal meningiomas and neurinomas is generally good. The results of numerous clinical studies show that despite partly severe paresis outcome is favourable in 83–100% of all treated patients. Moreover even initially paraplegic patients may benefit from surgery since quoted rates of a retrieval of gait function in this group of patients range from 50% to 75%.

Results after removal of intradural intramedullary tumours are naturally less favourable. About 50% of the patients with ependymomas experience immediate but temporary postoperative worsening in terms of sensory disturbances due to posterior column retraction. If the data of the pertaining literature are analysed with regard to functional outcome the reported rate of favourable results shows a large variability ranging from 18.3% to 89%.

### Table 4.2.1 Epidemiology of spinal tumours in children

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramedullary</td>
<td>40% of spinal tumours</td>
</tr>
<tr>
<td>Low-grade astrocytoma</td>
<td>35% of ITM; more frequent: &lt; 10 years old, cervical or cervicothoracic</td>
</tr>
<tr>
<td>High-grade astrocytoma</td>
<td>10% of ITM</td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>30% under 3 years of age</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>12–15% of ITM; more frequent: &gt; 10 years old, conus-cauda</td>
</tr>
<tr>
<td>Haemangioblastoma</td>
<td>7% of ITM</td>
</tr>
<tr>
<td>Cavernoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Lipoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Intradural extramedullary</td>
<td>25% of spinal tumours</td>
</tr>
<tr>
<td>Cauda ependymoma</td>
<td></td>
</tr>
<tr>
<td>Dermoid</td>
<td></td>
</tr>
<tr>
<td>Nerve sheet tumour</td>
<td></td>
</tr>
<tr>
<td>Meningioma</td>
<td></td>
</tr>
<tr>
<td>Extradural</td>
<td>35% of spinal tumours</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
</tr>
</tbody>
</table>

ITM intramedullary tumours

### 4.2.9 Specific Aspects of Spinal Tumours in Children

**Beatrice Cioni**

Tumours within the spinal canal are relatively rare, and in children the rate of spinal tumours versus intracranial tumours is lower.

Spinal tumours may be classified into three types according to their location with respect to the dura and to the parenchyma (Table 4.2.1):
1. Intradural intramedullary: 40% of all spinal tumours in childhood, the most common location
2. Intradural extramedullary: 25% of all spinal tumours
3. Extradural: 35% of paediatric spinal tumours

#### 4.2.9.1 Intramedullary Tumours

**4.2.9.1.1 Epidemiology**

The intramedullary tumours are the most common spinal tumours in childhood, being 55% of all intradural
tumours. These tumours are almost equally distributed between the sexes.

They are evenly distributed along the cord, and usually span several vertebral levels. Holocord tumours are not infrequent.

Astrocytomas account for 40–45% of them, followed by gangliogliomas (30% under the age of 3 years). Low-grade tumours are prevalent compared to high-grade: low-grade astrocytomas represent 35% of intramedullary tumours while high-grade astrocytomas are 10% in children. Ependymomas represent only 12–14%; hemangioblastomas (7%) are usually associated with von Hippel-Lindau disease and cavernomas are very rare in children.

The mean age of onset is 10 years; astrocytomas and ganglioglioma are more prevalent in the younger age group, while ependymomas are more frequent in the older age group. In children under 10 years of age a spinal cord tumour above the conus has a 75% chance of being an astrocytoma and only a 10% chance of being an ependymoma, a feature which distinguishes paediatric from adult spinal cord tumours.

4.2.9.1.2 Clinical Presentation
Progress is often insidious in low-grade tumours, and diagnosis may be established months or even years after initial presentation of symptoms. In contrast malignant tumours have a rapid progression. Cavernomas, generally at the cervical level, have an abrupt onset due to intratumoural haemorrhage.

Neck or back pain occurs in two thirds of patients, pain being diffuse, rarely radicular and more intense at night in the recumbent position. Young children may complain of abdominal pain which in contrast with the spine pain is not a localising sign. Motor weakness in the lower extremities, with frequent falls and motor regression are early symptoms. In the upper extremities in young children, switching handedness may be the first manifestation of weakness. Sensory symptoms are less frequently reported, as well as sphincter dysfunctions, and are difficult to detect in young children. Kyphoscoliosis is present in one third of patients and torticollis in one fifth. In children, a spinal deformity associated with neurological deficit should always be investigated by MRI to rule out the presence of an intramedullary tumour.

Hydrocephalus is associated with as many as 15% of intramedullary tumours, the incidence being higher with malignant tumours than with benign tumours, and in cervical tumours. Mechanisms for hydrocephalus may be obstruction of the fourth ventricle outlets in cervicomedullary tumours, or increased concentration of protein in the CSF, arachnoidal fibrosis and subarachnoid dissemination.

4.2.9.1.3 Diagnostic Studies
- **Magnetic resonance imaging** is the study of choice for extramedullary and intramedullary neoplasms. T1- and T2-weighted images before and after i.v. injection of gadolinium should be obtained to study the solid component as well as tumour-associated cysts.
- **Plain radiographs** are mandatory in children with scoliosis as a baseline for future management of the spinal deformities. After extensive laminectomy or laminotomy, plain x-rays of the vertebral column should be obtained at regular follow-ups for early detection of spinal deformities.
- **Myelography and computed tomography** today are reserved for the cases in which MRI is impossible to perform or to interpret and when bone involvement needs to be studied.

4.2.9.1.4 Surgical Treatment
Intramedullary tumours are rare and should be referred to centres of excellence where all the most advanced surgical adjuncts are available, particularly intraoperative neurophysiological monitoring (SEPs and MEPs).

4.2.9.1.4.1 Technique
An osteoplastic laminotomy is preferred to laminectomy for prevention of postoperative spinal deformities: laminotomy permits replacement of bone which is a nidus for subsequent osteogenesis and posterior fusion. A standard posterior midline approach with subperiosteal dissection of the paraspinal muscles is used to expose the spinal laminae; care is taken to preserve the facet capsules. The epidural space is exposed through an interlaminar fenestration. A high-speed drill is used for cutting of the target laminae bilaterally, median to the facets, en bloc or one by one. The ligamenta interspinosa and flavum are cut and the laminae are dissected free from the underlying epidural space and then removed and stored in saline-soaked gauze. Abundant irrigation is important during cutting in order to avoid a thermal lesion of the bone, which would prevent bone healing, and in order to remove all metal dust for further follow-up imaging using MR. The bone removal should expose the solid component of the tumour. The rostral and caudal cysts, if present, do not need to be removed. Perioperative ultrasonography is useful in visualising the tumour and its relation to the bone removal. The dura is opened in the midline and then the arachnoid which is secured to the dura by dural clips. The approach to the tumour is generally through the posterior midline raphe. Sometimes it may be difficult to visually identify the precise midline, even under microscope magnification, because the spinal cord is expanded, rotated and distorted. In these cases, the identification of the dorsal root entry zone bilaterally may be
of help or a neurophysiological mapping of the dorsal column midline may be performed. A myelotomy may also be performed using a contact laser system because of its precision and its minimal thermal effect. Pial traction sutures attached to the dura gently open the myelotomy incision and further expose the tumour.

Low-grade astrocytomas or gangliogliomas have a glassy appearance. There is not a true plane between tumour and normal spinal cord, so the neoplasm is removed from the inside out, starting from the midportion of the tumour. Small residual portions may be removed from the normal spinal cord using the contact laser. A gross total or subtotal (75–85%) removal is the goal of surgery. The area of major risk for the surgical removal corresponds to the anterior extension of the tumour, and intraoperative monitoring of the motor pathways is of great help in deciding when to stop.

Ependymomas, characterised by a red and dark grey appearance, can be detached from the spinal cord; one of the poles of the tumour is identified and the cleavage plane is separated. The feeding vessels of an ependymoma originate from the anterior spinal artery and this should be preserved when detaching the tumour from its anterior bed.

Cavernomas are resected in an inside-out fashion. Haemangioblastomas should be resected en bloc and cannot be debulked from within because of the high vascularisation of these tumours. Spinal angiography and eventually a preoperative embolisation may be indicated.

Intramedullary lipomas are densely adherent to the spinal cord, although well demarcated from it. They may remain silent for years; when symptomatic they may be debulked using the contact laser that vaporises the fatty tissue with minimal surgical trauma to the spinal cord. No further therapy is needed, even in cases of partial excision.

After tumour removal and haemostasis, the arachnoid is closed and then the dura in a watertight fashion. The laminar roof is replaced and sutured with non-absorbable sutures, or the better option is with titanium miniplates fixed with screws. The miniplates may be adjusted and bent to achieve optimal realignment of the laminae. The interspinous ligaments are finally sutured at the cranial and caudal ends; muscles and fascia are closed without tension. Attention should be paid to closing the skin in several layers, particularly in cases of reoperation or in children who received radiation therapy.

### Table 4.2.2 Recommended treatment options

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Treatment of choice</th>
<th>Recurrence</th>
<th>Other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade astrocytoma</td>
<td>Surgical gross total or subtotal removal</td>
<td>Second operation</td>
<td>Radiation therapy: surgery not feasible or documented rapid regrowth Chemotherapy</td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>Surgical gross total or subtotal removal</td>
<td>Second operation</td>
<td>Radiation therapy: surgery not feasible or documented rapid regrowth</td>
</tr>
<tr>
<td>High-grade astrocytoma</td>
<td>Surgical debulking</td>
<td>Second operation</td>
<td>Plus radiation and/or chemotherapy</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Surgical gross total removal</td>
<td>Second operation</td>
<td>Radiation and/or chemotherapy: surgery not feasible, dissemination, high proliferation index</td>
</tr>
<tr>
<td>Haemangioiblastoma, cavernoma</td>
<td>Surgical total removal</td>
<td>Second operation</td>
<td></td>
</tr>
<tr>
<td>Intramedullary lipoma</td>
<td>Surgical debulking</td>
<td>No further treatment</td>
<td></td>
</tr>
<tr>
<td>Intradural extramedullary</td>
<td>Surgical total removal</td>
<td>Second operation</td>
<td>Radiation therapy for malignant variant</td>
</tr>
<tr>
<td>Extradural tumours</td>
<td>Chemotherapy or radiation therapy</td>
<td></td>
<td>Surgical decompression: rapid neurological deterioration</td>
</tr>
</tbody>
</table>

4.2.9.1.4.2 Intraoperative Neurophysiological Monitoring

It is highly recommended for spinal cord surgery. The monitoring protocol includes: motor-evoked potentials (MEPs), somatosensory-evoked potentials (SEPs) and, in cases of conus-cauda surgery, the bulbocavernous reflex (BCR). A general total intravenous anaesthesia is used, avoiding muscle relaxants after intubation. MEPs are evoked by electrical transcranial stimulation over the motor cortex using the single stimulus technique and recording the corticospinal tract descending volley with an epidural electrode placed caudal the level of surgery. The so-called D-wave is monitored: it is a linear measurement of the number of activated fast corticospinal axons, and
therefore the warning criteria is a decrement in amplitude of the response; this decrement is usually progressive, giving time for the surgeon to react. A short train of electrical stimuli should be used to elicit muscle responses following transcranial electrical stimulation. Muscle-evoked responses are a non-linear measurement of activated fast corticospinal axons, of alpha motor neurones, peripheral nerves and muscle end plates, and therefore a presence or absence of muscle response is evaluated. Muscle responses can be evoked in newborns and in premature infants. Under general anaesthesia, muscle MEPs following a short train of stimuli can be elicited in children of 2 months of age. But this is not true for the D-wave. The youngest child with a D-wave present in the lower thoracic spinal cord was 21 months of age. This is probably due to the incomplete myelination of the corticospinal tracts before 24 months of age.

Motor-evoked potentials showed high monitorability in children undergoing intramedullary tumour removal: the D-wave is monitorable in two thirds of patients without severe motor deficits and muscle MEPs in all of them. The technique of MEP monitoring has a sensitivity of 100% and a specificity of 90%. This means that, in children with intramedullary tumour, the presence of a muscle response at the end of the operation is always associated with a good motor outcome (no false-negatives are reported in the literature). The absence of the motor response and a decrement of D-wave amplitude >50% are associated with a significant postoperative permanent motor deficit. The absence of the muscle response and the presence of an unchanged or decreased <50% D-wave is associated with a temporary motor deficit. Unfortunately, the combination of these two techniques is not possible under the age of 2 years and in these cases only muscle responses can be evaluated.

As long as the MEPs remain stable during the operation, the surgical dissection and removal of the tumour can be safely continued. When a deterioration of the potentials appears, the surgeon is required to stop the dissection, to irrigate the surgical field with warm saline, to wait for the recovery of the potentials or alternatively to start and work on a different part of the tumour. When the muscle response permanently disappears and D-wave amplitude decreases to 50% of baseline it is time to stop the intervention. In benign gliomas the long-term outcome is no different with gross total removal than with subtotal removal. If the residual tumour needs to be removed, it is better to operate in stages than to risk a neurological disaster by prolonging the surgical manoeuvre in order to obtain the total or subtotal excision of the tumour at the first operation.

Somatosensory-evoked potentials give information on the somatosensory system and should not be used as an indirect measure of the functional integrity of the motor system, particularly in intramedullary tumour surgery where motor and sensory tracts may be individually injured. Somatosensory mapping of the dorsal columns may help in identifying the precise posterior midline.

The BCR is evoked by the dorsal penile or clitoral nerve using a short train of stimuli and recorded from anal sphincter. It is used to monitor conus-cauda surgery together with anal sphincter muscle motor responses evoked by transcranial electrical stimulation of the motor cortex.

4.2.9.1.5 Mortality and Morbidity
Surgical mortality is very low, in some series 0%. Long-term survival in children with low-grade tumours seems to be better than in adults after gross total and subtotal removal. The 5- and 10-year survival rates are generally 85–89% and 75–82%, respectively. For high-grade tumours the 5-year survival is 15–18% regardless of the type(s) of treatment.

4.2.9.1.6 Adjuvant Therapy
Radiation therapy has a deleterious effect on the developing nervous system and bone. In children, postradiation myelopathy has been reported for doses of 30 Gy. Spinal deformity is also a complication of radiation therapy. A higher rate of deformities seems to be associated with younger age at time of radiation, doses greater than 20 Gy and asymmetrical radiation fields. Furthermore, there is no clear evidence that radiation therapy will improve the outcome in benign gliomas of the spinal cord. Therefore, radiation therapy should be withheld in cases of ependymomas and low-grade astrocytomas that have undergone gross total or subtotal removal. It should be reserved for cases where a rapid tumour regrowth is clearly documented in spite of previous chemotherapy.

Radiation therapy may be indicated for high-grade malignant tumours; nevertheless glioblastomas invariably progress. Modern protocols of chemotherapy are used for high-grade tumours, but there is no evidence that they alter the outcome (Table 4.2.2).

4.2.9.1.7 Functional and Oncological Outcome
The functional outcome is related to histology and to the preoperative neurological deficit. Children in McCormick grades I and II have a less than 1% incidence of paralysis; children in grades III and IV are more likely to deteriorate postoperatively. One third of the children may experience a motor deterioration immediately after surgery, but over the long term two thirds of them are in McCormick grades I or II, and when a surgical deterioration is present, this is usually by one grade. Improvement in motor deficit usually precedes improvement in sensory syndromes, and urinary dysfunction typically
resolves much longer after surgery. The risk of persistent postoperative motor deficit is increased with older age, unilateral symptoms and urinary dysfunction. Impaired proprioception may be a problem in children because it usually requires extensive rehabilitation therapy.

### 4.2.9.18 Late Surgical Complications

#### 4.2.9.18.1 Postoperative Spinal Deformities

In children deformities of the spine can be a major problem either before or after surgery. The incidence of spinal deformities after multilevel laminectomy varied from 25% to 72% and correlated with the patient's age (the younger the patient, the more likely its occurrence) and the level of laminectomy (highest for cervical tumours, lowest for lumbar tumours). There is a higher rate of spinal deformities in children who were irradiated. However only one third of these children required a stabilisation procedure. It is important to follow all patients operated on for spinal tumours with plain radiographs of the spine for early detection of deformities. It should be kept in mind that a developing spinal deformity, particularly if associated with neurological deterioration, may be the index of tumour recurrence; in these cases an MRI study is indicated.

An osteoplastic laminotomy is performed instead of a laminectomy in order to prevent such spinal deformities. The laminotomy clearly reduces the incidence of deformities but does not abolishes the problem.

Risk factors for progressive spinal deformities requiring fusion are preoperative sciotic deformity, an increasing number of resected laminae, age less than 13 years, and surgery spanning the thoraco-lumbar junction. A grading scale based on the presence or absence of these four preoperative variables has been suggested to assist in the process of surgical decision-making and preoperative evaluation. Children at high risk of developing postoperative progressive scoliosis may be subjected to single-stage laminectomy, tumour resection and fusion.

#### 4.2.9.18.2 Cerebrospinal Fluid Leak

Its incidence is higher in children undergoing a second operation or who have previously had radiation therapy.

### 4.2.9 Intradural Extramedullary Tumours

Cauda ependymomas and dermoids are the most prevalent types of intradural extramedullary tumours in children. Nerve sheath tumours are usually associated with neurofibromatosis. Meningiomas are rare, and more frequently aggressive than in adults. Usually intradural extramedullary tumours involve one or a few spinal levels. Medulloblastomas and ependymomas of the posterior fossa often disseminate to the spinal subarachnoid space, but rarely give a spinal syndrome.

The majority of these tumours are benign and gross total removal should be the goal of surgical therapy. Cord manipulation during surgery should be avoided. Radiation therapy is reserved for malignant variants.

### 4.2.9.3 Extradural Tumours

They account for 35% of spinal tumours in children. Sarcomas and neuroblastomas are the most common. Surgery is indicated for diagnosis or in cases of cord compression. These tumours are sensitive to radiation therapy and to chemotherapy.

Neuroblastomas have a 5-year survival rate of 70%. Half of the patients have neurological symptoms related to cord compression. The suggested treatment is chemotherapy. Laminectomy and surgical decompression should be reserved for patients showing a rapid neurological deterioration in spite of chemotherapy. After treatment most of the children experience some neurological improvement, and half of them have a complete neurological recovery. The frequency of such complete recovery inversely correlates with the severity of the neurological presenting symptoms, and it is similar in patients treated with chemotherapy and in those treated with laminectomy.

### Selected Reading

4.3 Degenerative Disease

RÜDIGER GERLACH, GERHARD MARQUARDT AND VOLKER SEIFERT

4.3.1 Cervical Spine

4.3.1.1 Cervical Disc Herniation

4.3.1.1.1 Definition
Protrusion of the disc into the spinal canal or foramen with compression of neural structures.

4.3.1.1.2 Aetiology/Epidemiology
Disc degeneration occurs due to mechanical stress to the annulus resulting in small tears. Part(s) of the nucleus may protrude through these tears causing compression of the nerve root or spinal cord and subsequent neurological symptoms (radiculopathy or myelopathy).

4.3.1.1.3 Symptoms
- Painful limitation of neck motion with pain aggravation on neck extension.
- Radiating pain occurs according to the involved spinal nerve root sensory distribution.
- Arm elevation may relieve the pain.
- Muscle weakness and diminished reflexes according to the involved segment (see Table 4.3.1).
- C6/7 is the most frequently involved segment followed by C5/6.

4.3.1.1.4 Diagnostic Procedures
- CT
- MRI (Fig. 4.3.1)
- Plain x-ray

4.3.1.1.5 Therapy
- Non-operative treatment: immobilisation, physical therapy, medications. The vast majority of patients with acute radiculopathy will improve without surgery.
- Operative treatment. Indications are:
  - Failed non-operative treatment with persisting radicular complaints, or severe, disabling radicular pain
  - Spinal cord dysfunction (motor weakness, cervical myelopathy)
  - MRI signs of cervical stenosis and increased signal within the spinal cord
- Operative techniques:
  - Anterior cervical discectomy and fusion (Cloward, Smith Robinson) with or without plating. The decision about which material is inserted into the disc space depends on the surgeon. The use of autologous bone is widely replaced by the use of non-autologous bone graft, hydroxyapatite or cages derived from various materials in different shapes (titanium, PEEK, etc.) leading to a decrease in donor site morbidity.

Table 4.3.1  Cervical disc syndromes and clinical signs

<table>
<thead>
<tr>
<th>Cervical segment</th>
<th>C4/C5</th>
<th>C5/C6</th>
<th>C6/C7</th>
<th>C7/T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compressed nerve root and sensory distribution</td>
<td>C5</td>
<td>C6</td>
<td>C7</td>
<td>C8</td>
</tr>
<tr>
<td>Reflex diminished</td>
<td>Deltoid</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Finger jerk</td>
</tr>
<tr>
<td>Index muscle weakness</td>
<td>Arm abduction &gt; 90°</td>
<td>Elbow flexion</td>
<td>Elbow extension</td>
<td>Abduction little finger</td>
</tr>
<tr>
<td>Testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.3 Degenerative Disease

4.3.1.2 Cervical Spondylosis

Cervical spondylosis is sometimes synonymously used with cervical spinal stenosis, but implies a more widespread condition including various combinations of conditions, e.g. congenital spinal stenosis, focal stenosis restricted to the disc space (either disc protrusion ['soft disc'] or osteophytic bars ['hard disc'] and ligamentous hypertrophy.

4.3.1.3 Prognosis

- Lateral anterior cervical sequestrectomy.
- Posterior foraminotomy and sequestrectomy (Scooville, Frykholm).
- Anterior cervical disectomy and arthroplasty using artificial disc prosthesis (various disc prostheses on the market). This non-fusion technology was developed to reduce the incidence of adjacent level disease.

4.3.1.2.1 Definition

Cervical spondylosis refers to the bony overgrowths, so-called vertebral osteophytosis, associated with degenerative changes due to aging of the spine. It is considered the most common progressive disorder of the aging cervical spine [2].

Fig. 4.3.1a,b MRI of the cervical spine. T2-weighted axial (a) and sagittal (b) images depicting a left-sided cervical disc herniation
### 4.3.1.2 Aetiology/Epidemiology
Spondylosis is likely the end result of disc degeneration that has been present for a very long time. It is the natural process of aging and occurs in about 10% of individuals at the age of 25 years but 95% at the age of 65 years [3].

### 4.3.1.2.3 Symptoms
Three main symptom complexes:
1. Neck pain (acute, chronic)
2. Radiculopathy (acute, subacute, chronic, unilateral, bilateral): motor findings less common, sensory symptoms such as paraesthesia, hyperaesthesia, hyperalgesia
3. Myelopathy (see below)

### 4.3.1.2.4 Diagnostic Procedures
- Plain x-ray (static and dynamic)
- CT (size of the foramina)
- MRI
- Myelography (widely replaced by MRI)

### 4.3.1.2.5 Therapy
Usually non-operative unless neurological compression(s) requires operative treatment.
- Medical therapy:
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Muscle relaxants
  - Analgesics
  - Antidepressants
  - Anticonvulsants
- Non-pharmacological non-operative therapy:
  - Immobilisation with soft or hard collars
  - Acupuncture
- Physical therapy exercises:
  - Thermal therapy
  - Ultrasound
  - Traction
  - Isometric exercises
  - Proprioceptive re-education (slow neck movements)
- Interventional pain management:
  - Radiofrequency ablation
  - Facet joint infiltration

### 4.3.1.2.6 Prognosis
Axial neck pain usually disappears either with or without medical treatment in about 75% of patients. Mixed symptoms (axial neck pain, radicular pain) have good resolution in up to 60% of patients, with moderate or severe complaints in the remaining patients [4, 5]. No benefit of surgical versus medical treatment was found in patients with 3 years follow-up [6].

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### 4.3.1.3 Cervical Spinal Stenosis

#### 4.3.1.3.1 Definition
Narrowing of the spinal canal leading to radicular or spinal cord compression.

#### 4.3.1.3.2 Aetiology/Epidemiology
An important feature of disc degeneration is the reaction that the bone undergoes. There is a condition of instability. In an attempt to stabilise this excess motion, bone grows outwards, which results in osteophytes. Osteophytes can be found near the disc spaces and around the facet joints. If they grow in areas where nerves or the spinal cord are nearby, they can impinge on or compress these structures.

#### 4.3.1.3.3 Symptoms
Similar to spinal spondylosis: pain (head, neck, shoulders), radiculopathy or myelopathy and paraesthesia.

#### 4.3.1.3.4 Diagnostic Procedures
- Plain x-ray AP and lateral view: look for canal diameter (osteophytic bars) and malalignment (diameter of the spinal canal in adults is normally about 17 mm and less than 12 mm should be considered as stenosis).
- Additional flexion and extension shows the degree of instability if present.
- MRI: look for signal changes of the cord in T2-weighted images.
- Postmyelographic CT.

#### 4.3.1.3.5 Therapy
- Non-operative treatment: immobilisation, physical therapy, medications; see above
- Operative treatment. Indications are:
  - Failed non-operative treatments with persisting radicular complaints, or severe, disabling radicular pain
  - Spinal cord dysfunction (motor weakness, cervical myelopathy)
  - MRI signs of cervical stenosis and increased signal within the spinal column
  - Signs of instability with hypermobility in dynamic x-ray and signs of cord compression
- Operative techniques:
  - Anterior cervical discectomy and fusion with or without plating. Plating is usually performed if more than two levels are operated on.
  - Lateral anterior cervical foraminotomy.
  - Posterior foraminotomy radicular decompression.
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- Posterior extension of the spinal canal after laminoplasty using various techniques with or without additional instrumentation.
- Anterior cervical disectomy, decompression of the spinal canal and arthroplasty using artificial disc prosthesis (various disc prostheses are on the market). This non-fusion technology was developed to reduce the incidence of adjacent level disease.

4.3.1.3.6 Prognosis
- Depends on the clinical manifestation of the stenosis.
- If present, signs and symptoms of cervical myelopathy may not always improve after surgery but a progression may be prevented with surgical procedures (see below).

4.3.1.4 Cervical Myelopathy

4.3.1.4.1 Definition
Cervical spondylotic myelopathy is a well-described clinical syndrome, which might be caused by various mechanisms (traumatic, degenerative, tumorous or infectious).

4.3.1.4.2 Aetiology/Epidemiology
The common concept that a narrowed spinal canal causes compression on the spinal cord leading to ischaemia, injury and neurological impairment has been questioned in recent times [7]. There is evidence that spondylotic narrowing of the spinal canal and abnormal or excessive motion of the cervical spine results in increased strain and shear forces that cause localised damage to the cord [7]. Clinically significant cervical myelopathy typically appears in late adulthood in the setting of incremental degenerative changes causing progressive encroachment of the spinal canal by ventral and dorsal structures. These changes find their anatomical basis in cervical disc generation, osteophytic spur and bar generation, thickening of the ligamentum flavum and osteoarthritic facet hyper trophy. Patients with congenital stenosis are at higher risk compared to those with a wider spinal canal. Thus patients with a diameter of the spinal canal less than 12 mm in the sagittal plane have a strong association with cervical myelopathy, while a diameter larger than 16 mm appears to have a lower risk (for review see [7]).

4.3.1.4.3 Symptoms
Long tract signs are a hallmark of cervical myelopathy!
- Shock-like sensations in the limbs with rapid flexion/extension of the neck (Lhermitte’s sign)
- Ascending numbness in the lower extremities with neck extension
- Gradual signs of cord dysfunction with spasticity, hyperreflexia, abnormal reflexes (Babinski’s sign, Hoffmann reflex) and clonus
- Spastic weakness of the hand and forearm muscles
- Hand numbness and impaired fine motor function
- Painful paraesthesias
- Lower extremities weakness
- Spastic gait, wide-based gait
- Atrophy and/or fasciculation
- Sphincter dysfunction

4.3.1.4.4 Diagnostic Procedures
- MRI (look for signal changes of the spinal cord!) (Fig. 4.3.2)
- Plain x-ray
- CT with additional two-dimensional reconstruction

Fig. 4.3.2 Cervical MRI, sagittal view in T2-weighted mode, showing a multisegmental cervical stenosis with signal increase
4.3.1.4.5 Therapy
- Non-operative treatment: immobilisation, physical therapy, medications; see above
- Operative treatment: Controversy remains concerning the optimal timing and indications for surgical interventions. Indications are progressive muscle weakness, gait disturbance, urinary frequency or incontinence, loss of coordination of the hands and decreased fine motors skills. The choice for the operative procedure with the anticipated greatest benefit for an individual patient depends on multiple factors responsible for the myelopathy (direction of compression, focal or diffuse/multisegmental disease, concentric compression, presence or absence of instability or deformity. Generally the least invasive operative procedure with adequate decompression of the cord should be considered.
  - Anterior approach for decompression: (We personally prefer the anterior approach for surgical treatment of cervical myelopathy, especially if the compression is localised to the interspace and associated with instability or kyphotic deformity.)
    - Anterior cervical discectomy and fusion (ACDF) (single or multiple level procedures) with or without plating in cases with ventral compression located at the level of the intervertebral disc.
    - Anterior cervical corporectomy and fusion (ACCF) using autologous bone graft or different spacer. Additional plating should be performed to avoid graft dislocation.
    - Anterior oblique multilevel corporectomies [8].
  - Posterior approach for decompression:
    - Laminectomy (single or multiple level): consider the risk of swan neck deformity. A pre-existing cervical kyphosis is a contraindication for multilevel laminectomy alone. In these cases fusion and posterior instrumentation (e.g. lateral mass screws and rods) should be performed.
    - Laminoplasty: multiple techniques are described, but many are modifications of the ‘open door’ technique.
  - Combined anterior–posterior approaches for decompression
    - Indicated in cases with compression from both sides. These cases are almost always associated with instability and therefore after ACDF posterior decompression and instrumentation is performed. The decompression procedure should be initially performed on the side of the major compression.

4.3.1.4.6 Prognosis
The natural history of cervical myelopathy is variable. Earlier studies suggested a progressive deterioration of neurological symptoms, but other studies reported long periods of non-progression and deterioration was the exception [5]. In the majority of cases an initial deterioration is followed by a static period lasting for many years [9]. Older patients with motors deficits are more likely to develop progressive deterioration and patients with milder disease may have a better prognosis. Comparing surgical and medical treatment for patients with cervical myelopathy, a more favourable outcome was reported in surgically treated patients [10]. Patients with high intramedullary signal changes on T2-weighted images who do not have clonus or spasticity may experience a good surgical outcome and have reversal of MRI abnormality, while a less favourable outcome is predicted for patients with low T1-weighted image intramedullary signal, clonus or spasticity [11].

4.3.1.5 Ossification of the Posterior Longitudinal Ligament
4.3.1.5.1 Definition
Abnormal ossification of the posterior longitudinal ligament (OPLL) is seen on lateral x-ray with the C-spine being most frequently affected.

4.3.1.5.2 Aetiology/Epidemiology
Ossification of the PLL has a high incidence in the Japanese and Asian populations, but is far less frequently found in Europe and the USA. There is a higher incidence in men and in older age groups. The pathophysiology is unclear. Disturbance of calcium metabolism is discussed but the significance of this abnormality is unclear. OPLL can occur concomitantly with other hyperostotic disorders such as diffuse idiopathic skeletal hyperostosis (50%), ankylosing spondylitis (2%) and ossification of the yellow ligament (6.8%) [12].

4.3.1.5.3 Symptoms
The progression rate is slow over the years and the majority of cases seem to be asymptomatic. However, if clinical symptoms occur cervical myelopathy is common and in patients with trauma severe neurological impairment may occur due to the pre-existing stenosis of the spinal canal.

4.3.1.5.4 Diagnostic Procedures
- Plain x-ray
- MRI
- CT (two- and three-dimensional reconstruction may be helpful)
4.3.1.5.5 Therapy
Cervical laminoplasty has become the standard technique for the treatment of patients with myelopathy due to OPLL. However, anterior decompression and fusion yielded a better neurological outcome at final follow-up than laminoplasty in patients with occupying ratio greater than or equal to 60% [13].

4.3.1.5.6 Prognosis
Young patients with continuous or mixed-type OPLL and C3 involvement of ossification had a risk for progression in OPLL thickness following surgery [14]. Surgical outcome was significantly poorer in patients with occupying ratio greater than 60%. Multiple regression analysis showed that the most significant predictor of poor outcome after laminoplasty was hill-shaped ossification, followed by lower preoperative Japanese Orthopedic Association (JOA) score, postoperative change in cervical alignment and older age at surgery [15].

4.3.1.6 Rheumatoid Arthritis

4.3.1.6.1 Definition
Rheumatoid arthritis (RA) is a disease of the synovial joints. Cervical spine is mostly affected. Chronic inflammation with destruction of bony and ligamentous structures leads to instability and deformation with malalignment.

4.3.1.6.2 Aetiology/Epidemiology
Controversy exists regarding the pathogenesis of cervical RA. Discussion is whether the initial site of involvement is the apophyseal joint with resultant facet destruction and progressive secondary instability of the disc or inflammation of the uncovertebral joint with primary disc destruction and secondary instability of the apophyseal joint [12]. Subluxation can be mild and clinically asymptomatic but also range to severe malalignment with compression of the brain stem and upper cervical cord. Two typical presentations are encountered and are frequently seen together: anterior atlantoaxial subluxation and basilar impression. Subluxation can be mild and clinically asymptomatic but also range to severe malalignment with compression of the brain stem and upper cervical cord. Two typical presentations are encountered and are frequently seen together: anterior atlantoaxial subluxation and basilar impression. Subluxation in the lower C-spine is less frequently seen and may resemble a ‘staircase’ subluxation due to ligamentous laxity and facet degeneration [12].

1. Anterior atlantoaxial subluxation: Occurs in up to 74% of patients with RA affecting the C-spine [16] and 25% of patients with RA [17]. The dens axis is surrounded by two synovial joints, ventral between the dens and the atlas and dorsal between the dens and the transverse ligament. Destruction of the ligament with ligamentous laxity is due to inflammation and destruction resulting in the loss of ligamentous integrity and anterior displacement. Dorsal displacement can occur if the dens itself has considerable osseous destruction. Involvement of C1/C2 joints may lead to lateral displacement. Pannus formation around the dens further contributes to the compression of the brain stem and upper cervical cord.

2. Basilar impression: Involvement of the atlanto-occipital articulation may lead to facet destruction and progressive collapse of the occiput at C1 and vertical displacement of the dens [12]. Occasionally the posterior arch of C1 protrudes superiorly through the foramen magnum and leads to a further compression of pons and medulla.

4.3.1.6.3 Symptoms
Pain (local referred), signs of myelopathy with hyperreflexia, paresis, spasticity and sensory disturbance.

4.3.1.6.4 Diagnostic Procedures
- Plain x-ray: look for atlantoaxial subluxation (anterior dental interval should not exceed 4 mm) (Fig. 4.3.3a).
- MRI: look for cord signal changes, the extent of pannus and subluxation. Sometimes head flexion helps to verify the compression of the cord hence normal MRI can mimic sufficient spinal canal diameter (Fig. 4.3.3b).
- CT (look for the anterior dental interval and, if you consider transarticular C1/C2 screw fixation, the course of the vertebral artery) (Fig. 4.3.3c).

4.3.1.6.5 Therapy
Almost all patients will progress over time and then develop cervical myelopathy, which may be irreversible. Severe myelopathy can cause sudden death, therefore all symptomatic patients should be surgically treated. In asymptomatic patients a risk evaluation may help with decision making. Consider the severity of atlantoaxial subluxation, age, the general health of the patient and any co-morbidities. However, asymptomatic patients with significant instability should be treated surgically.

Operative techniques:
- Pre- or intraoperative reduction of subluxation using x-ray and close clinical evaluation or neurophysiological monitoring.
- C1/C2 fusion or C0/C2 fusion: the latter has to be applied if decompression of the spinal canal (laminectomy) is necessary.
- Instrumentation and fusion needs to be enlarged in cases with subaxial instability.
- In rare cases transoral dens resection (odontectomy) may be necessary.
Fig. 4.3.3  a Plain x-ray (lateral view) of a patient with RA and C1/C2 instability and consecutive cervical stenosis. b The MRI shows an apparently sufficient diameter of the upper cervical canal in retroflexion (left) of the head, but in anteflexion (middle) you can see the compression of the medulla oblongata. The axial MRI (right) confirms the compression of the spinal cord. c The axial CT (bone window) shows the increased anterior dental interval. d x-ray of the cervical spine (AP view) after bilateral C1/C2 transarticular screw fixation and C1/C2 sublaminar wiring with autologous bone grafting to achieve fusion of C1 and C2.
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- Surgical techniques:
  - C1/C2 wiring and fusion using autologous bone graft with or without transarticular screw placement C1/C2 (consider poor bony quality and avoid additional fracture of the lamina(e) of C1 and C2 due to erosion and osteoporosis) (Fig. 4.3.3d)
  - For occipitocervical instrumentation various systems are available (Cervifix, Neon, Ransford loop, etc.)
- Postoperative immobilisation using a hard collar: some colleagues advise a halo vest for 8–12 weeks.

4.3.1.6.6 Prognosis
After surgery in two thirds of the patients there was relief or decrease of pain, and the functional capacity improved. Neurological deficits subsided in 53% of patients. Age, atlantoaxial subluxation other than horizontal and occurrence of complications were independent predictors of mortality [18]. After C1/C2 fusion a high rate of subsequent subaxial cervical spine instability may be encountered [19].

4.3.1.7 Ankylosing Spondylitis

4.3.1.7.1 Definition
Ankylosing spondylitis (AS) is an inflammatory disease affecting synovial and cartilaginous joints, primarily in the axial skeleton with a male predominance. Unlike RA in which the principal pathological lesion involves the synovial lining of the joints, the sites of involvement are the entheses. Inflammation of the ligamentous attachments, discovertebral erosions and new bone formations are the principal pathological findings [12]. This occurs in the context of a generalised osteoporosis of the vertebral body, calcification of the intervertebral disc material and ossification of the ligamentous structures leading to a radiographically square appearance of the vertebral bodies due to development of bridging osteophytes. Although the sacroiliac joints and lumbar spine are the initial sites of involvement, ultimately the entire spine is affected.

4.3.1.7.2 Aetiology/Epidemiology
The aetiology seems to be multifactorial with both genetic and acquired factors. About 129 of 100,000 people are afflicted in the USA. Predominance of adolescents and young adult men. HLA-B27 is positive in most affected individuals.

4.3.1.7.3 Symptoms
Diagnosis is often delayed due to unspecific symptoms. Pain and stiffness (accentuated in the morning) in the low back, upper buttock area, neck and the remainder of the spine, and gradual onset with progressive worsening over months.

4.3.1.7.4 Diagnostic Procedures
(The entire spine should be evaluated even after minor trauma, because remote additional fractures may be present).
- Plain x-ray: although less common compared to RA
- Look for occipitoaxial and atlantoaxial subluxation or basilar impression
- CT
- MRI

4.3.1.7.5 Therapy
Medical treatment consists of non-steroidal anti-inflammatory medications. Indomethacin is most effective, while sulphasalazine may benefit those with more severe involvement. Corticosteroids, such as prednisone, may suppress inflammation and slow joint damage in severe cases of AS.

Surgery may be indicated for the following conditions:
- Craniocervical instability may require posterior stabilisation and fusion.
- Pseudoarthrosis and stress fractures: Minor trauma can cause fractures in patients with AS (four times more frequently than in the unaffected population), occurring mainly at the level of the disc space. Fractures require 360° instrumentation with multisegment posterior instrumentation.

4.3.1.7.6 Prognosis
Ankylosing spondylitis is a progressive disease [20]. Antitumour necrosis factor therapy may decelerate progression of structural changes [21]. Cases treated surgically may be associated with severe complications due to the primary disease (pulmonary problems), trauma-related neurological impairment or surgery (associated fractures at adjacent or distant spinal level).

4.3.2 Thoracic Spine

4.3.2.1 Thoracic Disc Herniation

4.3.2.1.1 Definition
Protrusion of the intervertebral disc with radiculopathy and/or myelopathy depending on the direction and size of herniated disc material.
4.3.2.1.2 Aetiology/Epidemiology
Far less common compared to cervical and lumbar disc herniation (< 1% of all disc herniations). The lower thoracic segments are more frequently involved with T11/T12 being the most commonly affected. The causes of thoracic disc herniation are similar to those in the cervical and lumbar spine.

4.3.2.1.3 Symptoms
In general signs and symptoms of radiculopathy and myelopathy may be encountered. Severe pain (upper back, chest pain, axial back pain) is the most common followed by sensory changes (numbness, pain or tingling from the upper back and around the chest) and motor deficits (leg weakness).

4.3.2.1.4 Diagnostic Procedures
- MRI: look for signal changes of the cord, assure the correct level and be able to locate the affected level with intraoperative x-ray
- Lateral x-ray lumbar and thoracic spine: look for transitional vertebrae
- CT

4.3.2.1.5 Therapy
- Non-operative treatment: immobilisation, physical therapy, medications
- Operative treatment. Indications are:
  - Failed non-operative treatment with persisting severe, disabling pain
  - Spinal cord dysfunction (motor weakness, myelopathy)
  - MRI signs of thoracic stenosis and increased signal within the spinal cord
- Operative techniques: consider the risks associated with mobilisation of the cord during dissection. The intraspinal space can be very tight. Therefore all ‘posterior’ approaches for degenerative diseases of the thoracic spine should be considered as posterolateral approaches and a laminectomy without drilling off the more lateral structures should be avoided. Removal (partial) of the lamina and drilling the pedicle and/or a costotransversectomy can offer appropriate space.
  - Posterior approach (transpedicular, transfacet) or posterolateral approach (modified costotransversectomy, lateral extracavitary)
  - Anterior approach: anterolateral (transthoracic) or thoracoscopic (thoracic discectomy in cases of central disc herniation or patients with calcified disc protrusions which can not be removed by posterolateral approach)

4.3.2.6 Prognosis
One series retrospectively reviewed the natural course of thoracic disc herniation and found that 27% of patients eventually required surgery [22]. In the reported series most of the surgically treated patients (> 75%) improved with regard to radiculopathy and myelopathy. In a series in which no laminectomy was used in the approach, patient satisfaction was excellent or good in about 75% of cases [23].

4.3.2.2 Thoracic Spinal Canal Stenosis and Thoracic Myelopathy

4.3.2.2.1 Definition
Compression of the thoracic cord is a rare disease and can be due to disc herniation, spinal stenosis, OPLL and degenerative changes or, in rare cases, due to ossification of the ligamentum flavum.

4.3.2.2.2 Aetiology/Epidemiology
Pathogenesis is similar to that found in the cervical spine.

4.3.2.2.3 Symptoms
Uni- or bilateral claudication, radicular pain and paraesthesia. In cases with thoracic myelopathy, posterior column dysfunction and long tract signs as well as gait disturbance and bowel/bladder dysfunction can be present.

4.3.2.2.4 Diagnostic Procedures
- MRI: look for signal changes of the cord, assure the correct level and be able to locate the affected level with intraoperative x-ray
- CT or postmyelographic CT in cases where MRI is precluded for any reason

4.3.2.2.5 Therapy
- Non-operative treatment: immobilisation, physical therapy, medications
- Operative treatment. Indications are:
  - Significant static or progressive thoracic myelopathy
  - Posterior approach (laminectomy) in concentric stenosis or hypertrophy of the posterior elements
  - Posterolateral approaches in cases of significant ventral osteophyte or (calcified) disc (see above)

4.3.2.2.6 Prognosis
In properly selected cases decompression of the thoracic spinal canal provides patients with a long-term prognosis for improvement and/or resolution of their symptoms.
4.3.3 Lumbar Spine

4.3.3.1 Low Back Pain

4.3.3.1.1 Definition
Low back pain (LBP) is exceedingly common, affects both genders and most ages. LBP is responsible for a high number of medical consultations, sick leaves and also disability in people during their work and is therefore a relevant socioeconomic problem. Almost everybody will experience a period of LBP during their lifetime. However, specific diagnosis as the cause of LBP is rarely made (1–2%) and most of the complaints resolve with or without specific treatment within 1 month.

4.3.3.1.2 Nerve root pain is usually present in about 5% of patients with disc herniation or spinal stenosis. The most important point is to detect ‘red flags’ and to identify serious underlying conditions such as tumour, infection or spine fracture. Therefore a thorough history has to be obtained and some specific questions need to be addressed (history of cancer, trauma, infection, drugs, unexplained weight loss, duration of symptoms for more than 1 month, etc.).

4.3.3.2 Aetiology/Epidemiology
The prevalence of LBP in the developed world varies from 6.8% in North America to 28.4% in Canada and 33% in Belgium [26]. In Australia the one year first incidence of LBP was reported to be 8.0% [27]. Many individual, psychosocial and occupational risk factors for LBP have been identified and, in particular, psychological factors have an important role in the transition from acute to chronic pain and related disability. Non-specific LBP (85–90% of all patients seeking care) indicates that no precise structure has been identified causing pain and includes common diagnoses such as lumbago, myofascial syndromes, muscle spasms, mechanical LBP, back sprain and back strain.

4.3.3.3 Symptoms
Kyphosis, pain and, in rare cases, neurological complications secondary to severe kyphosis, such as dural cysts and thoracic disc herniation, have been described.

4.3.3.4 Diagnostic Procedures
- X-ray
- MRI

4.3.3.5 Therapy
- Non-operative treatment: long-term therapeutic exercise, brace treatment, osteopathy, manual therapy, psychological therapy.
- Operative treatment with kyphosis correction by (anterior release and) posterior instrumentation depending on the reported retrospective series. Indications remain unclear since the natural history remains controversial with regard to pain, disability, self-esteem and deformity progression.

4.3.3.6 Prognosis
The question of kyphosis progression in the natural history of Scheuermann's disease remains unanswered. Patients without treatment were found to work in lighter jobs, had more severe back pain, but did not appear to be disabled by their symptoms [25].

4.3.2.3 Scheuermann's Disease (Juvenile Kyphosis)

4.3.2.3.1 Definition
Progressive dorsal kyphosis in the thoracic spine (> 40°) occasionally accompanied by compensatory hyperlordosis of the cervical and lumbar spine. Irregular vertebral end plates and disc space narrowing are other characteristics. Pathophysiology remains unclear [12]. Two different curve patterns have been described. A thoracic pattern (most common) is associated with a non-structural hyperlordosis of the cervical and lumbar spine. The thoracolumbar pattern is uncommon but thought to be the most likely to progress in adulthood.

4.3.2.3.2 Aetiology/Epidemiology
At present the aetiology is unknown, but a major genetic contribution is discussed while the environmental component is considered to be smaller. A review of a twin registry found a prevalence of 2.8% (2.1% among woman and 3.6% among men) [24].

4.3.2.3.3 Symptoms
Kyphosis, pain and, in rare cases, neurological complications secondary to severe kyphosis, such as dural cysts and thoracic disc herniation, have been described.

4.3.2.3.4 Diagnostic Procedures
- X-ray
- MRI

4.3.2.3.5 Therapy
- Non-operative treatment: long-term therapeutic exercise, brace treatment, osteopathy, manual therapy, psychological therapy.
- Operative treatment with kyphosis correction by (anterior release and) posterior instrumentation depending on the reported retrospective series. Indications remain unclear since the natural history remains controversial with regard to pain, disability, self-esteem and deformity progression.

4.3.2.3.6 Prognosis
The question of kyphosis progression in the natural history of Scheuermann's disease remains unanswered. Patients without treatment were found to work in lighter jobs, had more severe back pain, but did not appear to be disabled by their symptoms [25].
weakness of the muscles innervated by the root, decreased reflexes
  • Straight leg raising sign
  – Mechanical LBP:
    • Most common sign, resulting from strain of paraspinal muscles and or ligaments, irritation of the facet joints
  – ‘Red flags’ of LBP:
    • Acute onset of urinary retention or overflow incontinence
    • Faecal incontinence
    • Loss of anal sphincter tone
    • Saddle paraesthesia/anaesthesia
    • Weakness in the lower extremities

4.3.3.1.4 Diagnostic Procedures
If no ‘red flags’ are detected usually no further diagnostic work-up is necessary within the first month. Patients, which do not respond to medical treatment within 4 weeks should have further diagnostic work-up. The problem for now remains that individuals with or without non-specific pain in the lumbar spine may have similar findings on the images and that the findings are correlated poorly to the symptoms and signs.
  • X-ray
  • MRI, CT if lumbar disc herniation is suspected (see below)
  • Bone scan

4.3.3.1.5 Therapy
Non-surgical (exercising, manipulation), unless a serious underlying condition is diagnosed (see conservative management of lumbar disc herniation). Acute non-specific LBP largely is a self-limiting condition. For the majority of patients, minimal or no medical intervention is recommended. The most important message is for patients to keep as active as can be tolerated and for physicians not to recommend bed rest.

4.3.3.1.6 Prognosis
About 90% of patients will improve within 4 weeks. Rapid improvement occurs within the first 3 months, but improvements are gradual thereafter. Six months after onset, 16% of patients initially off work remain off work and at 12 months about 62% still have pain. Within 12 months of onset, recurrences of pain and recurrence of work absence were 62% and 33%, respectively [28, 29].

4.3.3.2 Lumbar Disc Herniation

4.3.3.2.1 Definition
Degeneration of a lumbar disc and displacement of disc material into the spinal canal with various degrees of extension of the disc outside its normal confines. Disc material can bulge through a tear in the annulus or can be sequestered. There is no standardised nomenclature for the various degrees of disc extrusion. In the majority of cases the disc herniation is lateralised to one side due to the greater strength of the posterior ligament in the midline leading to compression of the nerve root(s). Depending on the direction and the size of the sequestered disc either an isolated nerve root compression or a cauda equina compression can occur. The clinical symptoms depend on the impingement of the nerve roots. Lumbar disc herniation is most common in the L4/L5 and the L5/S1 segments. Usually the lower nerve root is compressed, but if the disc herniation is directed upwards the upper root is compressed.

4.3.3.2.2 Aetiology/Epidemiology
About 90% of disc herniations occur at L4/L5 and L5/S1 while in the upper lumbar spine they are less common. Some authors found that higher levels of disc herniation increased with age [30].

4.3.3.2.3 Symptoms
  • May start as LBP, which then develops to radicular pain (gradually or suddenly) with or without reduction of back pain. Sciatica is characteristic for lumbar disc herniation.
  • Pain may be relieved after flexing the knees.
  • Pain exacerbation may occur with coughing or sneezing.
  • Bladder symptoms include reduced sensation, urinary urgency and increased frequency.
  • Radiculopathy (see Table 4.3.2). Usually the herniated disc spares the nerve root exiting at the interspace and impinges on the root one level below. Seventy per cent of discs herniate downwards, but if the herniation is upwards the next higher root is compressed.
    – Dysfunction of the affected nerve root including pain, motor weakness, dermatomal sensory impairment, diminished reflexes, positive nerve root tension signs (Lasegue)
  • Cauda equina syndrome:
    – Acute onset of urinary retention or overflow incontinence
    – Faecal incontinence
    – Loss of or diminished anal sphincter tone
    – Saddle paraesthesia/anaesthesia
4.3.3.2.5 Therapy

An initial period of non-operative management should always be applied unless the herniated disc causes CES or profound motor deficit necessitating urgent surgical intervention (absolute indication for surgery). A relative indication for surgical treatment is severe pain that does not respond to adequate analgesia or persisting pain after failed conservative management without satisfactory improvement of the patient.

4.3.3.2.4 Diagnostic Procedures

- Plain x-ray: look for height of intervertebral disc space, osteophytes, abnormalities (spina bifida occulta). Not recommended for routine evaluation of patients with acute LBP within the first 4 weeks unless the patient shows signs of a severe condition (infection, malignancy, trauma).
- MRI: has widely replaced CT and myelography. MRI is the test of choice in patients with previous back surgery. Demonstrates impingement of thecal sac and/or nerve roots at origin or in their course through the neural foramen to exit the spinal canal. The level of the conus and intramedullary signal changes in the lower thoracic spine can be disclosed. MRI shows signal changes of the interspace disc, but is of limited value for bony assessment (see Fig. 4.3.4).
- CT: shows excellent bony details, adequately images soft tissue. If the only diagnostic image modality, the last three segments should be displayed and angulation should be in parallel to the disc space. Shows paraspinal structures and may detect lateral disc herniation or other pathology (tumour). Shorter imaging time for patients who can not stay still during the examination.
- Myelography and CT myelography: invasive examination with possible side effects (head ache), therefore almost no indication in patients with presumed lumbar disc herniation unless conditions preclude MRI (pacemaker) or limit the interpretation of MRI (severe scoliosis).

4.3.3.2.5.1 Conservative Treatment

About 85% of patients will improve with non-surgical treatment.

1. Activity modification: Within the acute phase (1-4 days) inactivation and bed rest may help to avoid painful movements and to reduce pressure on nerve roots and/or intradiscal pressure; best for patients with initial severe radiculopathy. Bed rest more than 4 days can have an adverse effect and a gradual return to normal daily activity should be achieved. In the subacute phase physical movement should be increased but avoiding painful movements and continuing activities of daily life. Heavy or repetitive lifting and bending or twisting of the back should be avoided. A gradual increase of the activity level is recommended but movements associated with pain or discomfort should be stopped. One or 2 weeks after the onset of pain, daily exercising as a physical therapy programme (walking, cycling, swimming) or conditioning exercises for trunk muscles (back extensors and abdominal muscles) can be helpful if pain persists. A graded activity programme may have the benefit of making the patients occupationally functional again [31].

2. Pharmacotherapy:
   a. Analgesics: NSAIDs, paracetamol, opioids (only within acute phase and replacement by NSAIDs within approximately 2 weeks).
b. Muscle relaxants: used either in isolation or in combination with other drugs (benzodiazepine and non-benzodiazepine muscle relaxants). The therapeutic objective is to reduce pain by relieving muscle spasm.

c. Epidural injections: may be an option for short-term relief in acute radicular pain.

3. Exercising programmes and manipulation therapy: A series of five to six manipulations in the acute stage of non-specific LBP, or a short course in pain treatment with five to six encounters with a therapist trained in the biopsychosocial approach reduces pain and disability in the short term [32]. The benefit of manipulation therapy after the first month is questionable; it should be avoided in acute radiculopathy with neurological deficit.

4. Education: proper posture, sleeping positions, lifting techniques.

5. Cognitive behavioural therapy: Treatment interventions include creative visualisation, imagery, progressive muscle relaxation techniques, problem-solving techniques and others. The goal is to have the patient understand, accept and gain control of the back pain problem and its possibly deleterious consequences (e.g. loss of self-esteem, fear of movement, depression, family problems, work loss, social withdrawal) by helping the patient develop adaptive coping behaviours and strategies (e.g. confrontation with activity, acceptance of pain, positive appraisal of the situation and problem solving) [32].

4.3.3.2 Surgical Treatment
- Indication for immediate surgery is a CES or severe (progressive) motor deficit associated with lumbar disc herniation in imaging procedures.
- No satisfactory reduction of sciatica with conservative treatment (pharmacotherapy and activity modification), remaining both severe and disabling for the patient, and radiographically identified abnormal findings that correlate to history and physical examination
are indications for surgery in patients with symptoms lasting more than 4 weeks.

- There is no indication for fusion or instrumentation unless lumbar disc herniation is associated with spondyloolisthesis and instability.

### 4.3.3.2.5.3 Surgical Approaches

- Microdiscectomy with minimal nerve root manipulation is a relatively safe and fast surgical procedure to remove the herniated lumbar disc. Except for intraforaminal and far foraminal disc herniations, microdiscectomy is performed via a posterior approach either in the prone (on an frame or chest role), knee chest or lateral position.
- Far lateral disc herniations can be operated on via a posterolateral approach without opening of the spinal canal.
- In endoscopic procedures a transformaminal discectomy via a lateral approach is possible at various levels, while the posterior approach is limited to L5/S1.
- Trends towards further less invasive procedures, such as pure sequestrectomy or endoscopic procedures, have shown similar results to standard microdiscectomy. Endoscopic procedures are increasingly applied for treatment of lumbar disc herniation.

### 4.3.3.2.6 Prognosis

- In general the symptoms of lumbar disc herniation can regress over time without surgery.
- Clinically improvement does not necessarily correlate with radiographically documented resolution of the disc herniation which may persist in about one third of patients [33].
- Prognosis after lumbar disc surgery is good or excellent in more than 85% of patients.
- In large series the complication rate of dural tears and nerve root injury is less than 2%.
- The rate of reoperation is about 5% [34].
- The Spine Patient Outcomes Research Trial (SPORT) assessed the efficacy of surgery for lumbar intervertebral disc herniation versus conservative management. Between-group differences in improvements were consistently in favour of surgical treatment for all periods but were small and statistically not significant except for the secondary outcome measures of sciatica severity and self-rated improvement [35].

### 4.3.3.3 Lumbar Spinal Canal Stenosis

#### 4.3.3.3.1 Definition

Narrowing of the lumbar spinal canal with clinical signs of claudication depending on the patient’s movement and/or posture. The term spinal stenosis comprises two different forms. **Central stenosis** is a narrowing of the canal in the AP diameter and **lateral recess stenosis** is a narrowing of the foramen intervertebrale. For central stenosis the dimension of the lumbar spine in the AP diameter is less than 15 mm, with less than 11 mm (from the spinolaminar line to the posterior vertebral body) considered as severe stenosis.

#### 4.3.3.2 Aetiology/Epidemiology

Spinal stenosis can be congenital (achondroplasia or congenital shallow spinal canal) or acquired (spondylolisthesis, posttraumatic) or superimposed on a relatively narrow spinal canal. It is most common in L4/L5 and L3/L4. Progressive narrowing of the canal can occur through facet hypertrophy, thickening of the ligamentum flavum, disc protrusion or associated spondylolisthesis, or a combination of all of these.

#### 4.3.3.3.3 Symptoms

The symptoms arise from the mechanical irritation of nerve roots. The classic sign is a neurogenic claudication (uni- or bilateral buttock, hip, thigh or leg pain) which has to be differentiated from vascular claudication. The discomfort is increased by standing or walking and patients feel relief when sitting or bending forward. Besides pain patients may have sensory deficits (paraesthesia), lower extremity weakness or walking difficulties. The walking distance should be evaluated. It is important to feel peripheral pulses, assess the pallor of the leg and skin temperature for differential diagnosis of vascular claudication. However, since patients with spinal stenosis of an old age and may have associated vascular problems, differential diagnosis can be challenging. Neurological examination can be normal but may show motor weakness, dermatomal sensory impairment and diminished reflexes.

#### 4.3.3.3.4 Differential Diagnoses

- Intermittent claudication (vascular claudication)
- Trochanteric bursitis
- Tumour of the lumbar spine
- Traumatic or osteoporotic changes
- Lumbar disc herniation

#### 4.3.3.3.5 Diagnostic Procedures

- Plain x-ray: shows dimensions of the spinal canal, osteophytes, spondylolisthesis (additional dynamic view may reveal pathological instability) or defects of the pars interarticularis.
- MRI: demonstrates impingement of the thecal sac and/or nerve roots (loss of CSF around neural structures)
Lumbar Spine due to facet hypertrophy, hypertrophy of the ligamentum flavum, bulging or herniated disc. MR myelography may help to diagnose symptomatic foraminal stenosis. The advantage of MRI is that the whole lumbar spine can be visualised in sagittal, axial and coronal planes using different sequences.

CT: shows excellent bony details such as facet hypertrophy and adequately images soft tissue.

Myelography and postmyelographic CT: invasive but excellent for patients in whom MRI is precluded; can be difficult in severe stenosis (see Fig. 4.3.5).

Fig. 4.3.5 Lumbar MRI with intrathecal contrast, which displays narrowing of the spinal canal with encroachment of the thecal sac, articular facet hypertrophy, thickening of the ligamentum flavum and bulging of the disc from ventral.

due to facet hypertrophy, hypertrophy of the ligamentum flavum, bulging or herniated disc. MR myelography may help to diagnose symptomatic foraminal stenosis. The advantage of MRI is that the whole lumbar spine can be visualised in sagittal, axial and coronal planes using different sequences.

- CT: shows excellent bony details such as facet hypertrophy and adequately images soft tissue.
- Myelography and postmyelographic CT: invasive but excellent for patients in whom MRI is precluded; can be difficult in severe stenosis (see Fig. 4.3.5).

4.3.3.6 Therapy

- Non-operative treatment: NSAIDs and physical therapy. Epidural injection is of less benefit in patients with spinal stenosis compared to patients with lumbar disc herniation [36], but other data showed significant improvement of patients [37].
- Operative treatment in cases with severe stenosis and failed satisfactory improvement after conservative treatment:
  - It is important that clinical symptoms are likely to be caused by radiographically seen pathological changes, otherwise the chance for clinical improvement is limited.
  - Degenerative changes shown by MRI are common and do not necessarily correlate to clinical symptoms [38].
  - Various options for surgical treatment ranging from minimally invasive decompression to major spine procedures have been described.
  - Five years after laminectomy, about 30% of patients develop a new spondylolisthesis and 73% show an increase of pre-existing spondylolisthesis during radiographic follow-up studies, but without clinical correlation [39].
  - There is no evidence that, in patients without instability, fusion has a better outcome compared to decompression alone. However, fusion has a higher incidence of perioperative complications.
  - In a prospective study, bilateral laminotomy was almost equally as effective as unilateral laminotomy [40].
  - Multilevel subarticular fenestration with foramotomy is very effective.
  - Usually there is no indication for fusion with or without instrumentation in patients with spinal stenosis.
  - In cases of associated spondylolisthesis and radiographic instability, posterior interbody fusion and instrumentation is an option compared to decompression alone.
  - The minimally invasive placement of an interspinous decompression systems (X-Stop) between the spinous processes of the affected level has been shown to be very effective in a randomised trial with 2 years follow-up [41].

4.3.3.7 Prognosis

- Natural history of patients with spinal stenosis is not well defined, however a substantial proportion of patients remained unchanged or improved after conservative therapy.
- After surgical decompression the short-term outcome is usually good and the rate of complications is low, which was also shown for patients older than 75 years [42]. However, restenosis may occur at the operated or adjacent level.
- Generally leg pain has a better prognosis compared to back pain after surgery.

4.3.3.4 Spondylolisthesis, Spondylolysis

4.3.3.4.1 Definition

Anterior subluxation of one vertebra on another. In patients with spondylolysis a defect in the pars interarticularis leading to translation of one vertebra over the other.
4.3.3.4.2 Aetiology/Epidemiology
The causes of spondylolisthesis can be traumatic, congenital or acquired as degenerative spondylolisthesis. If congenital it is most frequent in the L5/S1 segment and if degenerative the L4/L5 segment is affected. Spondylolysis occurs in about 2–4% of the general population and is more common in athletes. The degree of subluxation in patients with degenerative spondylolisthesis may increase with the degree of instability.

4.3.3.4.3 Classification
According to the extent of translation of the vertebra (Meyerding grade I–IV). Grade I is a subluxation of less than 25% of the size of the vertebra in lateral x-ray, grade II 25–50%, grade III 50–75% and grade IV more than 75%.

4.3.3.4.4 Symptoms
Instability may cause back pain, sciatica or radiculopathy. Radicular pain is more likely due to foraminal stenosis rather than canal stenosis. Patients with lumbar spinal stenosis may present with neurogenic claudication. About half of the patients with spondylolysis are clinically asymptomatic.

4.3.3.4.5 Diagnostic Procedures
- Plain x-ray: look for hyperlordosis, additional flexion and extension shows the degree of instability, oblique view shows typically the neck of the 'Scotty dog' in patients with spondylolysis
- CT
- MRI
- Myelography and postmyelographic CT

4.3.3.4.6 Therapy
In patients with spondylolysis the indication for treatment is reserved for the minority of cases with persisting complaints. Counselling of the patients should include recommendations for sport activities and if necessary reduction of body weight. Long-term follow-up with clinical surveillance is recommended. Conservative management includes analgesics and exercising.

Patients with degenerative spondylolisthesis and symptoms of LBP and sciatica should initially be managed conservatively (NSAIDs, physiotherapy). Surgery is considered as an option in patients with severe stenosis and neurogenic claudication after failed medical treatment. Options for surgical treatment are decompression of the spinal canal and/or nerve roots with or without instrumentation and fusion. Generally the authors favour a somewhat ‘conservative’ surgical management with a less invasive decompression of neural structures via a unilateral or bilateral approach depending on the severity of the recess stenosis. In cases with severe instability, decompression should be performed with additional posterior interbody fusion and instrumentation using transpedicular screw and rod fixation (see treatment of lumbar spinal stenosis). Caution has to be applied if intraoperative reduction of spondylolisthesis is achieved and nerve roots have to be observed during repositioning manoeuvres.

4.3.3.4.7 Prognosis
In patients with spondylolysis and sclerotic signs in lateral x-ray there is little chance of healing. The risk of further translation movement in adults is low.

Patients with degenerative spondylolisthesis and accompanying spinal stenosis may have the same benefit after surgical decompression as patients with spinal stenosis. Patients with decompression and fusion may have an increased risk for an adjacent segment disease.

4.3.3.5 Juxtafacet Cysts
4.3.3.5.1 Definition
Synovial and ganglion cysts of the spinal facet joint. Usually small lesions either attached or adjacent to the facet joints creating symptoms due to compression of exiting nerve root (radiculopathy) or the descending nerve roots (neurogenic claudication).

4.3.3.5.2 Aetiology/Epidemiology
Although juxtafacet cysts may occur throughout the spine they occur most frequently in the lumbar spine [43] and some consider the occurrence associated with spinal instability and/or spondylolisthesis.

4.3.3.5.3 Symptoms
Patients present with low back pain, unilateral or bilateral radiculopathy, neurogenic claudication or rarely with CES. Symptoms may be chronic with progressive worsening or of acute onset. Intracystic haemorrhage may occur and cause acute exacerbation.

4.3.3.5.4 Differential Diagnoses
- Lumbar disc herniation
- Lumbar spinal stenosis

4.3.3.5.5 Diagnostic Procedures
- MRI: T2-weighted image shows a bright hyperintense lesion arising from the facet joint. Cyst content can...
appear hyperintense compared to CSF due to proteinaceous content. In T1-weighted image the lesion is hypointense and the outer wall may enhance contrast. Juxtafacet cysts are usually located ventral to the facet joint but dorsal to the nerve roots (Fig. 4.3.6). Bilateral occurrence is not uncommon and after incomplete resection recurrence is possible.

- CT: displays low density round lesions located adjacent to the facet bulging into the spinal canal. Cysts are rarely calcified but sometimes haemorrhagic transformation occurs.

**4.3.3.5.6 Therapy**

- Non-operative treatment: Little is known about the natural history of juxtafacet cysts. Occasionally spontaneous regression has been described. Symptomatic treatment using NSAIDs and epidural injections may be beneficial.
- Surgical management: If patients complain of severe pain and have a radiographically confirmed juxtafacet cyst, surgery is a very effective treatment and therefore the treatment of choice. Various options for treatment have been discussed ranging from minimally invasive approaches and resection of the lesion to resection and spinal fusion of the affected level. However, resection can be difficult due to very strong adherence of the cyst to the dura and therefore dural tearing is a common complication of surgery. For complete removal and adequate resection frequently the exiting root above the segment and the traversing root of the affected segment have to be decompressed including the lateral recess.

**4.3.3.5.7 Prognosis**

Conservative management was rarely reported to a large extent and in smaller series most of the patients underwent surgery at a later time. However, surgical treatment was very effective and excellent results have been reported in a high percentage of patients.

**References**

4.4 Spinal Vascular Diseases

Uta Schick and Werner-Erwin Hassler

4.4.1 Introduction

Spinal vascular malformations are rare and often misdiagnosed entities. They comprise congenital cavernomas, arteriovenous malformations (AVMs) and presumably acquired dural arteriovenous fistulas (dAVFs). AVMs include perimedullary fistulas, glomerular AVMs, and juvenile AVMs (Table 4.4.1).

The intradural AVMs are supplied by spinal cord-supplying arteries, whereas the dural malformations are supplied by meningeal arteries as branches of the radicular artery (Fig. 4.4.1). Eighty percent of all spinal AVMs are dural fistulas with an incidence of 5–10/million/year. Dural AVFs first become symptomatic in later adult life, whereas medullary AVMs affect young adults.

4.4.2 Clinical Presentation

The clinical picture presents a slowly progressive myelopathy and/or radiculopathy with attacks of sudden or fluctuating deterioration up to a transverse lesion. A subarachnoid hemorrhage is rare in perimedullary fistulas and most frequent in angioma patients.

Clinical symptoms are a variable combination of lower motor neuron lesion, sphincter disturbance, sensory transverse lesion and partly additional signs of upper motor neuron involvement. Muscle pain and lower back pain were reported in 30% of patients with dAVFs, but not in angiomas. A distinct sensory level is present in most patients. The frequent discrepancy between the localization of the dural fistula and the spinal level re-

Table 4.4.1 Characteristics of the different types of AVMs

<table>
<thead>
<tr>
<th>Type of AVM</th>
<th>Dural</th>
<th>Perimedullary</th>
<th>Intramedullary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>80%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Men: women</td>
<td>8:1</td>
<td>3:2</td>
<td>1:1</td>
</tr>
<tr>
<td>Localization</td>
<td>Thoracolumbar</td>
<td>Lumbar</td>
<td>Cervical, lumbar</td>
</tr>
<tr>
<td>Arterial feeder</td>
<td>Meningeal</td>
<td>Spinal</td>
<td>Spinal</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;40 years</td>
<td>20–40 years</td>
<td>Childhood to 40 years</td>
</tr>
<tr>
<td>Subarachnoid hemorragh</td>
<td>Never</td>
<td>Sometimes</td>
<td>Frequent</td>
</tr>
<tr>
<td>Course</td>
<td>Slowly progressive</td>
<td>Acute deterioration</td>
<td>Slow improvement, changes with deterioration</td>
</tr>
</tbody>
</table>

Fig. 4.4.1 Schematic drawing of the different types of AVMs. Left dAVF, middle perimedullary fistula, right AVM
sponsible for clinical symptoms also supports the theory of inadequacy of the venous drainage system to cope with the blood volume. Fifty percent of untreated patients are disabled within 3 years.

Symptoms include:
- Thoracic sensorimotor myelopathy
- Spastic paraparesis
- Bowel and bladder dysfunction
- Spinal ataxia
- Back pain and radicular pain

4.4.3 Dural Arteriovenous Fistulas

The fistula itself is located laterally in the dural layer near the penetration point of the nerve root. This nidus is supplied by radiculomeningeal branches of the corresponding segmental artery. Venous drainage runs perimedullary along the spinal cord veins on the surface of the cord with retrograde filling, congestion and dilation of the coronal venous plexus. The local radicular venous drainage out of the intradural space is disturbed. The high venous pressure is presumed to be the cause of clinical symptoms, resulting in reduced perfusion, ischemia, and edema.

Dural AVFs first become symptomatic in later adult life. The strong preponderance of male patients is well known. In the majority of the dural lesions the arteriovenous nidus is located in the low thoracic or lumbar region. The direction of predominant venous drainage of most dAVFs is rostral.

The surgical treatment consists of intradural interruption of the draining vein. Alternatively, endovascular treatment with liquid embolic material is possible.
- Feeder: Meningeal, radicular, extradural feeder
- Fistula point: Lateral inside the dura near by the entering point of the nerve root
- Drainage: Perimedullary drainage, disturbed local venous drainage

4.4.3.1 Pathophysiology

The most important pathogenetic factor in dAVFs is the high venous pressure, resulting from arterialization of the veins. Because of the missing local venous drainage the increased venous pressure with the diminished arteriovenous pressure gradient leads to thrombosis of the spinal microcirculation and chronic spinal hypoxia. Finally, infarction with necrosis, demyelinization, and atrophy of the spinal cord and nerve roots occur.

4.4.4 Perimedullary Fistulas

Perimedullary fistulas are supplied by multiple branches of the anterior spinal artery. Drainage runs bidirectional along the venous spinal plexus. The fistula point lies outside the spinal medulla, hidden between the nerve roots, and covered by thickened arachnoidea. They are often associated with an aneurysmal enlargement or venous ectasia. The arterial drainage into the venous system with venous congestion and outflow obstruction is thought to cause chronic hypoxemia.

They present with the worst preoperative neurological status, improve dramatically postoperatively, and remain stable. The first step of treatment is the embolization with coils and/or liquid material. Embolization has to be as close as possible to the fistula. The second step is the surgical treatment. The surgical approach is performed in dorsally located fistulas via laminectomy or laminotomy with interruption of several fistula points outside the medulla.
- Feeder: Anterior spinal artery
- Fistula point: Outside the spinal medulla
- Drainage: Venous spinal plexus, venous ectasia

4.4.5 Angiomas

Angiomas may be supplied by multiple branches of the anterior spinal artery. Drainage is bidirectional into the venous spinal plexus.

They require a combined endovascular and surgical treatment. In angiomas, first the embolization of the main feeders with reduction of the blood flow should be performed with consecutive operations. Partial embolization of the nidus already reduces the risk of hemorrhage and leads to an improvement of neurological symptoms. Usually they show slight postoperative deterioration with partial recovery. There is no recurrence after complete excision of the nidus.

Without symptoms we recommend a "wait and see" attitude. Some symptomatic angiomas respond to reduction of the flow by embolization only.
- Feeder: Anterior spinal artery
- Nidus: Inside the spinal medulla
- Drainage: Venous spinal plexus

4.4.6 Diagnostic Imaging

The major problem in the management of patients with spinal dAVFs is the establishment of the diagnosis in a timely fashion.
4.4.10 Cavernomas

They constitute 5% of all spinal vascular malformations. Cavernomas are discrete, lobulated, and well-circumscribed, and are composed of dilated capillaries without functional tissue between the dilated vessels (Fig. 4.4.3).
4.4 Spinal Vascular Diseases

- They present with hemorrhage, calcification, and scarring with acute or progressive deterioration.
- T2-weighted MRI reveals a hypointense rim and an inhomogeneous hyperintense center. They do not appear on angiography.
- The treatment of choice is surgical resection.

Surgery for intradural AVMs should be carried out by experienced surgeons.

Acknowledgments. We thank Professor Brassel, Neuroradiology, Wedau Kliniken Duisburg, for the diagnostic imaging.

Suggested Reading


4.4.11 Conclusions

- Both endovascular and surgical treatment of spinal dAVFs result in a good and lasting clinical outcome in the majority of cases.
- Surgery for dAVF is an easy, safe and definitive treatment.
- Embolization should be attempted at the time of diagnostic angiography if the lesion is endovascularly accessible.
- Other malformations demand an interdisciplinary approach with neurosurgeons and interventional neuroradiologists.
- Cavernomas are surgical candidates.

4.4.12 European Recommendations

- Surgery is the recommended treatment with low failure rates for spinal fistulas and selected AVMs.
- Because of the progressive natural course with severe deficits we favor an early definitive treatment.
- An attempt at embolization should be made during angiography.
- No embolization should be performed in cases of extensive collateral vessels or feeding vessels.

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4.5 Infectious Disease of the Spine

M. NECMETTIN PAMIR

4.5.1 Vertebral Body and Disc Infections

4.5.1.1 Definition

- Infection may involve the vertebral body (spondylitis) or the intervertebral disc (discitis) [1].

4.5.1.2 Etiology/Epidemiology

- May be a complication of surgery or may occur through vascular spread.
- Spondylitis may be pyogenic or granulomatous caused by agents such as Mycobacterium tuberculosis (Pott’s disease), Brucella species, or fungi. Approximately 30–40% of spinal osteomyelitis is caused by *M. tuberculosis*.
- Pyogenic infections start at the subchondral bone and spread to the vertebral body or the disc.
- Tuberculous osteomyelitis starts at the anterior vertebral body; the disc space is spared and posterior elements are more commonly involved. Thoracic localization, slow progression, and calcified paraspinal abscesses are indicative of tuberculosis [2].
- Paraspinal abscesses may be seen as secondary extensions. Most commonly due to *Staphylococcus aureus* or *M. tuberculosis*.
- More commonly seen in men.

4.5.1.3 Symptoms

- Acute or chronic back pain.
- Focal tenderness on palpation.
- Neurological symptoms may follow.
- Fever and night sweats may be seen.
- Postoperative discitis starts within 1 month after surgery with severe back pain, fever, and vague radiating pain in lower back, groin, and scrotum.

4.5.1.4 Diagnostic Procedures

- MRI and CT are the backbone of diagnosis. MRI is the most sensitive and specific diagnostic test. Changes are detectable in 90–96% of cases and this incidence increases with time. Differential diagnosis from de-

Fig. 4.5.1a–c Pott’s abscess (spinal tuberculous spondylitis)
4.5.2.2 Etiology/Epidemiology

- Most commonly pyogenic in nature. Usually an extension of spondylitis or paravertebral abscess.
- Common in i.v. drug abusers or diabetics.
- M. tuberculosis is the second most common etiology.
- Fungal abscesses may be encountered in immunosuppressed individuals.
- Most commonly thoracic > lumbar > cervical.
- Most commonly dorsal to the thecal sac, ventral in 10–20%.

4.5.2.3 Symptoms

- Classic triad of backaches, fever, and spine tenderness.
- Acute or chronic back pain.
- Focal tenderness on palpation.
- A furuncle at the site may be seen in a minority of patients.
- Fever and night sweats may be seen.
- Neurological symptoms may follow.
- In postsurgical patients the clinical picture may be mild and consist only of pain in the area.

4.5.2.4 Diagnostic Procedures

- MRI reveals a peripherally enhancing spinal epidural mass (Fig. 4.5.2).
- Raised ESR, leukocytosis.
4.5.3 Transverse Myelitis and Human Immunodeficiency Virus Myelopathy

4.5.3.1 Definition

- Localized demyelinization of the spinal cord

4.5.3.2 Etiology/Epidemiology

- Is caused by an immune process resulting in small vessel vasculopathy, ischemia, and demyelinization.
- Differential diagnoses include demyelinization after immunization or due to multiple sclerosis, infarction, vasculitis, neoplasm, or radiation myelitis [11, 12].

4.5.3.3 Symptoms

- Clinical picture is identical to cord transection occurring over hours to a few days.
- Most common in the thoracic cord.
- Band-like chest pain mimicking acute myocardial infarction may occur before the onset of flaccid paralysis, sensory level, and urinary retention. Progressive rise in the sensory level may occur.

4.5.3.4 Diagnostic Procedures

- MRI shows enlargement of the cord, involvement of more than two segments, and involvement of more than two thirds of the spinal cord cross-section [11, 13, 14].

4.5.3.5 Therapy

- High-dose intravenous steroids [15]

References

4.6 Spinal Trauma

4.6.1 Surgery of Cervical Spine Trauma

Petr Suchomel

4.6.1.1 Introduction

Surgery for cervical spine trauma has undergone a major development during the past 20 years. The main goal of the modern approach is no longer to simply decompress neural structures but also to stabilise the spine in a single-stage operation. The restoration of physiological shape and function as well as good long-term outcome has to be on the priority list and, indeed, is expected of the surgeon. Cervical spine trauma represents approximately 30% of spine injuries. The classical indication for the surgery of cervical spine trauma is existing instability and/or compression of neural structures.

4.6.1.2 Trauma of Upper Cervical Spine (C0–C2)

Nearly one half of trauma victims suffering from upper cervical spine injury die at the scene of the accident, but 90% of survivors have no neurological deficit [6]. This means that adequate treatment of such injuries can dramatically reduce the risks associated with possible instability. Diagnosis is based on clinical status and morphological imaging. The first information is obtained from plain films including transoral imaging. Computerised tomography is superior in classification of bony trauma, especially if reconstructions or three-dimensional (3D) images are used. MRI is good for definition of soft tissue injury – neural structures, discs, ligaments. Supervised dynamic (flexion–extension) radiographs can be helpful in conscious patients.

The following sections briefly describe traumatic pathological entities of this region in a descending manner.

4.6.1.2.1 Atlanto-occipital Dislocations

Atlanto-occipital dislocations (AOD) are usually purely ligamentous injuries. Long-term survival is exceptional [5]. These injuries are classified into four types according to the direction of dislocation. Traynelis [27] and Harris [17] are the most frequently used classifications. Traction reduction should not be attempted in these injuries. Occipitocervical fusion is the treatment of choice in most of the surviving patients (Fig. 4.6.1).

Fig. 4.6.1a–c Type II atlanto-occipital dislocation (axial). a 3D CT reconstruction showing increased distance between atlas and occipital condyles. b Oedema of spinal cord and brain stem on MRI. c Occipitocervical fusion, Goel/Harms’ technique.
4.6.1.2.2 Fractures of Occipital Condyles
Fractures of occipital condyles are also rare. They are classified according to Anderson and Montesano [3] into three types. Most can be treated conservatively in a hard collar or halo vest (Fig. 4.6.2) and should only be operated on in rare situations. Surgery can be considered if there is a necessity to decompress neural structures, the avulsed or comminuted condyle cannot hold the weight of head or, in very rare cases, where there is a circular fracture of the foramen magnum. In such cases the shortest possible stabilisation should be chosen. Usually the instrumented atlanto-occipital fixation is sufficient.

4.6.1.2.3 Fractures of Atlas
The majority of fractures of the atlas are treated conservatively. There are several classification systems available [10, 15] but the final structural or functional status of the transverse atlantal ligament determines the stability of such injuries and thus the role for surgical intervention.

Fig. 4.6.2a,b Fracture of occipital condyle, type III (avulsion). a CT reconstruction in coronal plane. b 3D CT reconstruction of the same patient

Fig. 4.6.3a–c Incompetence of transversal atlantal ligament. a Transoral film showing the overhang of atlantal lateral masses. b Avulsion of bony atlantal ligament attachment on CT. c Lateral rupture of atlantal ligament on MRI

Fig. 4.6.4a,b Temporary fixation in compression of fracture of atlas. a Lateral radiogram. b Anteroposterior view
Integrity of this ligament can be estimated from dislocation of lateral masses (more than 7 mm) on a transoral picture or by direct visualisation on MRI (Fig. 4.6.3). When surgical treatment is indicated then either temporary internal fixation of atlas (Fig. 4.6.4) or atlantoaxial fusion are used as surgical alternatives. Currently also some intra-articular fractures can be considered for surgical intervention, especially if minimally invasive image-guided techniques are available (Fig. 4.6.5).

4.6.1.2.4 Fractures of Axis
Fifty percent of fractures of the second cervical vertebra involve fractures of the odontoid process, one quarter involve the vertebral ring, often called hangman's fractures, and the rest are so-called miscellaneous or non-classifiable injuries [13].

Odontoid process fractures are further classified according to Anderson and D'Alonso [2] into three subtypes:
Type I  The tip of dens
Type II  Fracture of the odontoid base
Type III  Broad-base fracture involving the C2 body (Fig. 4.6.6).

Most authors prefer direct osteosynthesis of the fracture of the base of odontoid process (type II) either with one or two screws [4, 8], which is the physiological treatment with highest fusion rate (Fig. 4.6.7). When the fracture line is extending to the body of the axis (type III), bracing is sufficient in most cases. However, when the fracture line passes through the joints, is shallow or halo fixation is either not possible or disadvantageous (old people), surgical treatment may be preferred even in such fractures. Type I fracture is very rare, biomechanically stable enough and treated with a hard collar. Atlantoaxial fu-

Fig. 4.6.5a–d Percutaneous CT-guided compressive osteosynthesis of intra-articular fracture of lateral mass of atlas. a 1.1-mm K-wire gradually passes through the C1 lateral mass according to preoperative plan. b K-wire attached to the battery-operated drill being introduced percutaneously. c Reduction of the fracture gap by the bicortical cannulated lag screw introduced along the K-wire. d Postoperative lateral radiogram
4.6 Spinal Trauma

The vast majority of hangman’s fractures are still treated with halo fixation. Despite numerous modifications of the classification system available [9, 21] it is still often difficult to distinguish the potentially dangerous instability on the ‘cool’ admission plain films from the stable injuries. The mechanics of the injury and anatomy at the maximal point of impact can only be estimated and the degree of instability is often underestimated. Precise analysis of CT reconstructions and MRI evaluation of soft tissue injury can be supplemented with supervised dynamic flexion–extension films in co-operating conscious patients (Fig. 4.6.8). If the C2/C3 segment is unstable and the intervertebral disc is destroyed, we recommend an anterior C2/C3 disectomy, graft and plate fusion (Fig. 4.6.9). If the segment is stable but the fracture gap as seen on CT scan is larger than 3 mm, a transisthmic compressive osteosynthesis according to Judet [20, 24, 26] can be advantageous especially if CT-guided technology is available (Fig. 4.6.10).

Atypical fractures of C2 called ‘miscellaneous’ according to Hadley [14] are treated individually and mostly by external support. Some of them are unstable and surgical treatment can be more valuable especially in old people with breathing problems in a halo vest or in poly-trauma ventilated patients where long-term traction or a halo vest could be disadvantageous (Fig. 4.6.11). The type of principal instability is the most important factor determining choice of treatment of C1 and C2 combined fractures (Fig. 4.6.12).

4.6.1.2.5 Traumatic Atlantoaxial Instability

This can be considered as an isolated entity only in cases of pure transverse ligament injury. It does exist as an acute injury but is frequently recognised later in a chronic phase on dynamic films where the distance between odontoid process and anterior arch of atlas is increasing to 3.5 mm or more. The treatment is atlantoaxial fusion. Osteosynthesis is technically demanding [12, 16, 22, 23, 25], but allows immediate patient mobilisation and attractive fusion rates in long-term follow-up (Fig. 4.6.13). Generally, in cases of traumatic C1/C2 instability, the surgeon has to bear in mind that surgical fusion can create up to 50% loss of cervical spine rotational mobility [19].
Fig. 4.6.8a–d Combined hangman type II fracture with odontoid type II fracture. a Plain admission film, sitting patient. b Dynamic X-rays (conscious co-operating patient) – flexion. c CT reconstruction. d Surgical treatment with two screws for odontoid fixation, graft and plate fixation for hangman's fracture.
Fig. 4.6.9a–c  Hangman’s type fractures indicated for anterior C2/C3 graft and plate fusion. a Dislocated fracture caused by hyperextension. b Dislocated fracture with distraction of the disc space. c Anterior plate and graft fusion (note bicortical screw purchase)

Fig. 4.6.10a–c  Posterior CT-guided compressive osteosynthesis (Judet) of hangman’s fracture. a K-wires gradually introduced under real-time CT control through the fracture. b Reduction of fracture gap by bilateral lag screws. c Postoperative lateral radiogram

Fig. 4.6.11a,b  Comminuted fracture of the C2 body involving the C2/C3 disc space, patient refused recommended halo-vest. a Preoperative sagittal CT reconstruction. b Postoperative lateral radiogram showing screw fixation between lateral masses of atlas, pedicles of C2 and lateral masses of C3
4.6.1.3 Trauma of Subaxial Cervical Spine (C3–T1)

There is a whole myriad of classification systems available to distinguish among various types of subaxial cervical spine injuries [1, 11, 18]. No one scheme is ideal and the degree of possible neurological deficit has to be added mostly using Frankel or American Spinal Injury Association (ASIA) scoring. A frequently used system is that of Allen [1] differentiating six types of fractures according to the mechanism of injury (Fig. 4.6.14):

- Type I is caused by compressive flexion and is further divided to five subcategories.
- Type II is caused by vertical compression and represents the failure of vertebral body (three subtypes) with the end point called a ‘burst fracture’.

![Fig. 4.6.12a–c](image1) Combined fracture of C1/C2 complex. Coincidental Jefferson’s fracture of atlas, hangman’s type II and odontoid type II fractures of C2. a Preoperative lateral radiogram. b,c Postoperative films depicting anterior atlantoaxial screw fixation, single screw odontoid fusion and C2/3 graft-plate stabilisation of hangman’s fracture

![Fig. 4.6.13a,b](image2) Currently the most frequently used techniques of posterior atlantoaxial fixation. a Magerl’s transarticular fixation supplemented with Gallie’s graft. b Goel/Harms’ technique of posterior C1/C2 fixation supplemented with Gallie’s graft
- Type III is the failure of posterior ligamentous complex due to distractive flexion (four subcategories; end point luxation).
- Type IV represents a failure of posterior bony elements under compression (three subtypes of arch fractures).
- Type V is a progressive failure of motion segment from anterior to posterior caused by distractive extension. This injury is well known as ‘fall on face’ in older people.
- Type VI is asymmetric bone compression usually caused by lateral flexion under load.

Algorithms used to classify cervical subaxial injuries vary between institutions and even among surgeons within single departments. There is no unified language for communication, research and education available. Therefore, recently, a new approach to classification of subaxial cervical spine injuries (SLIC) has been proposed by Vaccaro et al. [28] and the Spine Trauma Study Group (48 spine surgeons) and has been received with enthusiasm by the spine surgery community. The SLIC classification proposes three major injury characteristics:

Fig. 4.6.14 Schematic drawing of mechanistic classification of Allen. Modified from [1]
1. Injury morphology as determined by the pattern of spinal column disruption on available imaging studies from better to worse (compression, distraction, translation)
2. Integrity of disco-ligamentous soft tissue complex (intact, indeterminate, disrupted)
3. Neurological status of the patient (intact, root, incomplete cord, complete cord)

The system is based on a simple evaluation of radiographic and clinical characteristics together thus giving us the potential to decide between conservative and/or surgical treatment.

The majority of unstable middle and lower cervical spine injuries can be treated with an anterior approach following a closed reduction with traction (Fig. 4.6.15).

Non-reducible facet dislocations/fractures and predominantly posterior instabilities are usually treated with combined procedures often starting with anterior discectomy and release (Fig. 4.6.16).

At our institution, in surgical cases, a neurological deficit is an indication for urgent intervention. Even in patients with degenerative canal stenosis with hyperextension injuries who present with a typical neurological deficit, urgent surgical decompression and fusion would be performed. We frequently find tears of anterior longitudinal ligament on MRI as well as during surgery in these cases. They represent instabilities potentially dangerous for the spinal cord, especially in a stenotic canal.

Traumatic injury of cervicothoracic junction in patients with ankylosing spondylitis presents the surgeon with a different problem, as the fused spine tends to frac-

**Fig. 4.6.15a,b** Dislocated comminuted fractures of C5 and C6. a Lateral radiogram after traction. b Double-level corpectomy and graft/plate fixation, fusion in reduced position after 1 year

**Fig. 4.6.16a–c** C6/C7 luxation fracture with total spinal cord lesion. a MRI prior to reduction. b Situation after combined procedure: traction and posterior reduction with Magerl’s hook fixation, anterior discectomy, graft and plate fusion. c Postoperative sagittal T2 MRI showing the extent of spinal cord damage
Fig. 4.6.17a–c Fracture of cervicothoracic junction in patient with Bekhterev’s disease. a CT reconstruction showing the fracture and fragment in spinal canal. b Postoperative CT sagittal reconstruction documenting the reduction. The screws were introduced in pairs into lateral masses of subaxial cervical spine and transpedicularly into upper thoracic area, with the help of virtual navigation. c Progress of fracture healing 3 month after the surgery.

4.6.1.4 Conclusion

Thanks to decreasing frequency of complications, active surgical treatment has become more favourable than external bracing and thus follows the general trends in trauma surgery. Surgically treated patients can mobilise early and the overall fracture healing rate is also much improved.

It would be impossible to list an entire range of hardware available to surgeons nowadays, but the fundamental question remains: ‘Which procedure is the most appropriate one for my patient?’

Our operative work has to be as minimally invasive as possible, effective and most of all cause ‘no harm’ in order to achieve good long-term outcomes in our patients.

On the other hand, no reliable evidence is available that would ease the decision-making process regarding conservative versus surgical treatment or what surgical option should be utilised in each particular case.

References

4.6.2 Trauma of the Thoracolumbar Spine

DENIS L. KAECH

4.6.2.1 Introduction

The thoracolumbar spine, i.e., T11–L2, is a transition zone between the more stable T1–T10 spine, which is connected by the rib cage to the sternum, and the more mobile L3–L5/S1 spine. Although not every neurosurgeon is involved in the acute management of vertebral fractures and dislocations, a basic understanding of spinal injury classifications, and some checklists allowing to evaluate the degree of posttraumatic instability should be part of the learning and training programme.

4.6.2.2 Classifications and Review of the Recent Literature

The ‘historic’ AO classification of thoracolumbar fractures by Magerl et al. [26] was a work of five authors in 1994 and was based on three injury mechanisms (Fig. 4.6.18): A. Compression injury of the anterior column B. Distraction injuries with two column lesion C. Rotation injuries with three column lesion

These three groups are further divided into subgroups, which are listed in Table 4.6.1. Type A fractures are considered to have intact posterior bony and ligamentous structures, while types B and C do not.

The new proposal of Vaccaro et al. (Table 4.6.2; Fig. 4.6.19) results from a collaboration between 18 spine specialists in 2005 [27]: the Thoracolumbar Injury Classification and Severity Score (TLICS). It is based on three injury characteristics:

1. Morphology of the injury determined by radiographic appearance
2. Integrity of the posterior ligamentous complex (PLC)
3. Neurological status of the patient


Fig. 4.6.18a–c AO classification of spinal fractures [26]. a Compression. b Distraction: flexion (left), extension (right). c Rotation
<table>
<thead>
<tr>
<th>AO type A: Vertebral body</th>
<th>compression</th>
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<tbody>
<tr>
<td>A1 Impaction fractures:</td>
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<tr>
<td>A1.1 Endplate impaction</td>
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<tr>
<td>A1.2 Wedge impaction</td>
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</tr>
<tr>
<td>A1.3 Vertebral body collapse</td>
<td></td>
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<tr>
<td>A2 Split fractures:</td>
<td></td>
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<tr>
<td>A2.1 Sagittal split fractures</td>
<td></td>
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<tr>
<td>A2.2 Coronal split fractures</td>
<td></td>
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<tr>
<td>A2.3 Pincer fractures</td>
<td></td>
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<tr>
<td>A3 Burst fractures:</td>
<td></td>
</tr>
<tr>
<td>A3.1 Incomplete burst fracture</td>
<td></td>
</tr>
<tr>
<td>A3.2 Burst split fracture</td>
<td></td>
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<tr>
<td>A3.3 Complete burst fracture</td>
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<tr>
<th>AO type B: Anterior and posterior element injury with distraction</th>
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<tr>
<td>B1 Posterior disruption predominantly ligamentous (flexion-distraction injury):</td>
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<tr>
<td>B1.1 With transverse disruption of the disc</td>
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<tr>
<td>B1.2 With type A fracture of the vertebral body</td>
</tr>
<tr>
<td>B2 Posterior disruption predominantly osseous (flexion-distraction injury):</td>
</tr>
<tr>
<td>B2.1 Transverse bicolumn fracture</td>
</tr>
<tr>
<td>B2.2 With disruption of the disc</td>
</tr>
<tr>
<td>B2.3 With type A fracture of the vertebral body</td>
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<tr>
<td>B3 Anterior disruption through the disc (hyperextension-shear injury):</td>
</tr>
<tr>
<td>B3.1 Hyperextension-subluxation</td>
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<tr>
<td>B3.2 Hyperextension-spondylolysis</td>
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<td>B3.3 Posterior dislocation</td>
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<tr>
<th>AO type C: Anterior and posterior element injury with rotation</th>
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<tr>
<td>C1 Type A injuries with rotation (compression injuries with rotation):</td>
</tr>
<tr>
<td>C1.1 Rotational wedge fractures</td>
</tr>
<tr>
<td>C1.2 Rotational split fractures</td>
</tr>
<tr>
<td>C1.3 Rotational burst fracture</td>
</tr>
<tr>
<td>C2 Type B injuries with rotation:</td>
</tr>
<tr>
<td>C2.1 B1 injuries with rotation (flexion-distraction injuries with rotation)</td>
</tr>
<tr>
<td>C2.2 B2 injuries with rotation (flexion-distraction injuries with rotation)</td>
</tr>
<tr>
<td>C2.3 B3 injuries with rotation (hyperextension-shear injuries with rotation)</td>
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<tr>
<td>C3 Rotational shear injuries</td>
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<tr>
<td>C3.1 Slice fracture</td>
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<tr>
<td>C3.2 Oblique fracture</td>
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Morphology of the injury. The fracture patterns are:

- Compression (corresponding to the AO type A), with prefixes such as (a) axial, (b) flexion and (c) lateral, which may be used to more precisely describe the injury morphology.
- Translation Rotation (corresponding to the AO type C). NB: Considerable torsion and shear forces lead to more destruction of anatomy and therefore more instability than failure from compression only.
- Distraction (corresponding to AO type B) with subtypes such as (a) flexion, (b) extension and (c) compression or burst.

As combinations of these morphological patterns may occur, and also multilevel trauma, this classification may allow for some controversies, as do the previous ones (see 1–4-point scale for injury morphology in Table 4.6.2).

Integrity of the PLC:

- The supraspinous and interspinous ligaments.
- The facet capsule and ligamentum flavum, which are important as they function as a posterior tension band.
- Widening of the interspinous space, diastasis of the facet joints and facet subluxation are indicators of a disruption (3 points in this score), which generally requires surgery because of its poor healing ability. The evidence of disruption may also be subtle, or ‘indeterminate’ (2 points in this score), and the PLC may also be intact (0 points in this 0–3-point scale for PLC; Table 4.6.2).

Neurological status:

- It is an important parameter as incomplete (and progressive) neurological injury is generally accepted as an indication for surgery (0–3-point scale; Table 4.6.2).

In a subsequent paper with 32 authors, Vaccaro et al. [46] reported the results of 5 spine surgeons rating 71 cases on CD-ROM and re-rating the cases in a different order 1 month later, using the Thoracolumbar Injury Severity Score (TLISS) [46, 47]. The minor difference is that the injury mechanism or the fracture patterns are more precisely subscored: Simple compression = 1 point + 1 point for burst + 1 point for lateral angulation > 15° (Table 4.6.2). The worst level is used and injury is additive, e.g. distraction injury with a burst component without lateral angulation would receive 6 points: 1 for simple compression + 1 for burst + 4 for distraction! In all the scores proposed by Vaccaro et al. a score up to 3 points suggests non-operative treatment, whereas a score of 5 and more points suggests operative treatment [45–48].

In 2006 Schweitzer (with Vaccaro) et al. [38] published a survey of the Spine Trauma Study Group (STSG) entitled Confusion regarding mechanisms of injury in the setting of thoracolumbar spinal trauma. The TLISS and the TLICS have minor differences, as also shown in Table 4.6.2. Both TLISS from 2005 and TLICS from 2006 were compared in a 16-author paper published in 2007 [52]. The TLISS was found to be more reliable than the TLICS, suggesting that the mechanism of trauma may be a more valuable parameter than fracture morphology. Nevertheless both schemes exhibited excellent overall reproducibility.

Vaccaro’s TLICS: 1–4 Points for injury morphology

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<th>Fracture Pattern</th>
<th>Points</th>
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<tr>
<td>Compression</td>
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<tr>
<td>Burst</td>
<td>1</td>
</tr>
<tr>
<td>Translational/rotational</td>
<td>3</td>
</tr>
<tr>
<td>Distraction</td>
<td>4</td>
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Fig. 4.6.19 Thoracolumbar fracture injury classification system (TLICS) [45]
Spinal Trauma

cord deficit is considered to be a good surgical indication (surgery being recommended to fix cervical and thoracolumbar spines when 5 and more points are summarised using these scores: see also Table 4.6.2).

Lemaire and Laloux focus on the main traumatic, i.e., injuring vector to classify thoracolumbar fractures and to formulate a treatment algorithm [23]. Basically trauma cases with anterior major injury vector had cord compression and anterior column reconstruction, whereas a posterior reduction and stabilisation was performed when the main injuring vector was posterior. They classified:

A. Compression fractures, with different types of burst fractures due to a vertical anterior trauma vector. Neurological deficits occur in about 50% of patients, with posterior wall displacement around 25%, not correlating reliably to the neurological status. As a general rule > 25% posterior wall displacement is needed in the

<table>
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<th>Elements of evaluation</th>
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<tr>
<td>Morphology: injury mechanism/fracture patterns</td>
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<tr>
<td>Compression/(simple compression)</td>
<td>1</td>
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<tr>
<td>Compression burst</td>
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<tr>
<td>Lateral angulation &gt;15°</td>
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<td>Translational/rotational</td>
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<td>Distraction</td>
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<td>Integrity of the posterior ligamentous complex (PLC)</td>
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<td>Intact</td>
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<td>Suspected/indeterminate</td>
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<tr>
<td>Injured</td>
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<td>Neurological status</td>
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<tr>
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<tr>
<td>Nerve root injury</td>
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<td>Cord, conus: complete</td>
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<tr>
<td>Cord, conus: incomplete</td>
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<tr>
<td>Cauda equina</td>
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Table 4.6.2 Thoracolumbar Injury Classification and Severity Score (TLICS)/Thoracolumbar Injury Severity Score (TLISS) [45–47]

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<th>Elements of evaluation</th>
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<td>Morphology: injury mechanism/fracture patterns</td>
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<td>Lateral angulation &gt;15°</td>
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<td>Translational/rotational</td>
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<td>Distraction</td>
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<td>Intact</td>
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<td>Suspected/indeterminate</td>
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<td>Neurological status</td>
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<td>Cord, conus: complete</td>
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<td>Cord, conus: incomplete</td>
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<td>Cauda equina</td>
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Treatment modality

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<td>≤ 3</td>
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<td>≥ 5</td>
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Example

Translational, lateral compression burst injury with complete spinal cord injury and disrupted PLC

and validity. There are only minor differences, as shown in Table 4.6.2, and the derived treatment algorithms, i.e. non-operative treatment in scores of < 3 and operative treatment in scores > 5, are concordant in both systems!

It is interesting that Vaccaro et al. have also proposed an almost comparable ‘Subaxial Cervical Spine Injury Classification System’ [48]. The three main categories are:

1. Morphology
2. Disco-ligamentous complex (DLC, instead of PLC)
3. Neurological status: 0 points means intact neurology, 1 point root injury (versus 2 points in TLICS), 2 points complete cord injury, 3 points incomplete cord injury, with an additional point for ‘continuous cord compression in setting of neurodeficit (Neuro Modifier)’

This gives more points for the total score and shows that a neurological deterioration in a patient with no or partial cord deficit is considered to be a good surgical indication (surgery being recommended to fix cervical and thoracolumbar spines when 5 and more points are summarised using these scores: see also Table 4.6.2).

Lemaire and Laloux focus on the main traumatic, i.e., injuring vector to classify thoracolumbar fractures and to formulate a treatment algorithm [23]. Basically trauma cases with anterior major injury vector had cord decompression and anterior column reconstruction, whereas a posterior reduction and stabilisation was performed when the main injuring vector was posterior. They classified:

A. Compression fractures, with different types of burst fractures due to a vertical anterior trauma vector. Neurological deficits occur in about 50% of patients, with posterior wall displacement around 25%, not correlating reliably to the neurological status. As a general rule > 25% posterior wall displacement is needed in the
4.6.2 Trauma of the Thoracolumbar Spine

Thoracic, and > 30% is needed in the lumbar spine to cause neurological deficits. Lemaire and Laloux insist on the importance of a vertical split through the whole vertebral body (with increased interpedicular distance on x-ray and CT) with dislocation of disc material from the supra- and infrajacent disc into the fracture cleft, which is a well-known obstacle to bony healing, i.e. solid fusion. The anterior approach is chosen to fix such lesions (Fig. 4.6.20).

B. Flexion-compression injuries, i.e. the injury vector leads to an eccentric axial compression which induces a flexion moment. They found four subtypes, from a tear drop or anterior wedge fracture without neurological deficit, treated conservatively, to more comminuted fractures with kyphotic deformity, associated discal and posterior ligament injuries with neurological deficits in 40–80% (Fig. 4.6.24). Major cases needed anterior and posterior surgery.

C. Flexion-distraction injuries, with an oblique vector and a deceleration-shear mechanism. Subclassified are Chance fractures without dislocation and without deficits and fractures with luxation plus neurological deficits, treated by posterior fixation, the main traumatic vector being posterior.

Historically Chance [7] described in 1948 a fracture going from the spinous process through the lamina, pedicles and the vertebral body (see Fig. 4.6.21), corresponding to an AO type B lesion, typically caused by the classic seatbelt injury mechanism. Due to the large bone on bone contact such fractures will heal well after short segment fixation. The least stable variant includes a tear through the disc, the joint capsules and the posterior ligaments, which do not heal properly to restore stability. Surgical treatment is here essential, also for the combined bony and ligamentous “Chance type” injury.

D. Translation–rotation fractures, all with major neurological deficits, requiring posterior decompression and instrumentation mostly completed by an anterior approach. Here the injuring vector is posterior and transverse [23].

4.6.2.3 Indications for Fixation, Diagnostic Work-up and Defining Stability

- Stabilisation is indicated for unstable vertebral fractures and for disco-ligamentous instability. The goal of surgery is to eliminate or at least reduce pain and dysfunction.
- Fracture reduction and fixation will allow bony healing, and the fusion will provide stability [10, 11, 18, 19, 21–24, 27–32, 37, 40–48].
- The treatment strategy will depend on the amount of damage, not only to the spine but also to other parts of the body e.g. associated major chest injury. Also spinal cord and head injury can decrease the chance of survival or good functional outcome [1, 14].
- The surgical options are posterior approach, anterior approach and a combined approach resulting in a 360° fixation and will be discussed later. The surgical planning is based on a precise analysis of diagnostic imaging studies, including basic biomechanical knowledge [8, 19, 22–25, 35, 53].

4.6.2.3.1 Defining Stability

- A classical definition of instability was proposed by White and Panjabi [53]: ‘Clinical instability is defined by the loss in the ability of the spine under physiologic loads to maintain relationships between vertebrae in such a way that there is neither damage nor subsequent
irritation to the spinal cord or nerve roots. In addition there is no development of incapacitating deformity or pain due to structural changes.

- Shorter and older statements were by Nicoll in 1953: 'No deformity or neurological deficit increasing over time', and by Kelly and Whitesides in 1968: 'Unstable if progressive deformity results in increasing neurological compromise'.
- The panel, i.e. Vaccaro et al. [45–47] proposed the other way round to define stability:
  - Immediate mechanical stability (suggested by the morphology of the injury)
  - Long-term stability (indicated by the integrity of PLC)
  - Neurological stability (indicated by the presence or absence of a neurological deficit)

These terms are also used to describe the goals of spinal stabilisation procedures. The fixation should provide immediate postoperative mechanical stability, later long-term stability should be achieved by the bony fusion, including maintenance of the obtained correction of spinal deformity, and offer the best protection to the neural elements by eliminating harmful motion [5]. This is true not only for degenerative instability, but also for post-traumatic instability and for instabilities due to tumours, infections and postsurgical problems.

In their chapter about biomechanics of spinal column failure, Roger et al. [35] describe: 'Acute instability, with overt and limited instability', and 'chronic instability, with glacial instability and dysfunctional segment motion' (the latter terminology being also used for 'degenerative instability'). The term overt instability means that the spine is not able to support the torso during normal activity. This may be due to a combination of vertebral body or disc integrity loss combined with a loss of integrity of the dorsal elements: AO type B and C fractures, but also neoplastic or infectious destructions affecting 2–3 columns (see below). It is synonymous with gross instability and should be treated surgically in nearly all cases.

Limited instability is defined as the loss of either ventral or dorsal spinal integrity, with preservation of the other. Such is sufficient to support most normal activities (e.g. laminar fractures, or A1/A2 wedge or partial anterior burst fractures).

Chronic instability may be a sequel to an acute process or related to degeneration. Glacial instability means slowly progressing deformity. Dysfunctional segment motion generates a mechanically induced pain (with or without neurological symptoms/signs).

### 4.6.2.3.2 Checklist, Classification

The following knowledge is useful in the daily neurosurgical practice for assessing the stability of an injured spine. Some of these principles can also be applied to the degenerative spine.

The analysis of spinal structures using one of the three column spine models of Louis [25] or Denis [8] (Fig. 4.6.22) is a first step towards the diagnosis of spinal instability. In both models, the weakening of one column may be tolerated, but the weakening of two columns leads to instability. Louis’s model is useful also for evaluating degenerative and postoperative instability; Denis’ model is mainly used for traumatic cases.

René Louis’ three column spine [25] consists of an anterior column (vertebral body-disc-vertebral body, etc.) and of two posterior columns (the left and right articular facets with laminar chains between the upper and lower articular process). Approximately 80% of the loads go through the anterior column, which is the main weight-bearing part of the spine. A total facetectomy means an interruption of the posterior column – bony elements building a bridge are missing – and in isthmic spondylolysis there is only a fibrous union instead of bone in both posterior columns of the affected level. The facets act as a rotatory

---

**Fig. 4.6.21** Chance-type, flexion-distraction injury [7]: AO type B, (2-) 3 columns affected = unstable

**Fig. 4.6.22** Chance type injury flexion-distraction
brace; rotational instability may develop following larger facet resections. Recent papers have stressed that the fluid inside the lumbar facet joints is a valuable indicator of decreased stability [33].

Denis’ anterior column consists of the anterior longitudinal ligament, the annulus and the anterior part of the vertebral body and disc. The middle column consists of the posterior part of the vertebral body and disc, with the posterior longitudinal ligament and the pedicles. The posterior column is made up of the posterior arch with the facet joints, spinous process and inter- and supraspinous ligaments [8, 9].

The analysis of vertebral body damage is easier and more systematic with the load-sharing classification [19, 28]. It is based on the relationship between the amount and characteristics of vertebral injury and the risk of posterior instrumentation failure (e.g. screw breakage) following pedicular fixation: the amount of vertebral body comminution, the displacement of the fractured fragments and the correction of kyphotic deformity (angle) scored with 1–3 points indicate the load-sharing capacity of the anterior column (Table 4.6.3) [19, 28]. The maximum of 9 points mean no load sharing in a totally burst vertebra with markedly dislocated fragments and kyphotic deformity exceeding 10°. In Holt et al.’s series 10 out of 28 patients scoring 7–9 points experienced screw breakage [19]. In such cases, additional anterior stabilisation should be considered.

The load-sharing classification of thoracolumbar fractures has been validated biomechanically in vitro by Wang et al. [49]. By measuring the three-dimensional flexibility data of bovine T12–L3 specimens (subjected to axial compressive impact with 63.8, 107.8 and 137.2 J energy), they found an increasing load-sharing score with increasing levels of impact energy. Fractures with mild comminution (6 points or less) showed more stability as compared to those with more comminution (7–9 points).

Analysis of motion is an important diagnostic step in degenerative instability but is contraindicated in acute vertebral trauma to avoid displacement causing (further) neurological damage! Posttraumatic deformity with pathological angles and alignment of the vertebral column must be precisely assessed.

For a standardised description of displacement and motion the three-dimensional coordinate system proposed by White and Panjabi [53] can be recommended:
- The X-axis goes horizontally in the frontal plane (from left to right or right to left)
- The Y-axis is vertical (from rostral to caudal)
- The Z-axis is sagittal, ‘AP’ or dorsoventral

There can be isolated or more often coupled motion, i.e. translation along or rotation around one of the three axes (X, Y and Z), e.g. anterolisthesis means translation along the Z-axis, ‘vertical instability’ along the Y-axis and later-

Table 4.6.3  Load-sharing classification

<table>
<thead>
<tr>
<th>Comminution/involvement on sagittal plane section CT</th>
<th>Apposition of fragments displacement on axial CT cut</th>
<th>Deformity correction: kyphotic correction on lateral radiograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: &lt; 30% comminution</td>
<td>1: minimal, i.e. &lt; 2 mm</td>
<td>1: ≤ 3°</td>
</tr>
<tr>
<td>2: 30–60% comminution</td>
<td>2: &gt; 2 mm on &lt; 50% of body</td>
<td>2: 4–9°</td>
</tr>
<tr>
<td>3: &gt; 60% comminution</td>
<td>3: &gt; 2 mm on &gt; 50% of body</td>
<td>3: ≥ 10°</td>
</tr>
</tbody>
</table>

Fig. 4.6.22  T12 fracture with displacement of fragments exceeding 2 mm over > 50% of the surface of the vertebral body, scoring 3 points in the load-sharing classification [19, 28, 49]. Note the three column spine of according to Denis on the left [8], and on the right the anterior column according to Louis [25] (vertebral body-disc-vertebral body), NB: plus two (i.e. left and right) posterior articular columns.
olisthesis along the X-axis. Flexion–extension includes a rotation around the X-axis, with increased posterior gap during anteflexion and vice versa. Rotational instability around the Y-axis with deviation of the spinous process from the midline is seen in cases of facet subluxation or following facetectomy.

Analysis of fracture mechanisms and morphology: The parameters checked to score a thoracolumbar injury are summarised in Table 4.6.2 [38, 45–47, 52]. Table 4.6.4 summarises the suggested surgical approaches. White and Panjabi’s diagnostic criteria of instability are reported in Table 4.6.5 [53].

4.6.2.3 Diagnostic Work-up
Imaging studies are the basis for evaluating and classifying an injury, and for quality control during the follow-up period [22]. One must remember that discoligamentous tears are not visible on conventional radiographs and CT scans. MRI is the best modality for assessing not only neural structures and soft tissues, but also bone marrow, haematomas and syringomyelic cavities [18, 22, 51]; however, it is not available everywhere and not feasible in polytraumatised, intubated patients with ferromagnetic equipment. (NB: Bone marrow oedema can reveal a vertebral body fracture without comminu-

<table>
<thead>
<tr>
<th>Neurological status</th>
<th>Intact PLC</th>
<th>Disrupted PLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact</td>
<td>Posterior approach</td>
<td>Posterior approach</td>
</tr>
<tr>
<td>Root injury</td>
<td>Posterior approach</td>
<td>Posterior approach</td>
</tr>
<tr>
<td>Incomplete SCI or cauda</td>
<td>Anterior approach</td>
<td>Combined approach</td>
</tr>
<tr>
<td>Complete SCI or cauda</td>
<td>Posterior (+ anterior) approach*</td>
<td>Posterior approach*</td>
</tr>
</tbody>
</table>

\[SCI\] spinal cord injury

‘NB: In ASIA A, i.e. complete injury patients, some centres perform an aggressive decompression and reconstruction (combined posterior and anterior approach) to optimise any potential for recovery: reconstruct the vertebral column support, restore CSF flow to prevent syringomyelia and allow short segment fixation

<table>
<thead>
<tr>
<th>Elements of evaluation</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Anterior elements destroyed or unable to function</td>
<td>2</td>
</tr>
<tr>
<td>II. Posterior elements destroyed or unable to function</td>
<td>2</td>
</tr>
<tr>
<td>III. Radiographic criteria (maximum 4 points)</td>
<td></td>
</tr>
<tr>
<td>A. Flexion–extension radiographs</td>
<td></td>
</tr>
<tr>
<td>1. Sagittal plane translation: &gt; 4.5 mm or 15%</td>
<td>2</td>
</tr>
<tr>
<td>2. Sagittal plane rotation:</td>
<td></td>
</tr>
<tr>
<td>&gt; 15° at L1/L2, L2/L3, L3/L4</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 20° at L4/L5</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 25° at L5/S1</td>
<td>2</td>
</tr>
<tr>
<td>Or</td>
<td></td>
</tr>
<tr>
<td>B. Resting radiographs</td>
<td></td>
</tr>
<tr>
<td>1. Sagittal plane displacement: &gt; 4.5 mm or 15%</td>
<td>2</td>
</tr>
<tr>
<td>2. Relative sagittal plane angulation &gt; 22°</td>
<td>2</td>
</tr>
<tr>
<td>IV. Cauda equina injury</td>
<td>3</td>
</tr>
<tr>
<td>V. Dangerous loading anticipated</td>
<td>1</td>
</tr>
<tr>
<td>Unstable spinal segment: 5 or more points</td>
<td>≥ 5</td>
</tr>
</tbody>
</table>
4.6.2 Trauma of the Thoracolumbar Spine

4.6.2.4 Historical Steps in Spinal Surgery

The introduction of pedicular instrumentation by Roy-Camille [36, 37] and the improvements in technology by Magerl (external fixator) and Dick with the internal fixator for the thoracolumbar spine [10] allowed to stabilise even paraplegic patients with spinal fractures, reducing the length of hospital stay and the rate of complications due to immobilisation (by earlier mobilisation and rehabilitation).

The principle of ligamentotactic reduction using Dick's internal fixator [10] is based on the preserved integrity of the posterior longitudinal ligament in compression burst fractures. After insertion of pedicular screws and restoring lordosis plus distracting the fractured vertebral body, the tension placed on the posterior longitudinal ligament allows the repositioning of fragments inside the spinal canal (Fig. 4.6.24). The restored posterior alignment can be checked with fluoroscopy and even using intraoperative myelography.

Jackson [21] and later Steib [43] preferred 'in situ contouring', a fixation with pedicle instrumentation and reduction by adjusted contoured translating axes. For example, for an L1 fracture, the pedicle screws are inserted in T12 and L2 pedicles, sublaminar hooks under L2 and pediculotransverse claws at T10. The rods (T10–L2) are contoured and the repositioning work with bending irons is comparable to a scoliosis correction. By creating a lordotic curve with the rods between the pedicle screws the fracture is opened ventrally, thus treating kyphosis, and by creating a lordotic curve with the rods just below and above a pedicle screw the injured disc is opened.

Anterior grafting was added in cases where the correction within the disc exceeded 50% of the total segmental kyphosis correction. Steib et al. insisted on the fact that anterior grafting is imperative when the fractured vertebra has a frontal fracture line with intrabody disc herniation [43].

In Steib's series patients with thoracolumbar fractures were first treated by posterior fusion with a standard construct, including deformity reduction using the in situ bending (ISB) technique, with additional posterolateral articular bone grafting. A secondary grafting by an anterior, video-assisted approach was performed in 54% of the cases, in 17% during the same anaesthesia, in 20% within 45 days and in 17% after the 45th day following the first intervention, based on postoperative radiographs and CT scans. Anterior grafting is mandatory when the fractured vertebra has a frontal fracture line with intrabody disc herniation to avoid pseudoarthrosis. It is further proposed to patients who had a disc correction corresponding to more than 50% of the segmental kyphosis (SK = angle between tangent to the lower end plate of the injured vertebra and tangent to the lower end plate of the suprajacent vertebra). In 17% of the patients the over and underlying discs were grafted, in 37% the overlying disc only [43]. NB: Sagittal index = segmental kyphosis − X; SI = SK − X, where X = 0° at T12–L1, +5° in the (physiologically kyphotic) thoracic spine and −10° in the (lordotic) lumbar spine [12].

By correcting a kyphotic deformity a cause of posttraumatic spinal canal stenosis is eliminated with a second advantage of reducing the risk of syringomyelia within a contused cord.
Compression frac\tur of T12 and L1, (T11?)
NB. Kyphotic angle!
NB. 3 points for kyphosis correction in the load sharing classification

Fig. 4.6.24  a Case example of T12 compression fracture with kyphotic deformity, plus 'minor fracture' of L1 and suspected height loss of T11 vertebral body. This means probable trauma to the discs of the adjacent segments. In addition 3 points for kyphosis correction in the load-sharing classification [19, 28, 49]. b Postoperative radiographs showing restored height and correction of kyphosis following posterior instrumentation with Dick's internal fixator. c Follow-up after 6 months showing Schanz' screws eroding through the endplate into the T10/11 disc and recurrent kyphosis of T12. d Eighteen months after the injury. There has been progressive posttraumatic kyphosis following removal of the instrumentation after 1 year. NB: Load sharing in the anterior column was insufficient due to the important T12 comminution with marked kyphosis and three discs were injured. Note also the decrease of disc space height supra- and infralaminac to the operated T12 vertebral body, as compared to the preoperative picture in a. The disc damage is not well estimated on radiographs and CT scans! Lemaire and Laloux [23], Steib et al. [43] and Wang et al. [50] have pointed out the significance of disc height changes after thoracolumbar injuries
4.6.2.5 Recent Clinical and Research Developments

At the ARGOS Spine Meeting on thoracolumbar fractures in January 2006 [27, 29, 31, 41, 42] short segment fixations were proposed for AO type A fractures only in case of a complete burst with kyphotic deformity (e.g. 30°) or in the presence of neurological deficits. The stable partial anterior column fractures can be treated conservatively (AO type A fractures, particularly A1 and most of the A2).

Complete burst fractures (A3) may, however, benefit from surgery: Siebenga et al. [40] compared in a small randomised control trial (RCT) operative versus non-surgical treatment of thoracolumbar fractures. They concluded that patients with a type A3 fracture (even) without neurological deficit should be treated by short segment posterior stabilisation, as kyphotic deformity was less and functional outcome better in the surgical group (after a mean follow-up of 4.3 years).

In some major cases of complete burst with insufficient load sharing (AO type A3, load-sharing score 7–9), however, a second anterior procedure may become necessary.

Short constructs are indicated for type B fractures with lesions to the posterior column, and for fractures of the lower lumbar spine.

Long constructs will be needed for AO type C fractures, but also in cases of osteoporosis, Bekhterev’s disease (rigid spines) and multilevel trauma [27, 29–31, 41–43]. The use of hooks to the supra- and infrajacent levels instead of another pedicle screw should not be forgotten [39].

The combined anterior and posterior fixation offers more stability and allows an optimal curve correction and reconstruction of bony defects. It is lengthy and demanding surgery, routinely performed in some big centres, while many other surgeons prefer a primarily posterior fixation, when needed in emergency, leaving the option for a later anterior stabilisation open for selected cases.

A less invasive anterior column reconstruction using balloon-assisted end plate reduction and vertebroplasty with calcium phosphate cement in combination with short segment pedicle screw construct has been proposed by Oner et al. [32].

With the ongoing developments of new technologies an increasing number of implants are offered to modern spine surgeons, enabling them to reconstruct and stabilise spines with destroyed (‘missing’) bony and discoligamentous structures.

This chapter cannot provide information about all the implants and concepts and the author apologises for not referencing publications of Y. Cotrel, J. Dubousset, J. Harms, K. Kaneda, R. Louis, A. Steffee and other opinion leaders who have made great contributions in the field of spinal instrumentation.

4.6.2.6 Late Problems

The risk of a malunion exists in patients with kyphotic deformity exceeding 10°, if there is an associated malnutrition and/or infectious diseases. The probability of a malunion is almost certain if kyphotic deformity exceeds 30°. The treatment strategies include posterior wedge osteotomies, but also anterior corrections for selected cases with pain and/or increasing neurological problems [27, 29, 31, 42].

Kyphosis recurrence after short segment fixation of a burst fracture was most recently reported to occur primarily through disc space collapse after implant removal. According to Wang et al. [50] this disc space narrowing might be a result of an adaptation to morphological changes in the osseous end plate. The role of traumatic end plate damage with disruption of end plate vascularity promoting disc degeneration was also discussed. There was no significant loss in the (not always completely) reduced vertebral body after bony healing and removal of the posterior implants (performed 10–42 months, mean 12.5 months postoperatively). Eight patients (out of 27) with a sagittal index > 15° showed a higher incidence of moderate to severe pain (follow-up of 2–4.5 years, mean follow-up of 2.7 years). Wang et al. concluded that if the wedge angle of the fractured vertebral body is unacceptable after reduction (i.e. the vertebral body remains kyphotic with diminished anterior height after instrumentation), additional reconstruction of the anterior column may be necessary.

4.6.2.7 Controversies About the Use of Steroids in Acute Spinal Cord Injuries

A useful chapter entitled Pharmacotherapy for Spinal Cord Injury has been written by Casha et al. in 2007 [6]. Based on 85 references they summarise the present knowledge about methylprednisolone, other steroids, gangliosides, opiate antagonists, excitatory amino acid receptor antagonists, calcium channel blockers, antioxidants and free radical scavengers. Although some animal studies have indicated potential benefits, a substantial improvement in neurological function has not been convincingly proven to allow the breakthrough of a substance into daily practice.

The use of high-dose methylprednisolone (MP) has been advocated following publication of the National Acute Spinal Cord Injury Study II and III (NASCIS II and III) by Braken et al. [2, 3], including four papers between 1990 and 1998 about the 6- and 12-month data.

NASCIS II consisted of 24 h therapy with a 30-mg/kg MP bolus plus a 5.4-mg/kg infusion over the next 23 h or a 5.4-mg/kg bolus of naloxone followed by a 24-h infusion at 4 mg/kg versus placebo in patients randomised
within 12 h of injury. Patients treated with MP within 8 h showed improved neurological function over those given placebo [2].

For the NASCIS III study 499 patients were randomised and received a 30-mg/kg MP bolus dose before randomisation plus 24 h MP and 24 h placebo, 48 h MP, or 48 h tirilazad mesylate (48TM), a potent lipid peroxidation inhibitor. After 1 year, 145 patients could be assessed in the 24MP group, 145 in the 48TM group and 141 in the 48MP group. Patients treated within 3 h of injury showed essentially the same motor recovery in all three drug protocols: ‘As expected, overall recovery was much less pronounced in those in whom complete neurological injuries were diagnosed at the time they were in the emergency room (data not shown).’ Diminished motor function recovery was observed when 48TM was given between 3 and 8 h after the injury, but those in the 48 MP group showed greater 1-year motor recovery (recovery scores of 13.7 and 19, respectively, \( P = 0.053 \)) [3].

However, the reputation of MP seems not deserved, as stated by Casha et al. [6] after reading independent re-evaluations of the published NASCIS results: Improvement in function meaningful to the patient was not documented in either study and the risk of death from respiratory compromise was 6 times higher in the 48-h MP group, as compared to the 24-h group (NB: 6 versus 1 out of 166 randomised patients per group). This adverse effect was mentioned by Bracken et al. [3, 4] who called for caution, i.e. avoiding unnecessary 48-h MP use in patients who could be treated for 24 h, i.e. when treatment can be started within the first 3 h. MP is thought to affect lipid peroxidation and hydrolytic destruction of neuronal and microvascular membranes, and its beneficial effect is supposed to be lost after 8 h, after which its negative role in inhibiting immune cell activity and axonal sprouting may dominate [3].

In 2002, 83% of Canadian spinal surgeons were prescribing MP because of peer pressure or fear of litigation, versus 17% because they believed it worked [20].

In 2001 a supplement to number 24 of Spine volume 26 was dedicated to spinal cord injury with several papers about the use of MP. Bracken’s conclusions in his update of the randomised evidence was that ‘high dose MPP [methylprednisolone] given within 8 hours of acute spinal cord injury is a safe and modestly effective therapy that may result in important clinical recovery for some patients’ [4]. In his editorial Fehlings stated that the beneficial effects, admittedly modest, were limited to post hoc analysis of the NASCIS trials [14]. His summary of criticisms of NASCIS II included:

- Overall analysis of 487 patients negative
- Positive effect in a post hoc analysis of 193 patients who received treatment within 8 h

- Effect sizes small
- Functional importance and effect on long tract fibres is questionable
- Concern regarding effects on wound healing and sepsis

His criticisms of NASCIS III were:

- Lack of placebo group
- Overall analysis negative
- Effect limited to a post hoc stratification between 0 and 3 h and 3 and 8 h
- Modest improvement (\( P=0.08 \)) in one component of the functional independence measure (FIM; the components of FIM are self-care, sphincter control, mobility, locomotion, communication, social cognition) (48 h MP)
- Increased sepsis and pneumonia with the 48-h group

Despite the well-founded criticisms, clinicians should consider to use this drug, given the devastating impact of SCI and the evidence of a modest, beneficial effect of MP. The suggested indications were [14, 15]:

- NASCIS II protocol for acute, non-penetrating SCI < 3 h following injury (class II evidence)
- NASCIS III protocol (48 h MP) if the treatment can be started after 3 h but certainly within the first 8 h following injury (class II evidence)
- MP should not be administered if the injury occurred more than 8 h ago (class I evidence)
- MP is not recommended in acute penetrating SCI (class III evidence, showing lack of effect and increased wound complications)

NB: The same recommendations were suggested in another paper in 2005 [15].

In a summary statement of this dedicated 2001 Spine supplement, however, Fehlings reported that, after extensive discussion of the role of MP in acute SCI, the members of the spine focus panel could not reach agreement on key points! [13]. According to Emery [11] in 2007 these protocols are still contested and are considered as a treatment option that should be balanced against the adverse risks (e.g. severe infection, gastrointestinal haemorrhage): MP is no longer administered routinely after acute SCI in France.

In some centres around the world, the 24-h MP option is offered to younger patients, especially with partial or worsening neurology, in the very early phase, i.e. within the first 3 h following the injury.

We hope to read interesting and possibly concluding news in the November 2008 edition of Neurosurgical Focus dedicated to Acute Spinal Cord Injury: Experimental and Clinical (Topic Editor: Michael G. Fehlings).
4.6.2 Timing of Surgery

Concerning the timing of surgery [1, 16–18] there is presently no class 1 evidence study demonstrating that emergency surgery will improve prognosis! There are, however, studies providing evidence for non-neurological benefits of early surgical stabilisation, such as early mobilisation, decrease of intensive care unit stay, shortening of hospital stay and decrease in complications related to prolonged immobilisation [1, 16–18, 24, 30]. Generally speaking, early surgery for patients with partial and especially progressive neurological deficits is widely accepted.

The treatment algorithm for patients presenting with traumatic acute SCI from Barrow Neurological Institute includes plain radiography allowing to consider emergency traction in case of abnormal alignment and CT scan with reformatted images allowing to consider emergency surgery in case of compressive mass lesion. The next step, i.e. MRI as preferred diagnostic imaging modality (spinal cord, soft tissues, bone marrow assessment), should not be a reason to delay surgery in case of neurological deterioration, if plain radiography/CT scan have already shown the responsible compression. This institution favours aggressive management and treatment of SCI patients [18].

Fehlings and Perrin [16] from Toronto have designed an RCT to assess the effect of early, i.e. < 12 h, versus late, i.e. > 24 h, decompressive surgery (STASCIS study). This Surgical Treatment for Acute Spinal Cord Injury Study (STASCIS) group was founded in 1992 and published first results of a multicentre retrospective study in 1999 [44].

4.6.2.9 Future Questions and Direction

There is a trend towards less invasive surgical techniques and improvement of precision of spinal instrumentation using navigation tools. The emerging efforts to establish spine surgery as its own speciality with a mixed orthopaedic and neurosurgical training is another step towards optimising the treatment of spinal trauma by increasing case load and surgical expertise.

After SCI the persisting neurological damage is still the unsolved problem. According to Robert [34], three axes emerge for future research:
1. Neuroprotection, with the aim to fight, in the early stages, against spontaneous aggravation of the primary injury.
2. Fighting against the glial barrier, which hinders axonal regrowth.
3. Management of the spinal cord below the injury level. This could include cell replacement and gene therapy.

4.6.2.10 Conclusion

- It is hoped that this summary of trauma to the thoracolumbar spine will increase the awareness of doctors on call that while scores may help to systematically analyse patients’ data and create a comparable database for reproducibility of treatment algorithms, they will never perfectly fit all cases.
- Remembering spectacular falls during a downhill skiing contest or some stunts in action movies, one realises that repeated and various impacts to the spine during ‘one accident’ can lead to injuries that may not always fit into a well-defined classification scheme.
- ‘Routine schemes’ should not prevent us from thinking critically and analysing each patient individually. This summary should provide some ‘basic knowledge’, stressing points to look for in order to understand and correctly evaluate patients with spinal trauma.
- The surgeon is responsible for the timing of surgery and for the choice of the surgical technique. The spinal surgeon must also be aware of associated injuries and co-morbidities before starting a ‘maximally reconstructive’ procedure.

References

4.7 Syringomyelia

JÖRG KLEKAMP

4.7.1 Definition

Syringomyelia is a chronic disorder of the spinal cord which describes a slowly expanding intramedullary cyst. The syrinx contains clear fluid which appears to be indistinguishable from cerebrospinal fluid (CSF) or extracellular fluid (ECF).

4.7.2 Pathophysiology and Aetiology

Syringomyelia is not a disease in its own right. Syringomyelia is a feature or a late complication of an underlying, chronic disease process, which has caused either a disturbance of CSF flow in the spinal canal (Fig. 4.7.1a, b) or impairs spinal cord mobility, or may be associated with a spinal cord tumour (Fig. 4.7.1c). Up to the present, no commonly accepted pathophysiological concept exists as to how or why a syrinx may develop. Whereas most authors in the past century assumed that the fluid inside the syrinx was CSF and produced theories how CSF may be forced into the spinal cord, recent papers explained the development of a syrinx on the basis of altered ECF dynamics: due to alterations of CSF flow and/or spinal cord mobility or due to intramedullary tumours, ECF may accumulate in the spinal cord [3, 6].

On the basis of this concept, almost any disease of the spinal canal may cause a syrinx [7]: CSF flow obstructions and impaired spinal cord mobility may be associated with malformations of the spinal canal, degenerative disorders of the spine, spinal leptomeningeal diseases, neoplastic lesions or may be a late complication of spinal trauma or spinal surgery. In a series of 1,115 patients with syringomyelia, 414 were associated with craniocervical

Fig. 4.7.1 a Sagittal T2-weighted MRI scan of a 27-year-old woman with a Chiari type I malformation and a huge septated syrinx throughout the entire spinal cord. She presented without any neurological deficits but a slowly progressing scoliosis. b Sagittal T2-weighted MRI scan of a 51-year-old man with a complete spinal cord lesion at T7 and a posttraumatic syrinx extending up to C6. The patient developed a progressive sensory loss in his arms more than 30 years after the accident. c Sagittal T1-weighted MRI scan with contrast of a 35-year-old man with an intramedullary ependymoma at C3/C4 and a syrinx above and below the tumour
malformations (Fig. 4.7.1a), 331 with spinal arachnoid scarring (Fig. 4.7.1b), 114 with intramedullary tumours (Fig. 4.7.1c), 57 with degenerative diseases of the spine, 21 with spinal dysraphism and 178 presented as dilatations of the central canal (Fig. 4.7.2a) (see below). In cases of posttraumatic syringomyelia, a lesion of the spinal cord is not required to produce a syrinx! The posttraumatic syrinx is the consequence of CSF flow obstruction at the level of the trauma and may be related to posttraumatic arachnoid scarring and/or posttraumatic spinal stenosis (Fig. 4.7.1b) [7].

As a general rule, a syrinx requires a long time before symptoms appear. For instance, most of the patients with a Chiari I malformation – one of the commonest diseases associated with syringomyelia (Fig. 4.7.1a) – are in their forties before symptoms appear even though the CSF flow disorder had been present since early childhood. On average, posttraumatic syringomyelia becomes symptomatic about 10 years after trauma. As a general rule, a syrinx starts at the level of CSF flow obstruction and progresses from there either in an upward or a downward direction. In other words, serial examinations can disclose the spinal segment of the underlying pathology. Likewise, the clinical course may allow to conclude whether the cause of syringomyelia should be expected at the lower or upper pole of the syrinx. A rising spinal level for neurological symptoms points towards the lower pole of the syrinx and vice versa.

### 4.7.3 Clinical Presentation

Analyses of clinical presentations of patients with syringomyelia have to account for the underlying disease that caused the syrinx and the syrinx itself. In other words, the patient may present symptoms and signs of both. This appears to be the major reason why the severity of clinical problems does not correlate to the size and extent of the syrinx. Especially in patients without an obvious cause of syringomyelia, a carefully taken clinical history may disclose this underlying disease, because it had been present years before the syrinx started. In most cases, the first symptoms belong to the underlying disease with symptoms of syringomyelia appearing much later. In the overwhelming majority of patients, symptoms progress slowly and gradually. Stepwise or rapidly deteriorating neurological symptoms are exceptional but do occur. Commonly, patients report sudden neurological changes associated with minor trauma.

The commonest symptoms of a syrinx are a dissociating sensory loss, dysesthesias and pain. The dissociating sensory loss describes a loss of temperature and pain sensation with a preserved sensation for light touch. Pain associated with a syrinx is often described as a burning type. The pain may be present constantly or be provoked with Valsalva manoeuvres, coughing or sneezing. Sensory symptoms as well as pain are perceived in those dermatomes corresponding to the extent of the syrinx. With growing size of the syrinx signs of spinal ataxia, sphincter disturbances and vegetative disturbances such as abnormal sweating and motor weakness develop. Late signs are atrophies of small hand muscles in cases of cervical syringomyelia or so-called trophic changes of skin, finger nails or even joints.

### 4.7.4 Radiology and Differential Diagnosis

Not all signal changes in the spinal cord appearing as cystic lesions should be diagnosed as syringomyelia [7].

1. **Syringomyelia**: Syringomyelia is a cystic lesion of the spinal cord of slowly increasing size and extent. It contains a fluid similar to CSF and ECF. The syrinx may be located in the centre of the cord lined by ependymal cells or in posterior parts of the cord lined by gliotic tissue. A syrinx may display septations (Fig. 4.7.1a–c).

2. **Hydromyelia**: Hydromyelia describes a dilatation of the central canal caused by CSF flowing down from the fourth ventricle. Such dilatations can be quite easily produced in animal experiments [4]. In humans, however, such a phenomenon is an extremely rare occurrence and requires an obstructive hydrocephalus with occlusion of all foramina of the fourth ventricle [11].

3. **Glioependymal cysts**: Glioependymal cysts or ependymal cysts are space-occupying cysts lined by collagenous tissue and cuboidal cells with no separate basement membrane and are commonly located in the conus medullaris. They may, however, affect any part of the spinal cord. On sagittal images they appear as symmetrical cysts without contrast enhancement of the cyst wall and no septations (Fig. 4.7.2b). Most of them are asymptomatic [8].

4. **Myelomalacia**: Myelomalacia describes an intramedullary cystic necrosis as a result of trauma or ischaemia. It never causes a space-occupying effect.

5. **Cystic tumours**: Cystic tumours can be distinguished from a syrinx due to contrast uptake of the neoplastic cyst wall and the signal pattern of the cyst content, which has a higher protein concentration compared to CSF (Fig. 4.7.2c).

6. **Persistent central canal**: In humans, the central canal of the spinal cord obliterates with increasing age [5, 10]. With improving MR technology parts of the central canal may be detectable, raising the differential diagnosis of syringomyelia. Characteristic features are the small diameter, the central location and the lack of a space-occupying effect (Fig. 4.7.2a).
It may not always be possible to decide right from the start what kind of intramedullary cyst a patient has. Sometimes, only follow-up examination will disclose its true character. If the diagnosis of a syrinx has been made, radiological examinations have to determine the entire extent of the syrinx and the cause of syringomyelia. MRI is the diagnostic method of choice. To disclose the cause of the syrinx, an examination with gadolinium is mandatory to rule out an intramedullary tumour. Once that has been established, the craniocervical region should be evaluated to rule out a Chiari malformation. As soon as tumours, craniospinal malformations and dysraphic lesions associated with a tethered cord are excluded from the list, the shape and extent of the syrinx should be examined carefully for evidence of arachnoid adhesions and cord displacement or compression by arachnoid cysts. Cardiac-gated cine MRI can demonstrate CSF flow and is the most sensitive tool to identify areas of CSF flow obstruction [7].

**Fig. 4.7.2** a Sagittal T2-weighted MRI scan of a 42-year-old man with a dilatation of the central canal at T3/T4. The dilated central canal leads to no space-occupying effect. The patient presented with back pain and slight sensory disturbances in his arms which are certainly unrelated to a process at T3/T4. b Sagittal T2-weighted MRI scan of a 39-year-old woman with a 4-year history of a slowly progressing paraparesis due to this large glioependymal cyst at T12/L1. c Sagittal T1-weighted MRI scan with contrast of a 22-year-old woman with a cystic astrocytoma at C2/C3. There is some contrast enhancement at the lower part of this cyst wall.

Ideally, syringomyelia should be treated by addressing the underlying disorder, i.e. in cases associated with intramedullary tumours, the tumour should be removed; in cases with spinal arachnoid scarring, normal flow of CSF should be established; and so forth. Depending on the underlying disorder, surgery should be indicated as soon as neurological symptoms are present or as soon as symptoms progress. In cases with intramedullary tumours, surgery is indicated as soon as the diagnosis is made. In patients with a Chiari malformation, decompression of the foramen magnum should be recommended as soon as symptoms have appeared. In patients with Chiari type I malformation, additional features such as hydrocephalus, craniocevical instability or ventral cord compression due to basilar invagination may be present and need to be addressed in such cases as well. With arachnoid scarring in the spinal canal or foramen magnum area, surgery should be reserved for patients with progressive neurological symptoms. In such instances, CSF flow is restored and the subarachnoid space enlarged with a duraplasty. Surgical indications for spinal dysraphic malformations – usually those associated with a syrinx also feature a tethered cord syndrome – depend on the complexity of the malformation: the more complex the malformation, the higher the threshold to recommend surgery. For patients with degenerative spinal diseases, treatment should be based solely on the degenerative process, as these syrinx
Syringomyelia is the result of a chronic disease process involving either an obstruction of CSF flow, impaired spinal cord mobility or an intramedullary tumour. Neuroradiological examinations have to demonstrate the entire extent of the syrinx and its cause. MRI is the diagnostic method of choice. Examinations of CSF flow by cardiac-gated cine MRI are especially helpful to demonstrate areas of impaired CSF flow.

Clinical symptoms may be related to the syrinx as well as to the underlying pathology. In most instances, the underlying pathology will cause symptoms long before the syrinx will.

Treatment should aim to deal with the underlying pathology first. If that is successful, no further measures are required. Syrinx shunting should never be the first line of treatment but be reserved for patients in whom the underlying pathology cannot be treated.

As a general rule, symptoms related to the underlying pathology may improve after surgery but those related to the syrinx are usually left unchanged even if the syrinx size decreases.

**References**

4.8 Treatment and Rehabilitation of Patients with Spinal Cord Lesions

FIN BIERING-SØRENSEN

4.8.1 Epidemiology

The incidence of traumatic spinal cord lesion (SCL) is between 10 and 50 per million per year in Europe. Most persons with traumatic SCL are men. The age has increased over recent decades from late teens or twenties to an average age in the thirties to forties. Most often they are injured in traffic accidents and falls. Tetraplegia (cervical SCL) and paraplegia (more caudal SCL) occur with equal frequency. The incidence of non-traumatic non-progressive SCL is higher than for traumatic SCL. The causes of non-traumatic SCL are slipped discs, infections, arteriovenous malformations (AVMs), tumours, spinal stenosis, etc.

4.8.2 Survival and Causes of Death

The mortality within the first year of a traumatic SCL was 60–80% before World War II, decreasing to 30% in the 1960s, 15% in the 1970s and down to 6% in the 1980s. The reasons for this have probably been the development of specialist units for SCL and regular follow-up visits. In addition, improved emergency services, antibiotics, etc. have also contributed.

Until the 1970s renal failure and urinary tract complications were the leading causes of death. Today respiratory complications, particularly pneumonia, are the leading causes of death. Other major causes are unintentional injuries and suicides, cardiovascular diseases and septicaemia.

4.8.3 Prognosis After Traumatic Spinal Cord Lesion

After an acute SCL the reflexes are abolished corresponding to the isolated spinal cord – the spinal shock phase. This can last from only hours to several weeks. It is probably due to the sudden interruption of the supraspinal tracts, which normally support a sustained condition of depolarisation in the spinal motor neurons. Due to the shock phase it is often impossible to predict the future functional level of the SCL in the first weeks after the injury. When the spinal shock diminishes, reflexes, spasticity and reflex bladder and bowel function return.

If the SCL is incomplete the prognosis is better. Patients with incomplete SCL may show improvements in their functions over months and even years after the SCL. However, if a complete SCL has been unchanged over the first few weeks and the reflexes have returned there will be little chance for improved function below the level of the neurological lesion.

4.8.3.1 Classification

The International Standard for Neurological Classification has been widely accepted. It represents a reasonable, valid, precise and reliable minimum data set to assess individuals with SCL (Fig. 4.8.1). In addition, it provides a way of estimating the functional prognosis.

4.8.4 Consequences of a Spinal Cord Lesion

An SCL may affect any function below the level of the neurological lesion, and is therefore probably the one disability with most general impact on the overall function of the human being. Examples of common influences the SCL may have:
- Paresis/paralyses, with muscle atrophy, spasticity/spasms, contractures, heterotopic ossifications, paralytic scoliosis
- Impaired/absent sensitivity with risk for pressure ulcers, osteomyelitis, Marjolin’s cancer
- Respiratory problems when the lesion is in the cervical or high thoracic spinal cord
- Cardiovascular disturbances, with increased risk of deep vein thrombosis and lung embolus, low blood pressure and pulse in high spinal cord lesions, autonomic dysreflexia in those with lesion at or above T6, lower extremity oedema
4.8.5 Acute Treatment of the Spinal Cord Lesion

The ultimate goal for treatment of SCL is to restore function. It will take many years before it will be possible to achieve regeneration of the neurological lesion in the spinal cord. In the meanwhile attempts are carried out to decrease the secondary delayed injury after the initial immediate traumatic injury with compression, laceration and contusion of the spinal cord. In this situation treatments of acute SCL are to preserve damaged nerve cells, to reduce tissue damage and bleeding, and to facilitate recovery of function. The secondary delayed injury is due to various biochemical processes leading to ischaemia, neurogenic shock, haemorrhage, vasospasm, ionic derangements, neurotransmitter accumulation, production

- Urinary bladder pareses with risk of incontinence, retention, infections, urinary stones, kidney function deterioration
- Bowel pareses with risk of incontinence, constipation, haemorrhoids, megacolon
- Disturbed sexual function and in addition for men impaired fertility
- Endocrine and metabolic disturbances in part due to the physical inactivity
- Osteoporosis with increased risk of lower extremity fractures
- Impaired temperature regulation, which in particular for those with cervical SCL make them very susceptible to the ambient temperature, and reflex sweating
- Pain is prevalent, both nociceptive, at e.g. shoulders, and neuropathic, at and not least below the level of the neurological lesion

Fig. 4.8.1 The International Standard for Neurological Classification endorsed by the American Spinal Injury Association (ASIA) and the International Spinal Cord Society (ISCoS). The most updated version can be downloaded free of charge from http://www.asia-spinalinjury.org/. An e-learning program is available at the same web-site
of free radicals, inflammation and apoptosis. For these reasons various drugs including methylprednisolone, tirilazad, ganglioside (GM1), insulin, erythropoietin (epo) and others have been and will be tried. The debate on the use of steroids has been addressed by several societies and the current state is: The use of steroids for acute SCL is a treatment option (unclear clinical certainty, based on level II or III data) and it is not endorsed as either standard of care (supported by level I study) or a guideline (moderate clinical certainty supported by at least one level I study). The argument for the use of steroids is that no other clinically proven treatment option exists, and even small effects can lead to a significant change in lifestyle for individuals with SCL. The drugs that have been tested have different ways of action and work at different times during the injury and recovery phases. Thus, a possible approach in the future is to treat acute SCL with more than one drug and within different time windows after the injury.

4.8.5.1 Respiration

The more cranial the SCL the more respiratory muscles may be paralyzed, and if it is a cervical SCL the patient will primarily ventilate using the diaphragm. With SCL above C5 even the diaphragmatic innervation may be compromised and ventilator support may be necessary. Paralyses of respiratory muscles imply risk of stagnation of secretion, not least due to an insufficient cough, and thereby atelectases and pneumonia.

In all individuals with SCL above T6 the vital capacity should be controlled, and lung physiotherapy, continuous positive airway pressure (CPAP) or positive expiratory pressure (PEP) treatment initiated.

Phrenic nerve stimulation is a possibility for respiratory management of high tetraplegics. The advantages of phrenic nerve pacing compared to mechanical ventilation are better phonation; increased mobility, including the option that the patient may be transported without a ventilator; psychological and physiological benefits because the respiration is maintained through the normal respiratory tract, mouth and nose; and the body’s own respiratory muscle, the diaphragm, is used. Generally a better quality of life is obtained.

4.8.5.2 Cardiovascular Issues

Due to the increased risk of deep vein thromboses, in particular during the first 3–14 days after injury, anticoagulation with low molecular heparin is administered and compressing stockings are usually used for the first 3 months after injury. This may be supplemented with electrical stimulation to the lower limbs.

The arterial blood vessels dilate distal to the level of the SCL due to decreased sympathetic tone. Therefore the blood pressure will decrease the more cranial in the spinal cord the lesion is, i.e. in a tetraplegic individual a systolic pressure of 90–110 mmHg is normal. For this reason orthostatic hypotension is common, particularly in the post-injury period. Tilt-table training for gradual mobilising can be used. Because the heart correspondingly is innervated by the proximal part of sympathetic trunk (above T5), those with SCL above this level may experience a slower pulse.

Autonomic dysreflexia (or hyperreflexia) may occur in individuals with SCL at or above T6. The condition is caused by hyperactivity of the thoracolumbar sympathetic nervous system, which is without the normal supraspinal control. This means that a reflex vasoconstriction can be elicited with a blood pressure increase (300/160 mmHg), which via the baroreceptors gives vagal bradycardia, but without a coordinated regulation of the peripheral resistance. Due to the severe hypertension there is a potential risk of a cerebrovascular attack. The most common cause for autonomic dysreflexia is bladder distension, but almost any afferent stimuli below the level of the SCL may elicit this hyperreflexia. The symptoms are pulsating headache, nausea, nasal congestion, goose flesh and flushing. The patient should be calmed down, and compressive stockings, corsets, etc. removed. Treatable conditions are to be taken care of. Nifedipine can be used to control the blood pressure.

4.8.5.3 Pressure Ulcers

Among SCL individuals 7–8% may die from pressure ulcer-related complications. Pressure ulcers develop primarily from pressure or shear. The most common sites of development are the sacrum, ischium and trochanters. Maintaining adequate protein, calorie and fluid intake to prevent negative nitrogen balance and dehydration is essential. It is stressed that myocutaneous flaps are not a definitive cure for pressure ulcers. An educational programme to teach methods of preventing recurrence should accompany repair of a pressure ulcer. In prevention adequate nursing care is mandatory, which includes proper bed positioning and if needed turns every 2 h. Pressure relief must be encouraged to prevent ulceration. Special beds and madrases can be used.

4.8.5.4 Urological Management

With bladder-emptying difficulties intermittent catheterisation is the most frequently advised method for bladder emptying to ensure bladder filling is below 500 mL. The major complications are urinary tract infections (UTIs)
and urinary stones. However, bacteriuria should only be treated with antibiotics when there are symptoms of UTI. There is an increased risk of complications from the upper urinary tract and the kidneys, and therefore it is important to follow-up with urography or ultrasound and renography. Likewise urodynamics are essential for diagnosis and management of neurogenic bladder dysfunction, not least due to possible high intravesical pressures.

Pharmacotherapy is the cornerstone in the management of neurogenic detrusor overactivity (NDO). Injection into the detrusor muscle of botulinum toxin has gained much popularity as a very efficient treatment of incontinence due to NDO.

If a permanent catheter is necessary for a longer period, a suprapubic catheter is advisable to decrease the risk of urethral complications and in men epididymitis and orchitis. The increased risk for bladder cancer with an indwelling catheter should be recognised.

Sacral anterior root stimulation (SARS) has for years been used for micturition in selected SCL individuals (Fig. 4.8.2). The electrodes are placed at the efferent roots of S2–S4, and usually the afferent roots are cut to avoid the NDO. The benefits include improvement of bladder continence, capacity and compliance, diminution in upper tract dilatation and improvement in renal function, abolition of high-pressure ureteric reflux, decreased residual urine, reduction of active detrusor sphincter dyssynergia, fewer UTIs and abolition of autonomic dysreflexia triggered from bladder or bowel. However, irreversible procedures seem less attractive today due to many new developments, including various kinds of neuromodulation and new drugs within this area.

### 4.8.5.5 Bowel Management

In the acute period where there is risk of paralytic ileus, continuous enteral nourishment is advised. This improves the integrity of the intestinal mucosa and decreases the risk of sepsicaemia. As long as the bowel is atonic, digital evacuation and enema may be necessary to empty the bowel. Generally individuals with SCL may have severe problems with bowel management. The upper motor neuron bowel is characterised by faecal retention with impaction and incontinence. The bowel programmes may remain time-consuming processes that can be detrimental to quality of life.

Sacral anterior root stimulation implant-driven defaecation or implant-assisted manual evacuation is under development and may reduce the time that the SCL person needs to spend on bowel management, and it may abolish episodes of severe constipation.

### 4.8.5.6 Sexual Function and Fertility

It has been a belief that men with SCL are impotent and sterile. Fortunately this opinion has been completely reversed over recent decades. With drugs like sildenafil, tadalafil and vardenafil, 75–80% of all SCL men can obtain erection. Other drugs, vacuum devices and intracavernous injection of prostaglandin E1 are other options to obtain erection.

Today the majority of SCL men will be able to obtain ejaculation by penile vibratory stimulation (100 Hz, 2.5 mm amplitude), and the remaining will mostly respond to rectal electrostimulation. Retrieved semen may be used for vaginal or intrauterine insemination or in vitro fertilisation, including intracytoplasmic sperm injection.

Women with SCL may have decreased vaginal lubrication. If the vagina is dry the woman should use water-based lubricating cream to avoid irritation or ulcer of the vaginal mucosa during sexual intercourse. The women have normally fertility, but 60% have post-injury amenorrhea lasting on average 5 months.

### 4.8.5.7 Spasticity

Spasticity may be decreased for a short while by positioning, stretching, cooling and cutaneous electrical stimulation. Pharmacologically drugs like baclofen, diazepam, dantrolene, clonidine, gabapentin and tizanidine can be tried. When only a few muscles are involved botulinum toxin injections is an option.
Intrathecal baclofen delivered from an implanted pump (Fig. 4.8.3) is effective in the majority of patients with severe spasticity that is not manageable with other methods. Functions increase, particularly for bathing, dressing lower body, transfers and, in some cases, locomotion for paraplegics. For tetraplegics the sitting position is improved, and nursing may become easier and life comfort is enhanced. Some tolerance to the drug may develop. Mostly the efficacy remains stable after 6–9 months (see Sect. 8.6).

**4.8.5.8 Pain**

Pain following SCL has been reported to compromise the quality of life in nearly 70% of individuals with SCL. Steps have been taken to develop a taxonomy for SCI pain. This includes first a division into nociceptive and neuropathic pain. Secondly nociceptive pain is divided into musculoskeletal and visceral pain, and neuropathic pain into above-level, at-level and below-level pain.

Regarding management there is a general lack of controlled studies. Simple analgesics and opioids are helpful in the short term for musculoskeletal pain. Anticonvulsants, tricycle antidepressants and local anaesthetics have been used for neuropathic pain with limited success. Dorsal root entry zone (DREZ) lesion has been shown to be most effective for radicular rather than diffuse neuropathic pain below the lesion. There is a need for a multidisciplinary approach, which includes the psychological aspects (see Sect. 8.2).

**4.8.5.9 Posttraumatic Syringomyelia**

With a greater awareness and the increasing use of MRI, posttraumatic syringomyelia has been diagnosed more often. The most common symptoms are pain, sensory loss and increased motor weakness, but hyperhidrosis, changed spasticity pattern or other symptoms may be a clue to an early diagnosis. A regular and frequent follow-up of individuals with SCL is the best way to ensure that the posttraumatic syringomyelia is diagnosed and managed early in order to avoid further disability.

**4.8.5.10 Functional Electrical Stimulation**

Functional electrical stimulation (FES) may reduce the incidence of medical complications associated with immobilisation and promote improved healthier lifestyles. FES cycle ergometer training (Fig. 4.8.4) gives rise to, among other things.

![Fig. 4.8.3 Intrathecal baclofen pump in place](image)

![Fig. 4.8.4 Functional electrical stimulation cycle ergometer training. Used with permission from FADL's publisher](image)

![Fig. 4.8.5 Functional electrical stimulation for upper limb function with the implantable FreeHand System for C5/C6 tetraplegics. Up to eight electrodes are implanted in muscles in the upper limb. This tetraplegic individual was able to feed himself with the system](image)
other things, increased oxygen uptake, cardiac output, muscle mass and strength, fatigue resistant muscle fibres, insulin tolerance and bone mineral density, which is known to fall to 50% within a year of the SCL. The relative risk of femur fractures is 23 times greater for individuals with SCL compared to the non-SCL population.

Functional electrical stimulation may assist paraplegics transfer, stand and walk. Functional walking in complete paraplegics is difficult to achieve. FES for upper limb function is promising with the implantable FreeHand System for C5/C6 tetraplegics (Fig. 4.8.5).

**Suggested Reading**


An injury to a peripheral nerve may cause life-long functional disabling deficits, and have a considerable impact on the patient's quality of life. After a nerve injury outside the central nervous system, numerous reactions are initiated in the chain of neurones from the brain to the muscles and the peripheral receptors.

In 1941 Cohen introduced a classification system that was later popularised by Seddon [1]. Sunderland extended the system in 1951 with the definition of five degrees to describe the severity of the injury to the nerve [2]. The classification is based on the normal anatomy of the nerve. Finally MacKinnon added one more pattern of pathology in 1988 introducing the partial lesion, often described as a sixth degree of nerve injury [3]. The classification is illustrated in Table 5.1.1.

### 5.1.1 Aetiology

#### 5.1.1.1 Traumatic Injury

In making a treatment algorithm, one has to differentiate between the different types of injuries. A penetrating, open injury will immediately allow the surgeon to suspect which of the underlying nerves may have been injured, and the following operation will offer an opportunity to explore the nerve structures. The investigator faces a dilemma with a blunt trauma without penetration of the skin, in the form of a contusion or a fracture. Does the functional deficit indicate an exploration of the nerve?

A peripheral nerve consists of nerve fibres (axons), endoneurium, perineurium, epineurium and paraneurium (adventitia) [4]. The paraneurium involves blood supply to the nerves and serves as a movement support for sliding of nerve fascicles. Roughly 50% of a nerve is connective tissue [2].

The transection of the nerve can be sharp and clean or involve a larger segment of the nerve in a laceration, eventually with tissue loss. In addition, the nerve can be injured by a non-penetrating mechanism such as traction, thermal and electrical injuries, ischaemia caused by compression or exposure to radiation. Iatrogenic injuries demand special attention. An intramuscular injection of a drug or the application of a local nerve block may cause damage to the nerve from the needle itself. More often, the toxic effects from intraneural administration of the medicine or a haematoma will damage the nerve. Iatrogenic nerve injuries can also occur after osteosynthesis of antebrachial fractures, prosthetic surgery in the elbow and surgical treatment of varicose veins in the lower extremity [5, 6].

#### 5.1.1.2 Entrapment Neuropathies

Entrapment neuropathies are nerve injuries that result from compression of a peripheral nerve in a defined area.
5.1 Basics: Aetiology, Pathophysiology, General Symptomatology and Diagnosis of Peripheral Nerve Injuries

5.1.2 Pathophysiology

5.1.2.1 Trauma

A first-degree nerve lesion does not cause any significant changes to the anatomy. After an axotomy, a sequence of processes will be activated known as Wallerian degeneration [3, 5, 9–14]. The peripheral part of the axon will disintegrate and the myelin degenerates. After a period of 2–4 days, the distal axon will no longer be able to conduct electrical impulses. The Schwann cells surrounding the axon are activated during the first 24 h and will proliferate rapidly afterwards. Schwann cells and macrophages will clean up the tube and prepare the way for the regenerating axon. The cleaning process will be over after 5–8 weeks. After a more extensive injury with denervation of the endoneural tube, the sheath will shrink in a process that reaches a maximum about 4 months after the trauma. Collagen is deposited outside the Schwann cells, and the fibroblast proliferation will continue if an axon does not arrive. The endoneural tube will eventually be obliterated [15].

An inflammatory reaction takes place in the nerve gap after the tissue damage. As described for the endoneural tube, removal of the damaged tissue prepares the area ready for the regenerating axon. The proliferation of fibroblasts will contribute to the formation of scar tissue after a severe injury, and this will then form a barrier in front of the axon on its way towards the distal nerve end.

After a severe lesion, the structural changes can reach all the way back to the cell body, which means that the proximal segment will undergo Wallerian degeneration. In this case, changes in the cell body will occur, which when fully expressed will lead to the death of the neuron [14, 16]. This loss of neurones is most likely to happen in the sensory nerve pathways and in the cranial nerves. Moreover, the risk increases the closer the injured segment is to the cell body.

The extent of the retrograde Wallerian degeneration in the proximal part of the neuron will determine how far the axon has to travel before it reaches the gap. The neurones in the peripheral nerve system maintain the regenerative capacity for at least 12 months.

The outgrowth of the axon evolves without mitotic activity or cellular proliferation of the neurones. The axon begins to send out sprouts within the first 24 h after an axotomy, with an average number of five of these extensions per axon. These elongations will sweep over the surroundings in search of the distal nerve segment. When the axon passes the nerve gap, it will follow proliferating Schwann cells, which contribute to creating an attractive local microenvironment, including the production of growth factors. Many of the growth cones at the advancing axon tips will develop in an inappropriate direction, and will never establish contact with a distal endoneural tube. Alternatively, they will sprout into functionally unrelated tubes [17]. If the axon succeeds in establishing contact with a distal endoneural tube, there is a good chance that it will reach its destination with a growth rate of 0.5–1 mm per day. If the axon does not establish a distal contact, it will stop growing and a neuroma will form [18, 19].

5.1.2.2 Entrapment

If a nerve segment is exposed to an equally distributed external pressure by use of a pressure chamber or a cuff, the negative effect on the nerve function will mainly be in the zones between the compressed and uncompressed segments [20]. It is predominantly the peripheral part of the cross-sectional area that is influenced by the pressure, while the deformation of the central parts is less pronounced. In the carpal tunnel that is a closed hydrostatic space the normal pressure is between 5 and 15 mmHg. A pressure of 20–30 mmHg will cause changes in the intraneural microcirculation and the axonal transport [21, 22]. At a pressure of 30 mmHg the first neurophysiological changes occur and total blocked nerve conduction is found with pressures >50 mmHg. Daily the pressure fluctuates with its peak at 6 a.m. [21]. The nerve conduction is compromised if the pressure is increased to more than 50 mmHg in a dose-response pattern. Pressures of this magnitude will not be found in all patients with common entrapment neuropathies, which indicate that other factors can be involved. The nerve will react with perineural oedema followed by fibrosis, demyelination and finally nerve fibre degeneration. The ischaemia may not be sufficient to cause demyelination and Wallerian degeneration, but it can disrupt the axonal function anyway.

In a first-degree nerve injury, recovery will be expected within the first 3–6 weeks. If the compression persists for a longer period of time an increasing number of axons are involved in the neurotmesis with persistent symptoms as a consequence. There is no progressive migration of Tinel’s sign along the distal part of the nerve in that
Each specific nerve entrapment has a characteristic set of symptoms despite adequate treatment. The nerve will need more time to recover after a prolonged period of compression or an episode with high levels of compression. The most commonly used classification according to Seddon is found in Table 5.1.1.

### Table 5.1.2

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<thead>
<tr>
<th>Sensibility grading</th>
<th>Muscle strength grading</th>
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<td>S0</td>
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<td>S1</td>
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<td>S3+</td>
<td>M4</td>
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<tr>
<td>S4</td>
<td>M5</td>
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During the clinical examination, the level of the nerve injury is established and an assessment of the severity of the lesion is made. The sensibility can be evaluated by several methods [21, 29]. All these tests are subjective and factors other than sensibility may have an impact on the result. An area of the skin without sensory innervation is dry, shiny and does not ‘ wrinkle ’ when exposed to water. A survey of the different clinical gradings of motor and sensory function is found in Table 5.1.2. Jules Tinel described the phenomenon that percussion over a nerve lesion will generate a ‘ tingling ’ sensation [30]. A progressive advancement of Tinel’s sign in the distal direction is an indication of axonal regeneration. Lack of advancement is a poor prognostic sign [21].

The strength of the individual muscles is graded by a methodical examination and any motor loss is documented [31]. It is not sufficient to conclude that the limbs can be moved. Serial examinations during the rehabilitation period provide an opportunity to follow the evolution in regeneration of an injured nerve. Atrophy of the denervated muscles and the following asymmetry will occur later on.

### References

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5.2 Clinical Neurophysiology

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5.2.1 Electromyography

Electromyography (EMG) is the recording of the electrical activity of the muscle. The electrical activity is muscle action potentials from depolarised muscle fibres. Muscle fibres that belong to one motor unit are scattered throughout the muscle in such a way that fibres belonging to the same motor unit are rarely next to each other. When the motor unit is activated, all muscle fibres belonging to it are depolarised nearly synchronously and these muscle fibre action potentials summate to a motor unit action potential (MUAP).

Activity is recorded with a recording concentric or monopolar needle electrode inserted into the muscle. The spatial relation between the active muscle fibres in the pick up volume and the needle electrode has great influence on the configuration of the recorded muscle action potential. Only activity from muscle fibres in a small volume (0.5–1 mm$^3$) around the tip of the needle contribute to the peak to peak amplitude of the recorded muscle action potential. More remote muscle fibres contribute only to the beginning and end of the potential and thus determine the duration of the MUAP.

The number of active motor units present in the needle pick up volume depends on the strength of muscle contraction. In the normal muscle no electrical activity is recorded in the resting state, except when the needle is moved or placed in the end plate zone. During mild contraction, only one or a few motor units have active fibres in the needle pick up volume. It is therefore possible to record MUAPs that are isolated and not interfering with each other during mild muscle contraction. With increasing strength of contraction two phenomena take place simultaneously: The firing frequency of already activated motor units increases and new motor units are recruited. During maximal contraction, MUAPs will summate and produce an interference pattern in which the baseline is completely interrupted by action potentials.

During an EMG examination of a muscle, activity is recorded from several positions in succession inside the muscle, in order to measure activity from a representative part of the motor units. Activity is examined in the resting muscle, as well as during mild and maximal voluntary muscle contraction.

Properties of the MUAP (duration, amplitude, number of phases) as well as firing frequency during recruitment, configuration of the interference pattern, and spontaneous electrical activity of the resting muscle are some of the parameters obtained with the EMG.

The architecture of the motor units is changed differently in primary muscle disorders (myopathy) and following lesion of the motor nerves. The changed architecture is reflected in the EMG: Increased spontaneous activity in the resting state, increased or decreased duration and amplitude of the MUAPs, increased number of phases in the MUAP (polyphasic potentials) and alteration in the recruitment of motor units and interference pattern during maximal muscle contraction.

Spontaneous activity includes fibrillation, positive sharp waves, fasciculation potentials, myotonic discharges and complex repetitive discharges.

Fibrillation potentials and positive sharp waves are due to spontaneous depolarisation of single muscle fibres following denervation. They are often seen following neuropathic lesions and may be seen in primary muscle diseases. Fibrillations often appear earlier than positive sharp waves but may not be apparent until 2–5 weeks following acute denervation. Positive sharp waves are more apparent in totally denervated than partially denervated muscles.

Fasciculation potentials are thought to represent spontaneous activation of one or more synchronously firing motor units and are seen in chronic denervated muscles, especially when caused by affection of the motor neurone cell body, for example amyotrophic lateral sclerosis and other spinal pathology involving the anterior horn cells. Fasciculations may also be seen as a benign phenomenon in normal muscle especially in the gastrocnemius muscle.

Myotonic discharges and complex repetitive discharges are high frequency trains of muscle fibre action potentials seen in primary muscle diseases, although complex repetitive discharges may also be seen in chronic denervated muscles.

Changes in the number of muscle fibres in a motor unit, as well as loss of synchrony of fibre firing within a motor unit (seen in demyelination disorders and following re-innervation), affect the duration and amplitude of the MUAPs. If the number of functional muscle fibres
in the motor unit decreases, a decrease in MUAP duration occurs (mainly seen in myopathy, but may be seen in disorders of the neuromuscular junction and during re-innervation following lesions of lower motor neurones). A decreased number of muscle fibres per motor unit also causes the amplitude of the potentials to decrease. An increase in the number of muscle fibres in a motor unit caused by peripheral sprouting with re-innervation of muscle fibres increases the number of muscle fibres per motor unit and thereby the muscle action potential duration and amplitude.

In the newer EMG machines it is possible to obtain quantitative measures on both properties of MUAP samples at weak effort, for example multi-MUAP analysis, and on the interference pattern sampled at higher effort, for example turns-amplitude analysis. These methods require normal material, but offer quantitative reliable results that are less biased by the examiner than the traditional visual/auditory quantitative analyses.

5.2.2 Nerve Conduction Studies

In nerve conduction studies, applying a stimulus to the nerve evokes a response. In the study of motor nerves, an electric stimulus is applied to the peripheral motor or mixed nerve, while the recorded response is a compound muscle action potential (CMAP) from muscles innervated by that nerve. In the study of sensory nerves, stimuli are applied to the peripheral mixed or sensory nerve, while the recorded responses are nerve action potentials from another site of the same nerve.

5.2.2.1 Motor Nerve Conduction Studies

Nerve stimulation is performed with either surface electrodes or needle electrodes. Surface electrodes are placed over the course of the peripheral nerve where it has a superficial position, while the use of needle electrodes allows the stimulation of nerves even if tissue is interposed between the nerve and skin (e.g. fat or oedema, or nerves with an anatomically more profound course).

While gradually increasing the strength of the stimulation, an increasing number of axons in the stimulated nerve are activated, and increasing amplitude of the CMAP is recorded. The intensity of the stimulation is adjusted so that all axons are activated (supra-maximal stimulation).

The motor response evoked by peripheral nerve stimulation is recorded with electrodes placed at standardised locations over one or more muscles innervated by that nerve. Both bipolar surface electrodes and concentric needle electrodes (subcutaneous or intramuscular) can be used. When using surface electrodes, the active electrode is placed over the end plate zone and the reference electrode over the tendon of the muscle.

The evoked muscle response is termed the ‘M-wave’. Latency, amplitude, area, and configuration quantify M-waves. The latency varies directly with the distance between stimulation and recording sites. The area and amplitude of the M-wave are related to the number of motor units activated and the number of muscle fibres in the activated motor units. M-waves evoked from various sites along the peripheral nerve are compared as regard amplitude, area and configuration, and the motor nerve conduction velocity is estimated by dividing the difference in M-wave latency between two stimulation sites into the distance between the sites.

Another muscle response evoked by supramaximal motor nerve stimulation is the ‘F-wave’. It appears later than the M-wave with a latency of 20–50 ms. F-waves are CMAPs of a small number of motor units that are activated indirectly: Depolarisations propagate both proximally and distally from the site of nerve stimulation. The distally propagating action potentials evoke the above-mentioned M-wave, while the proximally propagating action potentials arrive at the cell bodies of the motor neurones in the anterior horn of the spinal cord. A small number of neurones that are in an excitable state are re-excited on the arrival of the proximally propagating potentials. When re-excited, action potentials propagate in the normal direction towards the muscle and evoke the F-wave. Minimum latency quantifies F-waves.

5.2.2.2 Sensory Nerve Conduction Studies

As in the study of motor nerves, stimulation is performed with either surface electrodes or needle electrodes. Surface electrodes are placed over a nerve where it is superficially situated, while needle electrodes may be used to stimulate or record from nerves otherwise not accessible. In addition, needle electrodes are used to record from nerves with small amplitude action potentials.

With increasing strength of the stimulation, an increasing number of axons are activated, and the amplitude of the nerve action potential increases. The nerve is stimulated supramaximally to ensure all axons are activated.

The nerve action potentials evoked by peripheral nerve stimulation are recorded with electrodes placed at standardised locations along the course of the nerve, either distal (antidromic) or proximal (orthodromic) to the site of stimulation. Monopolar needle electrodes placed near the nerve as well as bipolar surface electrodes can be used.

Nerve action potentials recorded with surface electrodes are not so influenced by the exact electrode positions, and the surface technique is quicker to perform and
more tolerable to the patients than the near-nerve needle technique.

The fact that estimation of conduction velocity in injured nerves and in other nerve disorders causing low amplitude potentials is subject to inaccuracy or not possible at all is a drawback. Using the near-nerve needle technique, potentials with greater amplitude are recorded due to the short distance between nerve and recording electrode, and the technique reveals details of small-diameter as well as large-diameter nerve fibres. The use of the needle technique also allows analysis of very low amplitude potentials resulting from peripheral nerve disorders.

Latency and amplitude quantify the nerve action potential. Latency is directly related to the distance between the stimulating and recording sites. Sensory nerve conduction velocity is estimated by dividing the latency into the distance between the stimulating and recording sites.

The amplitude of nerve action potentials is 100–1,000 times less than the amplitude of CMAPs. Amplitude is approximately proportional to the number of activated axons, but is influenced by the distance between the stimulating and recording electrodes (temporal dispersion). A low amplitude of the action potential means that it might disappear in the background electrical activity (noise) from, for example, muscle activity if the patient is not relaxed. To improve signal-to-noise ratio, an averaging technique is applied: Many (up to several hundreds) stimuli may be applied, and the responses are averaged which causes random (not stimulus-bound) electrical activity to level out and the nerve action potential (stimulus-bound) to become more clearly defined, reliable and reproducible.

### 5.2.3 Clinical Application of Electromyography and Nerve Conduction Studies

The electrophysiological examinations (EMG and nerve conduction studies) are used to identify, localise, characterise and prognosticate disorders affecting the motor units.

Abnormal neurogenic EMG findings are not specific for a particular disease, but provide support in the diagnostic process. Through an electrophysiological examination, the clinical relevance of lesions indicated by imaging studies may be determined.

Electrophysiological examinations provide information about the localisation of a lesion within the motor unit (lower motor neurone [LMN], neuromuscular junction or muscle fibre). In case of lesions affecting the LMN, the quality and distribution of electrophysiological abnormalities allows to localise the lesion to the cell body of the LMN or the axons of the LMN (nerve root, nerve plexus or peripheral nerve). The type of lesion, either demyelinating, axonal or both, is established.

Conduction studies during surgical procedures are used in the identification of nerves and for monitoring function; this subject is covered elsewhere in this book.

#### 5.2.3.1 Lower Motor Neurone Lesions

An acute focal LMN lesion (involving the anterior horn cells, nerve roots, nerve plexus or peripheral nerves) causes abnormalities in the EMG and nerve conduction independent of the mechanism being compression, traction, laceration or ischaemia. The distribution of electrophysiological abnormalities depends on the site of lesion, and the muscles and nerves selected for electrophysiological examination depend on the symptoms and signs of the patient.

Both lesions of the anterior horn cells, interruption of the continuity of axons and focal demyelination (neurapraxia) immediately produce changes in the EMG recruitment and interference pattern as well as in nerve conduction studies. These changes are unspecific and may be difficult to differentiate from, for example, lesions of upper motor neurones or submaximal muscle contraction.

In the EMG, firing frequency of surviving motor units increases in order to produce a given muscle contraction strength with fewer motor units, and the interference pattern at maximal muscle contraction may also be reduced if the number of surviving units is sufficiently low. In the second week, increased spontaneous activity (fibrillation potentials, positive sharp waves and fasciculations) appears, but is not present in most affected muscles until the following 3–5 weeks. Indications of re-innervation because of collateral sprouting within the muscle from viable axons, spared by the lesion, appear after the first month: Increased number of polyphasic MUAPs precedes increased duration and amplitude. Early re-innervation by outgrowth of axons from the site of lesion may result initially in small, small amplitude, polyphasic potentials followed by potentials with increased duration.

In the conduction studies acute focal lesions of peripheral nerves produce different abnormalities if the nature is demyelinating or axonal loss.

In focal demyelination, the myelin sheet is disrupted and propagation of nerve action potentials across the site of lesion is impeded or prevented. The corresponding electrophysiological findings are a decrease in conduction velocity or a conduction block, respectively. A conduction block can be complete or partial.

In case of slowing of conduction, the amplitude of muscle action potentials is normal following stimulation both proximal and distal to the lesion. Conduction is
completely blocked if propagation of the motor nerve action potentials is not possible across the site of demyelination. In lesions causing distal conduction block (between the distal stimulation site and the muscle), muscle action potentials are not evoked either at proximal or distal sites. In a complete motor block, normal muscle action potentials are evoked distal to the lesion while no response is evoked by stimulation proximal to the site of lesion. In a partial block, propagation of nerve action potentials is only prevented in a fraction of the axons. Consequently, amplitude of the muscle action potential recorded following stimulation proximal to the lesion is reduced as compared to distal stimulation.

After an acute axonal lesion, the part of the axon distal to the lesion undergoes wallerian degeneration. Electrophysiologically, muscle action potentials either have small amplitudes or are not evoked following stimulation both distal and proximal to the lesion. In the chronic phase of an axonal lesion, re-innervation may have taken place, and in these cases the amplitude tends to underestimate the extent of axonal loss. Conduction velocity may be slightly reduced due to loss of the fastest conducting nerve fibres.

As wallerian degeneration starts only 2 days after axonal discontinuation, the part of the axon distal to the lesion remains excitable until degeneration is complete. Not until 10 days following an axonal lesion is wallerian degeneration complete. Therefore, to be able to document or classify the lesion as demyelination or axonal, electrophysiological examination must be postponed to at least 11 days after the lesion. Following complete wallerian degeneration, EMG examination helps to localise the lesion, as neurogenic abnormalities are only found in muscles innervated by branches arising distal to the lesion. EMG can also be used to estimate the progress of the re-innervation process.

5.2.3.2 Peripheral Nerve Lesions

Nerve conduction studies and EMG examinations are important in the differential diagnostics of nerve entrapments.

A clinical picture resembling an entrapment but caused by tender points or other painful musculoskeletal conditions will reveal normal results in nerve conduction studies. This is seen, for example, in tender points of the infraspinatus muscle, where paraesthesia is common in the ulnar part of the hand and forearm, or in lateral epicondylitis where paresis may be seen in the extensor muscles of the fingers and wrist.

Electromyography in plexus lesions and root lesions will show neuropathic findings outside the entrapment site. For example, in lesions affecting the lower trunk of the brachial plexus, in addition to abnormalities in the muscles innervated by the ulnar nerve (as in an entrapment of the nerve behind the medial epicondyle), abnormalities will be present in the abductor pollicis brevis muscle (innervated by the median nerve) because of the course of the nerve fibres from spinal segments C8 and T1 through the lower trunk to the median nerve.

In polyneuropathy, nerve conduction studies will show abnormalities outside the entrapment site. Often, abnormalities are seen in the peroneal nerve where it passes around the head of the fibula, but decreased sensory conduction velocity in the sural nerve at the ankle or increased distal latency to the extensor brevis muscle indicates more widespread pathology.

5.2.3.3 Plexopathies

The brachial and lumbosacral nerve plexuses are complex structures. Detailed knowledge about their anatomy is required in order to localise lesions, and it is often necessary to examine several muscles and peripheral nerves. Differential diagnostics between root avulsions and plexus lesions is important following traction trauma. Sensory conduction studies reveal normal nerve action potentials and conduction velocities in case of root lesions (see below), while nerve action potentials have decreased amplitude or are absent in plexus lesions when examined following complete wallerian degeneration (more than 10 days after the injury). The findings of neurogenic abnormalities in muscles innervated by two or more peripheral nerves that share a common course through the plexus, support the diagnosis of a plexus lesion.

5.2.3.4 Radiculopathy

Lesions of nerve roots cause wallerian degeneration of motor neurones in the peripheral nerves made by contributions from the root and, later, neurogenic abnormalities are found in muscles innervated by these nerve fibres. In contrast, sensory nerve fibres in the peripheral nerve do not undergo degeneration because their trophic centre in the dorsal root ganglion is spared. Therefore, in root lesions, normal sensory nerve action potentials and conduction velocities are found together with neurogenic EMG abnormalities in a segmental myotomal distribution. In radiculopathies (and lesions involving the anterior horn cells), in contrast to more peripherally located lesions, nerve fibres innervating paraspinal muscles and muscles innervated by branches arising very close to the intervertebral foramen (e.g. serratus muscle) are affected, and neurogenic EMG abnormalities could be found in these muscles.
5.2.3.5 **Spinal Lesions**

Lesions involving the motor neurones in the anterior horn of the spinal cord cause EMG and motor nerve conduction abnormalities as seen in radiculopathies. The distribution of abnormalities and the additional findings suggesting lesions of upper motor neurones support the diagnosis of a spinal lesion.

5.2.3.6 **Upper Motor Neurone Lesions**

In spinal lesions no abnormalities are found in sensory or motor conduction studies of nerves with segmental contribution from below the lesion. In the EMG examination no spontaneous activity is seen and the MUAPs have a normal configuration. The only electrophysiological abnormalities seen in spinal lesions are reduced interference pattern at maximal contraction and reduced firing frequency of motor units. These abnormalities could also be found in hysterical weakness except for a more irregular firing in this condition.

**Suggested Reading**


Liveson JA, Ma DM (1992) Laboratory reference for clinical neurophysiology. Davis, Philadelphia
5.3 Therapy of Peripheral Nerve Lesions

BENT LANGE AND JENS HAASE

5.3.1 Compression Syndrome, Entrapment Neuropathies

Operative treatment is indicated when the conservative options do not provide the expected result. The goal of the operation is to release the nerve and restore normal function. A simple in situ decompression is the procedure most often used. Transposition of the nerve, osteotomy, tenosynovectomy, neurolysis and epineurotomy are other ways of achieving decompression [1–5].

5.3.2 Trauma

5.3.2.1 Timing of Surgery

There are some variations in the literature concerning the definition of the concepts of primary and secondary nerve sutures. Surgery within the first 48 h is termed primary while delayed primary treatment describes a therapy option initiated within the first week after the trauma. A repair performed later than that is a secondary procedure. In this phase it is necessary to excise scar tissue from the nerve ends before the suture can be performed. Secondary repair has been promoted from a practical point of view and is based on the theoretical assumption that the regenerating neurone has a greater growth potential if the operation is delayed for some weeks. At this time the nerve cell has an accelerated metabolic activity. Laboratory settings as well as clinical studies suggest that immediate nerve repair offers the best options for axon regeneration and return of function. However, it can be difficult to determine the extent of the nerve damage immediately after a stretch-related or laceration trauma. The demarcation of the atrophy, necessary for such judgments, will appear more clearly after a delay of 3–4 weeks. Contamination of the wound is another factor in favour of a secondary procedure. In connection with a secondary procedure. The sutures in connection with a secondary procedure. The sutures will reduce the retraction of the nerve stumps, which may allow an end-to-end suture without the need for a nerve transplant.

When planning a secondary procedure it can be necessary to consider other factors, such as accompanying fractures or tendon injuries. In a nerve lesion without an open injury, the normal practice will be to wait and see if it is a neurapraxia or a more severe damage with discontinuity of the nerve fibres. The patient should be clinically monitored closely in the observation period, and a baseline electrodiagnostic study performed about 4 weeks after the trauma. A decision has to be made 3 months after the nerve injury. If there are no signs of progressive regeneration of the axons, the nerve must be explored and, if necessary, repaired. Nerve transplantation will often be necessary. If the clinical, electrophysiological or radiographic evaluations suggest ongoing axon regeneration, the observation period is extended. It is important to realise that early positive signs do not guarantee a good functional result. No later than 6 months after the primary injury, a definitive decision is made whether surgery should be carried out (Figs. 5.3.1, 5.3.2) [2, 3, 6–8].

5.3.2.2 Principles of Surgery

Nerve repair is best performed using optical magnification, such as surgical loupe (with at least ×4 magnification) or an operative microscope, so that microsurgical techniques can be applied [1, 9]. The use of microsurgical instruments is a given principle.

The nerve ends must be prepared before they are sutured. Non-viable tissue is resected and the ends of the nerve are shortened, if required, so that all the fascicles are visible and have the same length. It is particularly important when performing a secondary suture that the nerve ends are cut back to ensure that all scar tissue is resected [10]. It is technically demanding to achieve a clean transection of the nerve, but several techniques and surgical devices are available. A nerve suture must never be performed with a non-physiological tension over the gap [6, 11]. Tests on animals have shown that suture pull-out can occur after a 17% elongation of a nerve section.
5.3 Therapy of Peripheral Nerve Lesions

5.3.2.3 Suture Techniques

The choice of methods when a nerve is sutured includes an epineural repair, fascicular repair or a group fascicular repair. The epineural technique is valid in a proximal lesion with multiple fascicles (and fascicular crossover), as well in a transection of peripheral nerves with only a few fascicles. The group fascicular suture technique can be applied in an injury on a mixed sensory/motor nerve where specific function is related to the topographical arrangement of fascicles. This method will secure an acceptable orientation of the fascicles but it will not guarantee an increase in specificity when the individual axons grow out in the peripheral endoneural tubes. It is technically demanding to suture a group of fascicles or individual fascicles, usually with a 10-0 suture. Clinical randomised studies have not been able to demonstrate any convincing differences between the above-described suture techniques concerning functional results [6, 12–14].

It should be attempted to orientate the fascicles in a correct manner when performing an epineural suture and the epineural vessels can be used as cursors to ensure the right rotation. The nerve ends are trimmed back to a level without obvious nerve damage. Two 8-0 sutures are placed in the external epineurium to secure the right rotation in larger nerves. The tension is unacceptably high if an 8-0 suture is unable to adapt the nerve ends. The repair is completed with 9-0 or 10-0 sutures, which are

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**Fig. 5.3.1** Closed nerve injuries: timing of surgery. 1 In a few cases, a nerve compression syndrome can emerge with symptoms so pronounced that surgery has to be been performed as fast as possible. 2 Symptoms from the nerves can occur together with an acute compartment syndrome caused by ischaemia

**Fig. 5.3.2** Open nerve lesions: timing of surgery

<table>
<thead>
<tr>
<th>Closed nerve injury</th>
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<tbody>
<tr>
<td>Acute nerve compression (1)</td>
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<tr>
<td>Acute compartment syndrome (2)</td>
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<tr>
<td><strong>Acute/early operation</strong></td>
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<tr>
<td><strong>Early passive/active mobilisation</strong></td>
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<tr>
<td><strong>Clinical assessment</strong></td>
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<tr>
<td><strong>Serial electrodiagnostic tests, MRI, ultrasonography</strong></td>
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<tr>
<td><strong>Consider operation after 3 months</strong></td>
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<table>
<thead>
<tr>
<th>Open nerve injury</th>
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<tbody>
<tr>
<td><strong>Sharp nerve transection</strong></td>
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<tr>
<td><strong>Laceration</strong></td>
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<tr>
<td><strong>Significant tissue loss or contusion</strong></td>
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<tr>
<td><strong>Contaminated wound</strong></td>
</tr>
<tr>
<td><strong>Acute/early operation &lt; 72 hours</strong></td>
</tr>
<tr>
<td><strong>Secondary suture after 3–6 weeks</strong></td>
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</table>

**5.3.2.3 Suture Techniques**

The choice of methods when a nerve is sutured includes an epineural repair, fascicular repair or a group fascicular repair. The epineural technique is valid in a proximal lesion with multiple fascicles (and fascicular crossover), as well in a transection of peripheral nerves with only a few fascicles. The group fascicular suture technique can be applied in an injury on a mixed sensory/motor nerve where specific function is related to the topographical arrangement of fascicles. This method will secure an acceptable orientation of the fascicles but it will not guarantee an increase in specificity when the individual axons grow out in the peripheral endoneural tubes. It is technically demanding to suture a group of fascicles or individual fascicles, usually with a 10-0 suture. Clinical randomised studies have not been able to demonstrate any convincing differences between the above-described suture techniques concerning functional results [6, 12–14].

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the only sutures used on small nerves. The suture material should be a monofilament, non-absorbable synthetic suture. Extensive use of suture material will increase the risk of fibrosis. The sutures are only meant to adapt the fascicles and must never be so tight that there is a herniation of fascicles between the sutures or the fascicles are deflected within the gap.

In addition to the anatomical identification, there are intraoperative histochemical and electrophysiological methods to obtain the right matching of the sensory and motor fascicles. With electrical stimulation it is possible to identify sensory fascicles proximal to the lesion and hopefully the distal motor fascicles [14]. Alternatives to the classic suture technique, such as gluing or laser welding, have so far not gained a place in clinical practice.

5.3.2.4 Nerve Grafting

There is always a spontaneous retraction of the nerve ends after a transection because of the elastic properties of nerves. Nerve grafting is required when it is impossible to perform a suture without tension [6, 15]. In practice, this means that a defect of more than 3 cm on a larger nerve and 1 cm on small nerves (digital nerve level) requires the use of transplants. It is incorrect to put the nearby joints in extreme positions in order to minimise the tension over the suture. It is uncomfortable for the patient and the mobilisation of the joints afterwards will have an effect on the nerve anyway. The nerve transplant has to survive several days on diffusion without vascular perfusion. Small nerves and segments of nerves used as transplant is will be revascularised faster than a nerve trunk with a greater volume. The most commonly used donor nerves are found in Table 5.3.1.

5.3.2.5 Nerve Conduits

Many different types of materials and biological tissues have been used to bridge the gap as an alternative to nerve transplants [16]. If the distance between the two ends of the nerve is less than 3 cm the axons will be able to reach the distal segment and a tabulation technique is a possibility. A piece of a vein can be used to establish a tubular connection. Tubes made of silicone or a bioabsorbable material are commercially available. The nerve stumps are drawn into each end of a tube with a suitable diameter, and secured with a single stitch in each end. The results after use of a conduit are comparable with those after conventional suture techniques, but the patients are not left with a functional deficit after removal of the donor nerve [6, 17, 18].

5.3.2.6 End-to-side Suture

If the tip of a damaged nerve is sutured to the side of an uninjured nerve (terminolateral neurorrhaphy), collateral axonal sprouting into the recipient nerve has been observed in experimental settings. The biology of this process is yet not fully understood, and it is still under debate if it is necessary to make an incision into the donor nerve. This technique has been used to reconstruct a peripheral sensory nerve track in the absence of the proximal nerve segment. A nearby unaffected sensory nerve will serve as an in situ donor nerve without alteration of its original function. It remains controversial if this technique can be used to re-establish motor functions [19, 20]. What is often forgotten by surgeons is the postoperative treatment. The cortical representation of the hand will be influenced by training. Thus, nowadays, an integrated part of surgical treatment is postoperative training of the hand/foot/ankle/shoulder in order to obtain the optimal results [21].

5.3.2.7 Direct Motor Neurotisation

In case of a distal avulsion off the motor nerve or brachial plexus injuries, the nerve can be applied directly against the muscle. This method has not yet gained credibility in the clinical setting [22, 23].

Table 5.3.1 Potential donor nerves for nerve grafting

<table>
<thead>
<tr>
<th>Potential donor nerves for nerve grafting</th>
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<tr>
<td>Distal posterior interosseous nerve</td>
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<tr>
<td>Lateral antebrachial cutaneous nerve</td>
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<tr>
<td>Medial antebrachial cutaneous nerve</td>
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<td>Sural nerve</td>
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ments. In these cases anticonvulsant or antidepressant drugs can be an alternative [1, 24]. Many therapists practise mobilisation of a nerve segment under influence of pressure but the medical evidence for this treatment is not clear. Physical therapy can be an important treatment option in the early stages of an entrapment neuropathy, and is indispensable in the rehabilitation period to regain the strength of the muscles [25]. The patient should be informed how to avoid aggravating activities, in order to prevent further irritation of the nerve.
5.4 Nerve Compression Syndromes in the Extremities

BENT LANGE AND JENS HAASE

5.4.1 Upper Extremities

5.4.1.1 Median Nerve

The common median nerve entrapment syndromes are:
- Pronator syndrome
- Anterior interosseous syndrome
- Carpal tunnel syndrome

5.4.1.1.1 Proximal Entrapment of the Median Nerve

The median nerve can be engaged at several levels in the forearm. The pronator teres muscle (PT) is involved in most of the proximal nerve compressions, but the fibrous arch of the superficial digital flexor muscle and the bicipital aponeurosis can also apply pressure on the nerve [26, 27]. The main complaints of patients with pronator syndrome are pain in the proximal part of the forearm and weakness of the muscles. The syndrome can be associated with paraesthesia in the hand but in contrast to carpal tunnel syndrome it primarily occurs during the daytime. There is no intrinsic atrophy. Physical examination reveals tenderness corresponding to the focus of compression. Provocative tests and electrodagnostic testing are often inconclusive. Conservative treatment consists of modification of the provocative activities or immobilisation in a long arm splint. If there is no response to this treatment, surgical decompression should be carried out.

5.4.1.1.2 Anterior Interosseous Entrapment

The anterior interosseous nerve (AIN) arises from the median nerve. The pronator teres muscle or the brachial fascia can affect this branch. Entrapment of the AIN is a pure motor syndrome [28]. Pain in the proximal forearm can occur, but it often disappears when the paralysis arises. The patient will be unable to perform active flexion of the interphalangeal joint of the thumb and/or the distal interphalangeal joint of the index finger. The condition must be differentiated from a rupture of the flexor tendons. Surgical decompression is done if there is no sign of spontaneous improvement.

5.4.1.1.3 Carpal Tunnel Syndrome

The aetiology of carpal tunnel syndrome (CTS) is considered to be an entrapment syndrome caused by compression of the nerve. Nosographically it is therefore mandatory for the description to document pressure changes in the carpal tunnel. The carpal tunnel volume may be decreased due to external factors or to intrinsic factors, both giving rise to symptoms [1, 29–31].

Carpal tunnel syndrome is the most common entrapment mononeuropathy. Frequently the area of compression is the part of the flexor retinaculum made up of the transverse carpal ligament. Tenosynovitis of the flexor tendons or inflammatory changes in the transverse carpal ligament have often been suspected of playing a major role in the pathology of idiopathic CTS. Research has not convincingly confirmed these ideas and both the ligament and the tenosynovium are normal in many patients [32]. There seems to be a tendency that patients with CTS have a smaller carpal tunnel suggesting an anatomical predisposition [33]. Intrinsic CTS is caused by factors that increase the volume of the content of the carpal tunnel. The compressions of the nerve seen during pregnancy or in patients with metabolic disorders are examples of this pathology. In extrinsic CTS there is a change in the dimensions of the carpal channel which can be seen after a wrist fracture or with arthritis in the wrist joint. With MRI using a T2-weighted fast spin-echo fat-suppressed technique (chemical shift selection or inversion recovery) oedema and ischaemia inside the median nerve can be demonstrated. Anatomical data are obtained with T1-weighted imaging with planes parallel to and transversely along the nerve using phased-array coil [34, 35]. Sonography is also used to demonstrate anatomical structures in the carpal tunnel [36]. How these data are correlated with pressure increases and neurophysiology is not yet completely resolved. Classical symptoms are numbness or tingling in the hand corresponding to the distribution of the median nerve. Nocturnal symptoms are often more disturbing for the patients than symptoms during the daytime. They often complain of sleep disruption with relief of the sensations by shaking the symptomatic hand. Pain over the carpal tunnel may occur. Dropping objects out of the hand is commonly reported [1, 37–39].
There is a great likelihood that the patient with the above-described symptoms has CTS [1]. A simple questionnaire can be a helpful tool in the diagnosis [40]. The hand should be inspected to see if there is thenar atrophy, a symptom that appears late in the course of the condition. The abductor pollicis brevis muscle is tested for weaknesses. Tinel’s sign, Durkan’s test and Phalen’s test are carried out, and the sensibility is evaluated by use of the two-point discrimination test or a monofilament test [41].

If CTS is defined upon clinical parameters alone several features should be included. Szabo [1, 40] showed that the combinations of a patient with a completed Hand diagram, presence of nightly pain, abnormal sensibility using monofilament testing and a positive Durkan’s test had both a high sensitivity and specificity. If all four parameters were abnormal the diagnosis of CTS was correct in 86% of patients (or as the presenters see it, incorrect in 14%).

Atroshi [42, 43] found that 30% of patients with ‘typical clinical symptoms of CTS’ had normal neurophysiological examinations, that 32% with ‘uncertain’ clinical symptoms had positive neurophysiological studies and that 18% of persons without any symptoms had positive neurophysiology.

The clinical symptoms and the neurophysiological changes are often combined and CTS can be divided into four groups:
1. Intermittent ischaemia of sensory neurones, but with no significant sensory nerve conduction disturbances. Clinically these patients harbour acroparaesthesia, but no documented sensory disturbances.
2. Chronic ischaemia of sensory axons with focal reduction of sensory nerve conduction velocity (SNCV) due to paranodal demyelination and clinically presenting with minor hypaesthesia and nightly painful paraesthesia.
3. Axonal degeneration with reduced SNCV, decreased amplitude of sensory nerve potentials and denervation potentials in the abductor pollicis brevis muscle. Clinically sensory disturbances and the beginnings of muscle atrophy and palsy of the abductor pollicis brevis muscle are found.
4. Loss of many axons and subsequent significantly reduced SNCV and in end-stage perhaps no functioning fibres. At the same time persistent hypaesthesia/anaesthesia is found and fewer clinical symptoms, including a lack of the nightly paraesthesia, are found.

Due to this we must conclude that in order to document functional disturbances in the median nerve, clinical neurophysiological investigations must play a role in describing and defining the type of CTS that needs surgical decompression. Remember that group 1 is not a group where documentation of pressure changes is evident using neurophysiology [1, 31, 39, 44].

Imaging studies such as MRI or sonography can be helpful in evaluating the status of the nerve in the carpal tunnel. Electrodiagnostic methods are still considered to be the gold standard in the diagnosis of CTS. This is erroneous as the electrodiagnostic tests can be negative in spite of a clear cut CTS [1]. Technical factors such as amplifier gain, filter settings, electrode size, form and material, distance between electrodes and hand/arm temperature play an important role. Today, surface electrodes are predominantly used [1]. Technical neurophysiology focuses on muscles, alpha motor nerve fibres and large myelinated sensory nerve fibres, whereas autonomic functions and sensory functions mediated by the thin myelinated fibres or unmyelinated C-fibres are not systematically investigated. It is these fibres that are presumably those first involved in the CTS. Electrodiagnostics is however important as it is an objective description of the symptomatology and not merely subjective as given by the patient.

The Hand diagram evaluation is the method of choice in a large group of patients for screening [1]. Injection of steroid into the carpal tunnel can be beneficial but the effect is often temporary [45]. The effect of oral steroids can be observed, but this treatment is not recommended due to side effects. There is not enough evidence to recommend treatment with vitamin B6. In milder cases of CTS, for example during pregnancy, splinting of the wrist should be tried [1].

Surgical decompression of the nerve is the preferred treatment and can be performed with the use of open or endoscopic techniques [1, 47]. When correlating series, open surgery is considered to consist of ‘one procedure’, which is a mistake. Open surgery comprises multiple types of surgical intervention. The incisions alone may be placed proximal to the creases to the mid-hand, crossing creases in an oblique or straight fashion, transverse along the third interspace, towards the third finger, towards the fourth finger or along the thenar crease. Incisions may be straight, curved, double, S-shaped in combinations and with lengths varying from 2 to 8 cm. Magnification may or may not be used, but it seems inadequate for a neurosurgeon not to use an operative microscope. Even loupes are better than normal vision. The chances of recognising incorrect dissection, aberrant nerve structures and vessels are greater with the microscope and lesions of nerves are thus seldom found. Bipolar coagulation at a low setting is used and postoperative haemorrhaging is not seen [1].

All surgical decompressions can be performed by use of local anaesthesia, with or without a tourniquet. Several limited exposures have been described and special instrumentation is available for these. Most recently a combined endoscopic/microsurgical technique has been
developed by Krishnan [46]. The choice of technique is up to the surgeon depending on experience and training.

Since the motor branch has a variable departure from the nerve it is vulnerable during the procedure and special attention should be paid to this fact.

The results after the operation are impressive often with more than 90% of the patients satisfied. Some patients will complain of pillor pain in the postoperative period but this will often resolve spontaneously after some months [1].

It is often quoted that following endoscope decompression the time to return to work is shorter than with the open techniques despite no controlled series existing to prove this statement. In a recent review the problems of return related to type of work and eventually workers compensation was discussed and in a US series no differences could be found whereas in Scandinavia workers tended to stay longer off work than blue collar workers. This may indicate a difference in society structure. The frequency of complications seems to be the same as with the open technique but the severity of complications, for example nerve lesions and infections of the deep hand space, is much greater than with the open techniques. Consult Fig. 5.3.1 for timing of surgery.

The serious complications must be regarded as the result of ‘careless or inexperienced surgery and the established principle of surgery under direct vision has provided reliable protection against disaster’ [47].

5.4.1.2 Ulnar Nerve

The most frequent levels of ulnar nerve entrapment are:
• The cubital tunnel syndrome at the elbow
• At the wrist as the nerve passes the canal of Guyon (ulnar tunnel syndrome)
• Distal to the pisiform where the deep motor branch emerges

The cubital tunnel syndrome is the second most common entrapment syndrome in the arm [8, 49]. The nerve can be compressed in the groove on the epicondyle (cubital tunnel), distal to the epicondyle between the two heads of the flexor carpi ulnaris muscle or between the deep digital flexor and superficial muscles (flexor-pronator fascia) [48–58]. The clinical symptoms include paraesthesia and sensory loss in the ring and little fingers and the dorsoulnar aspect of the hand, and aching pain over the medial aspect of the elbow. Motor deficits are present in severe cases. The diagnosis is primarily clinical supported by electrodiagnostic studies. It is important to remember that cervical radiculopathy with paraesthesia in the forearm and hand, supplied by the ulnar nerve, is a differential diagnosis. Conservative treatment consists of patient education in order to modify provocative work habits and temporary immobilisation of the elbow in a splint or covered in a simple towel at night [52, 55, 57]. Several surgical procedures are available [49, 51, 53, 54, 56, 58]. The nerve can be decompressed in situ, transposed anterior using a subcutaneous or submuscular route, or a medial epicondylectomy can be performed. There is not enough evidence in the literature to support one of these techniques in favour of the others [49, 58].

Patients with distal entrapment of the ulnar nerve have normal sensibility on the dorsal hand. Depending on the level at which the nerve is compressed in the hand, one can find a combined sensory and motor syndrome or a silent paralysis without pain. Conservative treatment by use of a splint should be tried in mild cases. In cases with motor involvement and severe sensory deficits, the nerve should be explored and surgically released in Guyon’s canal and distally passed the hamate.

5.4.1.3 Radial Nerve

Compression of the radial nerve in the upper extremity can be seen at the following levels:
• Fracture-related entrapment in the spiral groove of the humerus
• In the radial tunnel
• Posterior interosseous nerve (PIN) entrapment
• Lesion of the superficial radial nerve

A lesion of the radial nerve is a well-known complication of fractures of the humerus [59]. Involvement of the nerve at the brachial level affects both sensory and motor functions distal to the elbow. The patient will be unable to perform normal active wrist and finger extension. The sensation is altered in the dorsoradial part of the hand. The diagnosis is quite obvious if the involvement of the radial nerve is caused by a fracture. If the origin is unknown, electromyography and nerve contraction studies can be helpful. The treatment algorithm follows the principles outlined earlier in this chapter, with delayed surgical exploration if there is no sign of spontaneous nerve regeneration.

The radial tunnel is approximately 5 cm long, situated in the proximal part of the forearm. The predominant symptom in radial tunnel syndrome is an aching, deep pain in the proximal/lateral part of the forearm. Nocturnal pain is frequent in contrast to what is seen in patients with a lateral epicondylitis. The sensibility is normal and motor involvement is infrequent. Electrodiagnostic testing has little value and there is a pure correlation between test abnormalities, peroperative observations and the results after decompression of the nerve. Conservative treatment including occupational therapy and splinting
should be tried. An overlapping lateral epicondylitis must be diagnosed and treated before surgery on the radial nerve is considered [60, 61].

Entrapment of the PIN will affect the extension of the wrist and fingers without loss of sensibility. The patient is unable to extend the metacarpophalangeal joints. The treatment is focused on the underlying causes such as fractures of the forearm, ganglions and tenosynovitis in patients with rheumatoid arthritis. A splint can be applied in the early stages and surgery undertaken if there is no response [62].

Lesions to the superficial branch of the radial nerve are often a complication of an operation for de Quervain’s tenosynovitis or application of an external fixator during the treatment of a distal radius fracture. Tenosynovitis, a ganglion or external compression from a cast can affect the nerve branches. The patient’s concern is pain or dysaesthesia over the radial styloid and the dorsal part of the thumb and index finger. Most of the patients with an internal compression can be treated conservatively. A neurolysis can be helpful if the nerve is embedded in scar tissue after trauma [63]. Neuromas in this area can be disabling and the treatment is often challenging as the pain is of central origin (see Chap. 8.2).

5.4.1.4 Brachial Plexus

5.4.1.4.1 Thoracic Outlet Syndrome, Entrapment
Thoracic outlet syndromes (TOS) are a group of disorders that cause pain and abnormal nerve sensations involving a group of symptoms arising from the upper extremities and from chest, neck, shoulders and head. It is perhaps the most debated peripheral nerve compression syndrome and has been linked to certain (over?) enthusiastic surgeons removing scalene muscles, ribs, etc. in attempts to cure the symptomatology, but creates many lawsuits due to complications [29, 64].

5.4.1.4.1.1 Anatomy
The thoracic outlet is an area at the top of the rib cage, between the neck and the chest. Several anatomical structures pass through this area, including the oesophagus, trachea and nerves and blood vessels that lead to the arm and neck region. The area contains: at the bottom the first rib and the top of the lungs; in front the clavicle; the subclavian artery beneath the clavicle brachial plexus; the anterior scalene muscle is the anterior part of the scalene triangle and the middle scalene muscle the posterior part of this.

5.4.1.4.1.2 Symptomatology
Compression usually occurs at the location where the blood vessels and nerves pass out of the thoracic outlet into the arm. Pain and other symptoms may occur when the nerves or blood vessels in this area are compressed. For practical reasons we can therefore divide TOS in three types:

1. Neurogenic thoracic outlet syndrome: This is caused by a compression of the nerves in the brachial plexus. Neurogenic lesions of the lower part of the brachial plexus trunks lead to symptoms such as coldness of the hand, sensory disturbances ulnar of the arm and reduced handgrip, especially abduction of the fifth finger. Of all nerve fibres in the lower trunk, 20–30% are sympathetic. Vascular symptoms – white hands (Raynaud’s phenomenon) – if present are due to irritation of the sympathetic fibres and result in a cold hand, cyanosis and intermittent hand oedema.

2. Vascular arterial/venous thoracic outlet syndrome: This is caused by compression of the major artery leading to the arm, usually by either the first rib or an elongated transverse process of the seventh cervical vertebra. Thrombosis of the subclavian vein can be part of the syndrome, which is also found as part of rhabdomyolysis with extreme anaerobic exercise among very fit people. True arterial compression with thrombosis and distal vascular changes is very uncommon.

3. Questionable thoracic outlet syndrome: Describes patients who have chronic pain in the shoulders and arms and the underlying cause cannot be accurately determined; this is by far the most common found in the literature [64].

5.4.1.4.1.3 Differential Diagnosis
Differential diagnoses are many: cervical disc herniation, shoulder neuritis, tumours in or around the brachial plexus, rhabdomyolysis, double-crush syndrome and psychiatric personality changes. Double-crush syndromes are still very controversial.

5.4.1.4.1.4 Diagnostics Studies
Diagnostics studies are few and imprecise:
- White hand sign: A simple ‘objective’ test observing change of colours of the hands when the patient elevates the hands above the shoulder girdle with fingers pointed to the ceiling and palms facing the observer. If the hand/hands turn pale we have the so-called white hand sign.
- Two other non-specific tests that can suggest the presence of TOS are the Adson test and the hyperabduction test. These are often misjudged and not performed the same way by different examiners. The Adson test and the hyperabduction test are positive among >50% of normal persons and cannot be used for making a specific diagnosis.
- Neurophysiology: This includes nerve conduction velocity and somatosensory evoked potential testing. EMG/ENG may give clues when axonotmesis has occurred in the lower part of the brachial plexus, leading
to lowering of the action potential amplitudes proximal to the elbow and delay of the F-wave.

- **Angiography/plethysmography**: Vascular arterial angiography studies may be suggested but are also in most instances inconclusive unless the patient presents with severe ischaemic lesions in the hand.
- **Doppler ultrasound investigation**: Is paramount in cases of doubt.
- **Plethysmography**: Digital vasoconstriction is a manifestation of sympathetic hyperactivity and a digital pneumatic plethysmography tracing will show changes in the arterial digital waveforms.
- **Psychological assessment** is a mandatory part of the evaluation.

### 5.4.1.4.1.5 Treatment

This depends on the type of TOS being dealt with. It includes conservative and surgical modalities.

- **Conservative treatment**: The main treatment for TOS is physical therapy. Most commonly these syndromes should be treated conservatively, i.e., no surgery, and include physical therapy, avoidance of repetitive movements, postural exercises, NSAID drugs and diet. It should be suggested that the patients avoid carrying heavy bags over the shoulder.
- **Surgical treatment**: Surgery should never be used to treat ‘questionable thoracic outlet syndromes’. In a few cases, surgery can be considered, but always after a psychological profile has been carried out. Surgery consists of decompression of the plexus and includes surgical removal of the cervical rib, if this is causing the problem, or cutting of the anterior scalene muscles and inspecting and resecting the fibrous band from the middle scalene muscle, most often the cause of symptoms. Simple anterior scalene muscle resection is not indicated [64].

### 5.4.1.4.1.6 Prognosis

Surgical treatment of the very uncommon but ‘true’ neurogenic and arterial TOS is usually successful. Surgical treatment is the last resort. The ‘true’ TOS is very seldom diagnosed and all symptomatology indicating TOS should be reviewed carefully by neurosurgeons.

Operations for TOS syndromes have been among the most common failed operations in the world due to the lack of precise diagnostics.

### 5.4.1.4.2 Brachial Plexus Lesions: Trauma

Brachial plexus lesions are usually divided into groups according to the anatomical structure of the plexus. The anatomical development of the brachial plexus differs among adults and children. Therefore we divide these lesions into a neonatal or obstetric (OBPL) [65–67] group and an adult group [68].

### 5.4.1.4.2.1 Obstetric Brachial Plexus Lesions

Half of all brachial plexus lesions are considered to be of obstetric (neonatal) origin. In the Netherlands the incidence of brachial plexus lesions of obstetric origin is reported to be 2/1,000, and of these only a few percent of patients need surgical treatment per year.

The majority of children presenting with upper plexus lesions have a limp arm, abducted internal rotated shoulder and extended elbow, and pronded forearm with flexed wrist and fingers. Bilateral lesions are virtually never seen. Pain is not part of the paediatric syndrome contrary to radiculopathy and brachial plexus neuritis among adults. For the C8 and T1 level lesions the presence of a Horner’s syndrome is diagnostic. Dysfunction of the dorsal scapular (rhomboids) nerve and long thoracic (anterior serrate muscle) nerve indicates a root level injury. A lesion of the suprascapular (supraspinatus and infraspinatus muscles) nerve indicates trunk lesions. With a C4 root lesion, additional phrenic nerve palsy will be evident through respiratory problems.

Clinical evaluation includes the Mallet system (Fig. 5.4.1) grading the usable abduction and external and internal shoulder rotation and the child’s ability to reach the mouth with the hand. However this is difficult or impossible among newborns, where the capability of using the limbs is the best indicator of function [65, 67].

Neurophysiological information is difficult to access in the newborn. Despite muscle atrophy and neurogenic paresis, no denervation potentials may be found. EMG is sensitive to validate a reinnervation pattern but this pattern does not necessarily indicate clinical recovery. MRI demonstrates the larger pouches of avulsions, rupture of nerve roots and intraspinal cyst formations.

The treatment of OBPL involves conservative and active surgical principles (see Fig. 5.4.2):

1. **Conservative treatment**: Additional trauma to the shoulder joint has to be prevented among patients with OBPL. The parents can therefore help by avoiding abduction and posterior projection of the shoulder and by supporting the limb when holding the baby. The shoulder is rested for 3 weeks, while all other joints are mobilised. Traction or any immobilisation in a fixed position will increase pressures on the articular surfaces and cause deformity. Later active playing with the healthy arm is facilitated and after that use of the injured arm.

2. **Early surgery with neurotisation**: Avulsions seem more common among lesions of C6 and C7 levels. The plexus can be dissected through a supraclavicular transverse incision. The phrenic nerve is dissected and preserved when sectioning the C3 and C4 roots distal to this nerve. Grafting can be carried out between C3 and C5 and between C4 and C6 using sural grafts. At present outflow from intercostal nerves, distal accessory or higher cervical roots or descending
cervical plexus are thus anastomosed to more distal sites by the interposition of grafts. It is difficult for neurotisation to restore more than one distal function especially if it is far distal, for example the hand. In contrast to adults, hand function can be obtained due to the plasticity of the young brain. The use of the spinal accessory nerve for the suprascapular and upper root should be emphasised. Intercostal transfer to the musculocutaneous nerve has been successful in many cases.

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**Fig. 5.4.1** Obstetric brachial plexus lesions: Mallet scheme. (Modified from [66])

<table>
<thead>
<tr>
<th></th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tr>
<td><strong>Active abduction</strong></td>
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<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
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<td>less than 30°</td>
<td>30° to 90°</td>
<td>more than 90°</td>
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<tr>
<td><strong>External rotation</strong></td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
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<td>0°</td>
<td>less than 20°</td>
<td>more than 20°</td>
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<tr>
<td><strong>Hand to head</strong></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
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<tr>
<td>impossible</td>
<td>difficult</td>
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<td><strong>Hand to back</strong></td>
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<td>impossible</td>
<td>S_1</td>
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<td><strong>Hand to mouth</strong></td>
<td><img src="image13" alt="Image" /></td>
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3. Palliative/orthopaedic surgery: During the first period of 5 months the shoulder is most interesting. If the internal rotators and adductors have recovered well and the external rotators and abductors cannot counterbalance, a release of the subscapular muscle from the scapula and possibly a lengthening of the teres major tendon may be indicated through a posterior axillary incision, but must be performed before 1 year of age!! The second later period occurs when numerous synkinesias limit shoulder function. If the deltoid muscle is poor at age 2 years and the patient has a good functioning supraspinatus muscle, only limited movements will be obtained and surgery gives no benefit. If the opposite is the case, a transfer of the upper trapezius into the supraspinatus and the latissimus dorsi into the infraspinatus muscle may improve function. In older children even humeral osteotomy may be considered for better rotation of the shoulder. If elbow flexion is not satisfactory, the latissimus dorsi muscle may be transferred according to Zancolli’s technique. In cases of significant submuscular contraction botulinum toxin (Botox) injection in the muscle may be indicated.

5.4.1.4.2 Adults/Adolescence
This is usually a traumatic entity. The frequency of traumatic brachial plexus lesions in children and teenagers depends on age and the accident pattern. Roughly half of all injuries among adolescents are in industrialised countries in Europe caused by falls from heights, stab wounds, by glass or hit and run injuries. Motorbike accidents give a higher frequency of brachial plexus lesions among teenagers. Gunshot lesions are seen in the USA and countries at civil war. Cases of spine fractures/injuries among the youngest are almost never found, as the laxity of ligaments and the undeveloped spine up till the age of 8–9 years removes spine fractures from the clinical scenario, in contrast to the stretch type of plexus lesion. The spinal cord injury without radiographic abnormality (SCIWORA) is typical [65, 69], i.e. with neurological symptoms, but with no obvious lesion on CT or x-ray, and MRI is necessary to document ligamentous damage.

The treatment of adult brachial plexus lesions is difficult and the need for a specialised team is obvious if optimal results are to be obtained [69]. The complication of additional large vessel injuries is one of the more serious problems and often leads to indication for acute operations. Complete exposure of the brachial plexus can be obtained through a zigzag incision at the posterior border of the sternocleidomastoid muscle. For the lower roots an infracavicular approach through the deltopectoral groove can be used. It is advocated to dissect the suprascapular nerve and the musculocutaneous nerve. With severe vascular lesions these may be repaired first and the nerves subsequently when vascularisation of the arm is stable. For grafting, the sural nerve is mainly used but also the medial cutaneous nerves of arm and forearm can be used. If C8 and T1 is avulsed the ulnar nerve may be used as a graft.

The patients need a considerable amount of postoperative rehabilitation for many years. The results are promising but patients usually never regain full function.

Secondary procedures consist of local tendon transfers, unipolar and bipolar muscle transfers, and free transfer of vascularised and innervated muscle flaps. Tertiary procedures include functional arthrodesis.

Among the secondary procedures shoulder arthrodesis may be indicated if, for example, active glenohumeral motion is poor or if a flail shoulder causes excessive traction on the joint capsule. External rotation of the brachium can be performed with muscle transfers of teres major and latissimus dorsi muscles. Transfer of levator scapula...
muscle may obtain abduction. Steindler’s flexorplasty is indicated in C5/C6 lesions in order to improve elbow flexion.

Free vascularised muscle flaps may be those of gracilis, rectus abdominis, latissimus dorsi and tensor fasciae latae muscles.

In hand reconstruction, several specialised procedures may be indicated, which are for hand surgeons alone [70].

### 5.4.2 Trunk Region

#### 5.4.2.1 Lower Pelvic Plexus Lesions

The iliohypogastric, ilioinguinal and genitofemoral nerves can be exposed to entrapment, often as a complication of lower abdominal surgical procedures such as inguinal herniorrhaphy and appendectomy [71, 72]. The symptoms are pain, dysaesthesia and loss of sensibility in the affected dermatomes. The diagnosis can be confirmed by injection of a local anaesthetic with subsequent relief of the pain. Electrodiagnostic techniques are not available. A nerve block with or without steroid complemented with oral medication is the first step in the treatment. Surgical excision is an option if the symptoms are unacceptable despite the conservative treatment.

A lesion to the obturator nerve is often associated with a pelvic trauma, compression of the nerve during delivery of the foetus or a complication of a hip arthroplasty. The patient will complain of instability and weakness of the associated leg, especially in relation to exercise. If the nerve injury is complete, there is a loss of adduction and the foot is externally rotated. Surgery with decompression of the anterior branch of the nerve is often necessary [72].

Meralgia paresthetica is a neuropathy affecting the lateral femoral cutaneous nerve (LFCN) with dysaesthesia and pain in the distribution of the nerve [73]. The LFCN is subject to compression injuries at the inguinal ligament. Obesity with a protruding abdomen, pregnancy or external compression from a belt can cause this condition. Most often the nerve will pass through the lateral attachment of the inguinal ligament, but it can cross the iliac crest and be subjected to a lesion in harvesting an iliac bone graft. The diagnosis can be confirmed by injection of local anaesthetic around the LFCN at the anterior superior iliac spine. If the symptoms are relieved after this test it should be followed by a later injection of anaesthetic and steroid. Causal treatment such as weight loss and use of looser clothing is advised. Surgical treatment can be considered for those who fail to respond to conservative treatment [74, 75]. A simple decompression of the nerve should be performed in patients with minor symptoms or a short history of illness. If the symptoms recur after primary surgery, resection of the nerve should be considered. The same procedure seems to be the best choice in patients in which this condition has been the present for more than one year. The nerve should then be transected some centimetres posterior to the ligament.

#### 5.4.3 Lower Extremities

#### 5.4.3.1 Femoral Nerve

The femoral nerve can be injured due to a traumatic incident such as laceration injuries or compression/heat during a total hip arthroplasty. Entrapment neuropathies often occur below the inguinal ligament [76]. The patient’s concerns may include pain in the inguinal region and leg weakness caused by paresis of the quadriceps. Sensibility is affected with sensory loss or dysaesthesia over the anterior thigh and the anteromedial aspects of the leg, down to the foot. Electrodiagnostic testing reveals pathological changes in the nerve. The treatment depends upon the cause of the injury and the EMG changes. Status is monitored if the nerve is in continuity without severe axonal loss. The patient may need a knee brace during the recovery period.

#### 5.4.3.2 Sciatic Nerve

Patients with symptoms related to the sciatic nerve often have an entrapment of the nerve roots at the lumbosacral spine. A distal compression can be caused by the piriform muscle (piriformis syndrome is still a controversial diagnosis) as the nerve passes the sciatic notch in the gluteus region. The sciatic nerve is often involved in cases of nerve palsy as a complication of a total hip replacement. The symptoms vary according to the level of the pathology. The indications of entrapment are lower extremity pain in the sciatic nerve distribution, muscle weakness and sensory impairment. The physical examination and the history are reliable tools but MRI and nerve conduction tests are often necessary in the diagnostic procedure. Physical and injection therapies are possible conservative treatment procedures. Surgical decompression is necessary if a tumour or other external factors refractory to non-surgical therapy affect the nerve [77].

#### 5.4.3.3 Saphenous Nerve

The site of entrapment of the saphenous nerve is the adductor canal, approximately 10 cm proximal to the medial femoral condyle. Injury to the nerve can occur as a complication to surgery on the leg such as removal of
the saphenous vein. The patient will experience pain and paraesthesia in the cutaneous distribution of the nerve in the medial part of the lower leg [78]. When present, this compression is an often unnoticed cause of pain in the medial aspects of the knee after a trauma. A local injection of anaesthetic can be diagnostic as well as therapeutic, combined with adjustment of activities. Surgical intervention should be undertaken if this treatment fails.

5.4.3.4 Peroneal Nerve

The common peroneal nerve is particularly vulnerable as it courses around the fibular neck [79, 80]. Many aetiological factors can be involved in this neuropathy: external compression due to habitual leg crossing or prolonged compression due to immobility, various traumatic episodes including iatrogenic injuries during operations and internal compression from tumours. Idiopathic causes are common. The involvement of the nerve causes weakness of the muscles in the anterior compartment of the lower leg with foot drop as a consequence. There is loss of sensibility over the anterolateral part of the lower leg and the dorsum of the foot.

The gait of a patient with a foot drop is characteristic with a foot slap, because the descent of the foot is out of control. The diagnostic procedure is completed by an additional electrodiagnostic evaluation. Spontaneous recovery is expected after elimination of a transient external compression. The patient should be supplied with a brace during the period of paralysis to control the gait pattern. In idiopathic cases without recovery within a period of 4 months and in patients with internal compressions, operative exploration should be performed [81].

The superficial peroneal nerve can be entrapped as it exits the fascia 10 cm above the lateral malleolus. The complaints are purely sensitive with numbness/pain or paraesthesia in the anterolateral part of the distal lower leg, ankle and foot. Surgical decompression is the option if conservative treatment fails.

The deep peroneal nerve can be entrapped over the dorsal aspect of the ankle, beneath the extensor retinaculum. This condition is sometimes referred to as the ‘anterior tarsal syndrome’. The symptoms are aching pain at the dorsum of the foot and sensory changes in the first dorsal web space. Intrinsic muscular atrophy in the first dorsal web may be present. External compression should be eliminated, such as adjustment of the shoes. Complementary treatment is as mentioned above.

5.4.3.5 Posterior Tibial Nerve

The tarsal tunnel syndrome is an entrapment of the posterior tibial nerve in the fibro-osseous tunnel at the medial aspects of the ankle [82, 83]. It is the most common nerve compression syndrome in the foot and ankle area. The condition can be attributed to factors such as tenosynovitis, ganglion cysts, diabetes or post-traumatic fibrosis after a fracture/contusion. Increased valgus deformity of the foot is a possible predisposing factor.

The patient will complain of a discomfort or burning pain in the plantar foot. Standing or walking for a longer time will exacerbate the symptoms. The examiner will find a positive Tinel’s sign over the nerve at the side of compression. Plain radiographs will reveal osseous deformities. Electrodiagnostic tests are helpful in the diagnosis.

An external ankle support is often helpful. In cases with post-traumatic fibrosis or a space-occupying lesion, surgical release is indicated [84].

5.4.3.6 Plantar Digital Nerve

Morton’s metatarsalgia is an entrapment of the common plantar digital nerve at the level of the heads of the adjacent metatarsal bones, under the transverse metatarsal ligament [85]. The condition mainly affects women. The third intermetatarsal space is most often involved with an aching pain on the plantar aspect of the foot and entrapment site tenderness. The symptoms will usually increase in strength by walking. Conservative treatment consists of shoe modification including a pad proximal to the central metacarpal heads. A local injection of anaesthetic will eliminate pain for a short time and confirm the diagnosis. The most commonly performed surgical procedures are release of the intermetatarsal ligament and a neurectomy or a neurolysis [85].

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and tarsal tunnel release: clinical application. Neurosurgery 59:89–100
5.5 Peripheral Nerve Tumours

*IDA E. HOLM*

These tumours include primary tumours deriving from the nerve sheaths and can be benign or malignant. The major clinicopathological entities include schwannomas, neurofibromas, perineuriomas, malignant peripheral nerve sheath tumours and others.

### 5.5.1 Schwannoma

Peripheral schwannomas are painless mass lesions, whereas spinal tumours can present with radicular pain and nerve root and spinal cord compression, and vestibular tumours (eighth cranial nerve) result in cerebellopontine angle syndrome (deafness, tinnitus and disturbed facial sensitivity). Multiple schwannomas are seen as part of neurofibromatosis (NF2) and schwannomatosis. The tumours involve single nerve fascicles, grow slowly and rarely undergo malignant change. They can usually be dissected with microsurgical techniques and removed completely.

The tumour is composed of Schwann cells, spindle-shaped cells with eosinophilic cytoplasm and spindle-shaped nuclei. A typical biphasic growth pattern is often seen with cellular (Antoni A) areas alternating with hypocellular (Antoni B) areas. Mitoses can be seen and the tumour cells express S-100 and focally GFAP. Cellular, melanotic and plexiform variants are described (Fig. 5.5.1).

### 5.5.2 Neurofibroma

Neurofibromas are usually more painful. They can be solitary or multiple as part of neurofibromatosis von Recklinghausen (NF1) where other stigmata include café-au-lait spots and axillary freckling. Neurofibromas most often present as nodular cutaneous tumours (cutaneous neurofibromas), and more rarely as localised tumours in a peripheral nerve (intraneural neurofibromas) or as a plexiform swelling of one or more nerve trunks of a large nerve (plexiform neurofibromas). Cutaneous neurofibromas can easily be removed, whereas intraneural and plexiform neurofibromas involve more fascicles and therefore are more difficult to remove surgically. Malignant transformation to malignant peripheral nerve sheath tumour (MPNST) can occur in intraneural and plexiform neurofibromas.

The tumour consists of a mixture of Schwann cells, perineural cells and fibroblasts separated by a myxoid matrix containing collagen fibres. Mitoses are rare and

---

*Fig. 5.5.1* Schwannoma. Schwann cells in cellular Antoni A area with cell nuclei arranged in palisades

*Fig. 5.5.2* Neurofibroma. Schwann cells, perineural cells and fibroblasts are separated by a myxoid matrix containing collagen fibres
the tumour cells express S-100, but the number of positive cells is smaller than in schwannomas (Fig. 5.5.2).

### 5.5.3 Perineurioma

Rare benign tumours located in the nerves of the extremities in adolescents. The tumour consists of proliferating perineural cells forming concentric layers around nerve fibres (pseudo-onion bulbs).

### 5.5.4 Malignant Peripheral Nerve Sheath Tumour

Uncommon tumours arising from neurofibromas, usually plexiform neurofibromas, located in the thigh or in the brachial plexus. Fifty per cent occur in patients with NF1. The tumour usually resembles a fibrosarcoma, but epithelioid and glandular variants have been described, as well as a rhabdomyosarcomatous type (malignant Triton tumour).

### 5.5.5 Other Tumours

Involvement of peripheral nerves due to direct spread from malignant tumours in other organs is most commonly seen in the brachial plexus as spread from apical lung cancer or breast cancer.

### 5.5.6 Treatment of Peripheral Nerve Tumours

Primary tumours are removed radically using microsurgical techniques. Usually the surgeon can dissect the fascicle from which the benign tumour derives and resect the tumour in healthy tissue. Biopsy of the resection lines should always be made in these cases.

With sarcomas, besides removal of the tumour, acute limb amputation is usually undertaken. Different protocols of irradiation and/or chemotherapy are found in the literature.

### Suggested Reading

Scheithauer BW, Woodruff JM, Erlandson RA (1999) Tumors of the peripheral nervous system. Armed Forces Institute of Pathology, Washington DC


5.6 Autonomic Nervous System

JENS HAASE

5.6.1 Introduction

The autonomic nervous system consists of the sympathetic and parasympathetic systems. Its structure is found in Fig. 5.6.1.

In the parasympathetic system the autonomic nerve fibres follow normal peripheral nerves, e.g. in the hypogastric pelvic plexus. From the medulla oblongata of the brainstem, parasympathetic fibres are found in the 3rd, 7th, 9th and 10th cranial nerves.

In the sympathetic system, paravertebral sympathetic ganglia are found outside the vertebrae. Preganglionic fibres arrive at these through the motor root, and postganglionic fibres return via the posterior sensory nerve roots (Fig. 5.6.2). The cell bodies are found in the plexuses: superior cervical ganglion, inferior cervical ganglion or cardiac ganglion. The celiac and mesenteric ganglia serve the abdominal organs, as shown in Fig. 5.6.1.

Diseases of the peripheral nervous system that have been treated are hyperhidrosis and dystrophic pain.

Fig. 5.6.1 Structure of the autonomic nervous system
5.6.2 Primary Hyperhidrosis

This disease has an unknown aetiology. The patients sweat from hands and palms causing major social problems, for example when writing. It is common among Chinese populations and uncommon among whites.

The surgical treatment is bilateral thoracic sympathectomy carried out by endoscopic means. For facial sweating and erythema, the sympathetic chain is sectioned at the T2 level, while for hand sweating it is cut at the T2/T3 level. Axillary sweating is treated by sectioning from T2 to T4. Unfortunately the operation has a high morbidity as 89% of patients will develop a significant compensatory sweating from other parts of the body. In 35% of cases this will be so significant that they have to change clothes during the day. The most aggressive form of compensatory sweating is found after T2 to T4 sympathectomy for axillary sweating. Gustatory sweating, i.e. excessive salivation when eating specific foods, is found among 38% of those operated on.

As a consequence, 16% of patients are postoperatively unhappy with their operative treatment [1].

5.6.3 Complex Regional Pain Syndrome

Following simple lesions of the hand or other parts of the upper extremities unbearable painful conditions may develop. If based on trauma, immobilisation, etc. it is called complex regional pain syndrome (CPRS) type 1 and if it stems from peripheral nerve lesions it is CPRS type 2. The median nerve has approximately 70% of the sympathetic nerves to the hand. The pain has therefore been thought of as based on sympathetic overflow and was previously called reflex sympathetic dystrophy (RSD).

It is considered a nociceptive pain that changes into a central pain. CPRS develops through three stages. The first stage is characterised by swelling of the extremity, hyperaesthesia (allodynia), developing a skin that is warm and dry, and movements that aggravate the persistent pain. In the second stage proximal spread of pain and oedema is found and a cool and pale shiny skin with atrophic changes develops and joint stiffness occurs. In the third stage a progressive degree of atrophy with joint contractures is found and the patient claims ‘intractable pain’. It thus involves sensory, motor, vasomotor and sudomotor changes. A set of definition criteria has been set up by the International Association for the Study of Pain (IASP) [2].

Treatment in the first stages is physical therapy and, more questionably, corticosteroids. Many attempts have been made to solve the patient’s problem including use of sympathectomy due to the idea of sympathetic overflow. All papers on sympathectomy are based on a blend of poor quality and lack of evidence, being uncontrolled studies and based on ‘personal experiences’ [3]. The interested reader should consult Harden et al. [2] for further information.

References

The twelve cranial nerves, originating from the brainstem on both sides, have a well-known course and anatomical relationship in and through the base of the skull towards their end organs. This chapter deals with relevant pathologies of these nerves, some of which are pertinent to the realm of neurosurgery. They can be divided into nerve deficits and nerve compression syndromes mostly with hyperactivity as the primary feature.
Trauma, infection and tumours are the major causes of cranial nerve deficits. Tumours can be divided in those of the nerves themselves and tumours of the surrounding tissues. Therapies can be surgical as well as non-surgical. Details concerning these therapies are presented in the chapters dealing with these pathologies.

Some general remarks and statements are given here, as an overview. Surgery is appropriate when traumatic or tumoral compression can be alleviated without causing new or more deficits. Examples are traumatic optic nerve compression, skull-base meningiomas, chordomas and chondrosarcomas, cavernous sinus tumours and vestibular schwannomas. Today, for many of these, a combination of incomplete (“safe”) surgery with stereotactic radiation (radiosurgery) seems most effective and rewarding.

Deficits by nerve tumours themselves occur primarily from the olfactory, optic, trigeminal, facial, vestibular, glossopharyngeal and vagal nerves. The olfactory neuroesthesioblastoma is a very malignant tumour for which radical surgery combined with radiation therapy can lead to acceptable survival figures. The optic glioma can be very local, amenable by radical surgery, or be enlarged towards only partially or non-resectable tumours with involvement of the chiasm and the hypothalamus. Pilocytic (grade I) or diffuse (grade II) astrocytomas form the common histological feature; they can be sporadic or part of neurofibromatosis type I.

Schwannomas of the fifth and seventh nerve are slow-growing lesions. Surgery, as well as radiosurgery, is a sensible therapeutic option. In many cases, a watchful waiting policy is justified, depending on age, complaints and width of the tumour. The same holds true for the much more frequently occurring vestibular schwannomas. The latter can be sporadic, or occur in the context of neurofibromatosis type II. Glossopharyngeal and vagal schwannomas occur mostly in the context of neurofibromatosis I and II.
6.2 Cranial Nerve Compression Syndromes

Jan Jakob A. Mooij

Compression syndromes are vascular compressions of nerves that result in hyperfunction (hyperactivity). The most common are the trigeminal and the facial ones, resulting in trigeminal neuralgia and hemifacial spasm, respectively. But there are more, and we will discuss these here following the nerve numbers.

6.2.1 Trigeminal Neuralgia

6.2.1.1 Signs and Symptoms

The typical feature of trigeminal neuralgia (TN) is the lancinating, electrical current-like pain in the face located according to one or more of the trigeminal areas (divisions). The pain lasts only seconds up to a few minutes but can occur in repeated trains of these short flashes, resulting in agonizing pain attacks for hours or days. Pain is typically triggered by touch, cold wind, talking, eating, or shaving, but can also start spontaneously. The latter may suggest a toothache, leading many patients to a dental consultation first.

In typical TN, sensory and motor nerve function is normal. There is a yearly incidence of 4 per 100,000, with a mean age at occurrence of a little more than 60 years and a slight female preponderance (1.8:1). The right side is more frequently involved (60%); only in 1% does TN occur on both sides.

6.2.1.2 Cause

TN can be symptomatic or idiopathic. In symptomatic cases, there can be a peripheral cause like maxillary or mandibular (tooth-related) inflammation leading to irritation of the TN branches. A more centrally located lesion-like trauma, or a tumour of or on the nerve, may give neuralgiform pain, but almost always with a loss of function. This should be called “neuropathy”, with or without neuralgia. The most important centrally located cause of TN is multiple sclerosis (MS), based on demyelination of the central trigeminal pathways. Of patients presenting with TN, 2–4% may have MS, and 2% of MS patients develop TN.

When no causes like the above are found, TN is called idiopathic. But since the observations by Dandy, Gardner and Jannetta, we now know that in more than 90% of so-called idiopathic TN, the disease is caused by vascular (arterial or venous) compression of the nerve at its root entry zone. Axons of the trigeminal nerve at the root entry zone have a transition from Schwann cell isolation peripherally into oligodendroglial isolation centrally within the brain. Vascular compression is believed to result in the lateral spread of action potentials, resulting in abnormal activity in central pathways and nuclei of the trigeminal system.

6.2.1.3 Adjuvant Diagnostics and Differential Diagnosis

Neurological testing is necessary: sensory and motor function of the trigeminal nerve should be normal, as stated before. In some cases, neurophysiology (OOR) may show subtle changes, but in general, such tests are not reliable enough. Imaging, preferentially by magnetic resonance (MR), is necessary to rule out other pathology like MS, intrinsic vascular lesions (cavernomas) or tumour. The constructive interference in steady state (CISS) modality (MRI) may show the vessel–nerve relationship that is believed to cause the pain in TN. Sensitivity and selectivity, however, are generally not good enough to prove or deny a definite neurovascular compression. So, the most important aspect of the diagnostic work-up is the precise history of the patient. The typical TN can then be differentiated from dentogenic pain, cluster headaches, geniculate neuralgia, glossopharyngeal neuralgia, post herpetic neuralgia/neuropathy or sphenopalatine neuralgia. In long-lasting TN, the typical features (short attacks, triggers) may change gradually in a more sustained pain. It can be difficult to decide whether in these cases it is still typical TN, or the atypical form. The latter consists of a chronic burning pain in the face, without typical triggers, and is not caused by vascular compression. Only a careful history can lead back to the original features of the illness.
6.2 Cranial Nerve Compression Syndromes

6.2.1.4 Therapeutic Options

In all cases of craniofacial pain resembling TN, drug treatment with carbamazepine (Tegretol®) should be the first choice. In almost all cases of typical TN, it relieves the pain when given in adequate doses, which makes it even a diagnostic tool. Many patients are cured for a certain time and can even taper off the original dose. The main drawbacks of this drug are the side effects (nausea and dizziness), which prevent continuation of the drug in quite a percentage of patients. Variants like Trileptal®, or other antiepileptic drugs like Dilantin® and gabapentin, may replace carbamazepine.

When drug treatment fails, because of ineffectiveness or side effects, it is worthwhile to consider a more definitive treatment. Microvascular decompression (MVD), developed and propagated by Jannetta and others, is the most logical and causative treatment. It is surgery in a very delicate area under general anaesthesia: therefore, to balance the risk/benefit ratio, the patient’s general condition should be taken into account as well as the experience of the neurosurgeon.

When it seems wise not to operate for whatever reason, one of the ablative techniques can be chosen: a radiofrequency (RF) lesion of the Gasserian ganglion (GG); balloon compression of the GG; injection of glycerol in Meckel’s cave. Recently, experience with gamma-knife radiosurgery or linac-based stereotactic radiosurgery has proven to give results almost as good as the above-mentioned ablative procedures and should therefore be considered as a realistic alternative.

In symptomatic cases, especially in MS patients, these ablative methods are the first choice: the cause is presumably in the central nervous system itself, not at the root entry zone. Thus, diminishing the sensory input by some kind of ablation is a logical option.

6.2.1.5 Results

The best results, short term and long term, are obtained with the causal treatment – MVD. Short-term results are also almost as good with the ablative RF lesion or glycerol injection. These latter procedures carry an inherent morbidity (sensory changes), and the recurrent rate is rather high. Of course, these procedures can be repeated, and therefore they are a good second choice in genuine TN and in MS patients. When applied at a younger age, though, there is the risk of late serious deafferentation problems – the anaesthesia dolorosa phenomenon. That holds true also for the most radical ablative procedure, the Dandy operation, which involves cutting the nerve near the brain stem. Results are summarized in Table 6.2.1.

6.2.2 Hemifacial Spasm

Hemifacial spasm (HFS) is a severe disability with social and aesthetic impact in a patient’s daily life. The typical clinical picture, with unilateral involuntary contractions of the facial muscles, is easily recognised by those familiar with this disorder. Although a differential diagnosis has to be made, in most cases there will be no doubt about the diagnosis. The incidence (per 100,000) is 0.84 for females and 0.74 for males. Prevalence figures are 14.5 (females) and 7.4 (males) respectively. The peak age is between 50 and 60 years.

6.2.2.1 Signs and Symptoms

The typical clinical picture starts with involuntary contractions in the muscles around one eye, in due time (months, years) extending to the jaw, the cheek, and some-
times to the upper neck (platysma area). The contractions occur spontaneously, may be aggravated during activity or emotion, and may continue during sleep. When the contractions are severe, they result in a tonic cramp in the face, and almost closure of the eye, impairing reading and other visual functioning (e.g. watching television). It is a one-sided phenomenon. When double sided, a central dystonia, like Meige’s syndrome or blepharospasm, should be considered. Otherwise, the differential diagnosis consists of post-Bell’s palsy, myokymia, psychogenic tic, or another (central) dystonia or dyskinesia.

6.2.2 Cause

In almost all cases that have been surgically verified, vascular compression at the root exit zone has been found and considered to be the cause. One should be aware of the fact that the exit zone of the VIIth nerve comprises quite a few millimetres of the lateral brain stem, which means that compression can also occur at that area, where the nerve is not yet a free-running bundle. As in the trigeminal nerve, the axons of the facial nerve at the exit zone have a transition from oligodendrogial into Schwann cell isolation. Vascular compression is believed to result in lateral spread of action potentials, with abnormal responses in the facial muscles and kindling of the nerve cells in the nucleus within the brain stem, which causes a lowering of the threshold for firing.

6.2.3 Adjuvant Diagnostics

The clinical picture is in itself an almost 100% proof of the typical illness. Electromyography (EMG) and spontaneous and elicited responses can prove the so-called lateral spread, ephaptic response or "abnormal muscle response". The patient’s history should rule out a former Bell’s palsy or other dystonic phenomena. An MR scan will, in the first place, rule out other disease (compressing tumour, lesions in the brain stem), and with today’s quality of scanning, especially in the CISS modality, a suggestion of vascular compression is given in 60–80% of the cases. But in the experience of the author, in many of these cases, the really compressing artery is another branch (nearby, of course), and when MR images do not show compression, a vascular conflict is almost always found at surgery. In other words, the sensitivity and selectivity of MRI is not reliable enough, and imaging is only necessary to rule out other disease.

6.2.4 Therapeutic Options

Medical treatment for HFS is useless; the drugs that work so well for TN do not have a significant positive effect here. A good option in HFS is multiple local injections with botulinum toxin (Botox). The major drawback of this treatment is that the effect tapers off with time (3–4 months). So, patients need new injections 3–4 times a year, which becomes awkward after a while. In quite a number of patients, the reaction to the Botox differs per turn and decreases over the years. Some patients get a facial palsy that does not fully subside in time. There is no spontaneous mitigation of HFS in the long run. The only cure is the most logical therapy: decompression of the facial nerve at the exit zone – MVD. Best results are obtained when the physiological findings mentioned above are controlled intraoperatively. The main possible side effect of surgery is, besides general risks of surgery, damage to the VIIIth nerve, resulting in hearing loss. Figures differ among authors, but the risk of substantial hearing loss lies around 2% in general.

6.2.5 Results

Over the years, many reports have been published about the results of MVD for HFS. One can see (Table 6.2.2) that a cure rate somewhere between 80 and 95% can be promised to patients. It must be mentioned that the surgery is delicate and that the surgeon needs a great deal of experience, which means that he/she will improve over time. The use of intraoperative neurophysiologic monitoring adds, in our opinion and experience, to the success rate.

6.3 Tinnitus/Vertigo

Since the description by Jannetta and Møller in the late 1970s, the combination of tinnitus and vertigo has been considered a nosological entity that might be caused by neurovascular compression. The problem is that both tinnitus and vertigo are quite common complaints, with a great deal of variation and aspecificity in their presentation. Since the first description in 1861 by Ménière of the combination of progressive hearing loss with tinnitus and vestibular disturbance, most patients with such a combination have been considered to have Ménière’s disease or syndrome, with presumed inner-ear pathology. When differentiating between the two entities, it seems important to realize that the neurovascular compression syndromes are in fact hyperactivity syndromes, so tinnitus with good hearing and vertigo with sustained function of the vestibular system might both be consistent with the concept. Only small series on MVD for disabling vertigo, tinnitus or the combination have been published. Recently, the advanced imaging possibilities have added some arguments in certain patients for giving MVD a try.
6.2.3.1 Signs and Symptoms

In several patients successfully treated by MVD, tinnitus had been preceded by some form of hyperacusis, and hearing loss was absent or only mild. The tinnitus is mostly of a non-pulsatile character.

The vertigo is always of the disabling positional type, starting with movement of the head/body with no spontaneous attacks. In the most typical form, the vertigo combines with tinnitus.

6.2.3.2 Cause

Inherent to the coining of the name of this syndrome, compression of the cochlear and/or vestibular nerve by a vascular loop is considered to be the cause. Different from the trigeminal and facial nerve, the transition (and therefore vulnerable) zone from oligodendroglial towards Schwann cell isolation in these nerves is not confined to the entry zone. So the vascular conflict may not be restricted to the entry zone of the nerves. There have been some studies that relate the pitch of the tinnitus (and some hearing loss) to the place of compression along the nerve.

6.2.3.3 Adjuvant Diagnosis

Audiometry, vestibular tests (an abnormal caloric response, especially, seems to be indicative), tinnitus pitch, disabling scales and advanced MR imaging all help to exclude other diagnoses and make neurovascular compression the most likely.

6.2.3.4 Therapy

In light of the above, MVD is the most appropriate and logical option. With only (mild) tinnitus alone, nothing should be done. Alternatives are vestibular neurectomy or ear, nose and throat (ENT) procedures on the co-chlea. They have been performed for severe vertigo and its combination with tinnitus and progressive deafness, with variable success. In the coming years, neuromodulation procedures may prove to become a new and good alternative.

6.2.3.5 Results

MVD for vertigo cases, with or without tinnitus, results in a good outcome or improvement in 85%, comparable with MVD results for trigeminal neuralgia. In tinnitus alone, the results seem to be less successful and thus more unpredictable.

6.2.4 Glossopharyngeal Neuralgia

This is again a typical neuralgia (pain in the distribution area of a nerve) with pain attacks, lancinating character, no pain in between attacks, specific provocations and no...
nerve function loss (compare to TN). Concomitant involvement of the vagal nerve can be apparent; therefore, some authors describe the syndrome as vagoglossophrvyngeal neuralgia. The incidence is about 1% of that of trigeminal neuralgia.

6.2.4.1 Signs and Symptoms

In glossopharyngeal neuralgia, the patient complains of typical one-sided neuralgiform pain in the pharyngeal area, sometimes extending into the hindmost part of the tongue and/or the ear. Provocation occurs by swallowing, coughing or yawning. The paroxysms of pain tend to be longer but less lancinating than in trigeminal neuralgia. In some patients, the vagal involvement is evident through bradycardia during the attacks.

6.2.4.2 Cause

The pathophysiology is comparable to that in trigeminal neuralgia: vascular compression of the root entry zone of the glossopharyngeal nerve and the upper two rootlets of the vagal nerve. Also, an association with MS may exist, and tumours of the skull base and pharyngo-laryngeal region have to be ruled out.

6.2.4.3 Adjuvant Diagnosis

With a typical clinical presentation, adjuvant investigations are only necessary to exclude other pathology. So ENT inspection as well as MR imaging are the mainstays of what is necessary before concluding that vascular compression is the cause of the complaint. A provocative test by touching the tonsillar area, or a diagnostic alleviation of the pain by the local application of lidocaine, may further confirm the clinical picture.

6.2.4.4 Therapeutic Options

In typical cases, the logical treatment is MVD. In mild forms, or up front, symptomatic relief can be obtained with carbamazepine or gabapentin. MVD can be more difficult than in cases of HFS or TN, since the compressive vessel (mostly a PICA loop) can be held in place tightly by the vertebral artery. Sometimes the latter has to be moved also, which in itself is a surgical challenge. In the past, many attempts have been done with nerve section, intracranially as well as extracranially, with variable but acceptable results.

6.2.4.5 Results

The figures for cure and/or improvement, reported from small series, again reach 80% or even above, so with a good indication, MVD seems to be the best treatment option.

6.2.5 Other Neurovascular Compression Syndromes

Several observations during decompressive surgery for the above-mentioned entities have led to the concept that compression of the brain stem at the exit zone of the vagal nerve, or even more caudally, could cause, or at least contribute to, hypertension and even diabetes. Although very interesting data have been published, these are rather contradictory (for example as to the specificity of the side) and have not been tested in large enough series to draw solid conclusions. For the moment, it cannot be recommended, therefore, to try to treat hypertensive or diabetes patients in general by MVD. Further observations, and data from experimental studies, may give further clues as to selection for MVD treatment in some of these patients in the future.

The same holds true for patients with spasmodic torticollis: decompression of vascular conflicts of the accessory nerve was promising at first. But in most patients with this disease, neurophysiology shows many more muscles to be involved next to those innervated by the XIth nerve. That makes MVD of the accessory nerve inappropriate in most cases.

The better alternatives seem to be Botox injections and/or selective peripheral denervations of the muscles involved.
6.3 Conclusion

Jan Jakob A. Mooij

The cranial nerves can be involved in trauma, tumour growth, or neurovascular compression syndromes. Of the latter, trigeminal neuralgia, hemifacial spasm and glossopharyngeal neuralgia are the most clearly defined and rewarding for neurosurgical treatment, preferably by MVD. Tinnitus/vertigo patients are much more difficult to assess, but also here, with appropriate patient selection, MVD can achieve good treatment results. For patients with hypertension, diabetes and spasmodic torticollis, the relation with vascular nerve or brainstem compression is not so well established and for them, at this stage, MVD cannot be recommended in general.

Suggested Reading

Trigeminal Neuralgia


Hemifacial Spasm


Tinnitus/Vertigo


Glossopharyngeal Neuralgia


**Combined Studies**


**Hypertension and Diabetes**


**Spasmodic Torticollis**

Congenital Defects and Childhood Disorders

Edited by Concezio Di Rocco
7.1 Cranial and Spinal Dysraphisms

7.1.1 Encephaloceles and Related Malformations

Juan F. Martínez-Lage and Miguel Angel Pérez-Espejo

7.1.1.1 Introduction: Concepts and Definitions

The term *cranium bifidum* is used to designate a defective closure of the skull by analogy with that of its spinal counterpart (spina bifida). Both malformations are regarded as neural tube defects (NTD); however, only anencephaly is a true NTD. The term *encephalocele or meningoencephalocele* designates a protrusion of any of the intracranial contents through a congenital defect in the skull, whether at the cranial vault or at the base [1, 3, 4, 7]. An *encephalocele* includes brain parenchyma (Figs. 7.1.1–7.1.3), while a *cranial meningocele* (Fig. 7.1.4) contains only cerebrospinal fluid (CSF) and is lined by arachnoid [1, 3, 4, 7]. In certain cases, encephaloceles may comprise parts of a ventricle or choroid plexus [1, 3, 4, 7]. *Atretic cephalocele* (Fig. 7.1.5) refers to a small-sized midline subscalp lesion that contains no cerebral tissue but neural remnants [5, 7, 10]. There is no clear-cut limit to separate the diverse clinical forms that constitute the spectrum of cranium bifidum. At present, the terms cephalocele and encephalocele are used interchangeably to encompass all these lesions [7]. Table 7.1.1 summarizes the definitions of the spectrum of cranial congenital defects, and Table 7.1.2 classifies cephaloceles into four main types according to their composition.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranium bifidum</td>
<td>Any congenital defect of the skull and/or meningeal or cerebral tissue</td>
</tr>
<tr>
<td>Cranium bifidum occultum</td>
<td>Cranial defect covered by normal skin</td>
</tr>
<tr>
<td>Acalvaria</td>
<td>Congenital absence of the cranial vault</td>
</tr>
<tr>
<td>Anencephaly (acrania)</td>
<td>Absence of the skull vault and of cerebral tissue</td>
</tr>
<tr>
<td>Exencephaly</td>
<td>Severely malformed and exposed brain with absence of the skin and cranial vault; a forerunner of anencephaly</td>
</tr>
<tr>
<td>Cephalocele</td>
<td>Skull defect associated with herniation of some intracranial content</td>
</tr>
<tr>
<td>Encephalocele</td>
<td>Herniation of brain through a cranial defect</td>
</tr>
<tr>
<td>Ventriculoencephalocele</td>
<td>Same as above plus extracranial protrusion of ventricle</td>
</tr>
<tr>
<td>Cranial meningocele</td>
<td>Sac with herniated meninges and CSF through a skull defect</td>
</tr>
<tr>
<td>Atretic cephalocele</td>
<td>Small subscalp lesion with cerebral, vascular and meningeal rests</td>
</tr>
<tr>
<td>Subscalp heterotopic nodules</td>
<td>Small subscalp lesion containing vestigial tissues and no cranial defect</td>
</tr>
<tr>
<td>Scalp aplasia cutis congenita</td>
<td>Focal absence of the scalp with or without meningeal or cranial defect</td>
</tr>
</tbody>
</table>

Table 7.1.2 Classification of the four main forms of cranium bifidum according to their contents

<table>
<thead>
<tr>
<th>Brain</th>
<th>CSF</th>
<th>Neuroectodermal origin tissues</th>
<th>Skull defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalocele</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Cranial meningocele</td>
<td>−</td>
<td>+/+</td>
<td>+</td>
</tr>
<tr>
<td>Atretic cephalocele</td>
<td>−</td>
<td>+/−</td>
<td>+</td>
</tr>
<tr>
<td>Subscalp nodules of heterotopic tissue</td>
<td>−</td>
<td>+/−</td>
<td>−</td>
</tr>
</tbody>
</table>
7.1.1.2 Anencephaly

Anencephaly is a lethal birth defect characterized by the absence of all or part of the scalp and skull (acrania) that includes the most severe brain malformations [1, 4]. This condition has a worldwide incidence and affects all races and ethnic groups. Its prevalence ranges from < 1/10,000 to 2.5/10,000 births and shows a female to male predominance of 3:1. Most cases are sporadic, although anencephaly may be found in families with other NTD, such as spina bifida or encephalocele. Anencephaly has been reported as forming part of a syndrome, mainly Meckel’s syndrome. Anencephaly has been related with maternal diabetes mellitus, nutritional deficits (especially that of folic acid) and teratogens. Encephalocele seems to be a precursor of anencephaly and consists of the absence of skin and skull associated with an exposed brain whose tissues are highly disorganized and necrotic.

The diagnosis of anencephaly is readily made at birth by inspection. In anencephaly, the cranial vault and cerebral hemispheres are absent, and the skull base is relatively well preserved. The globes, orbits and vertebral column may be involved. There also may be associated systemic malformations. Prenatal diagnosis is made by maternal serum alpha-fetoprotein (AFP) screening and by ultrasonography from the 12th to 14th weeks of pregnancy. Often, the parents choose termination of pregnancy (90%). The remaining cases are either stillborn or survive a short time after birth, as the condition is incompatible with life. Live neonates with anencephaly are managed with only support measures. Ethical issues arise from termination of pregnancy and from considering anencephalic children merely as potential donors for organ transplant. The incidence (and recurrence) of this malformation has decreased due to the periconceptional intake of folic acid.

7.1.1.3 Encephalocele

Origin of Encephaloceles. The closure of neuroectoderm to form the neural tube starts on gestation day 22 in several places along the neural plate and then proceeds bidirectionally towards the anterior and posterior neuropores that close on days 25–26 and 27–28 respectively [1, 3, 4, 7]. The skull forms from the para-axial mesoderm that covers the prosencephalon. Cells derived from the neural crest develop this mesenchymal tissue that will result in cartilaginous neurocranium (chondrocranium) at the skull base. The mesenchyme surrounding the telencephalic vesicles forms the membranous neurocranium that will give rise to the skull vault. The natural development of the neurocranium and brain coverings requires a normal sequence in the neurulation process. The viscerocranium originates from the branchial arches between weeks 4–8 of gestation. Fusion defects of the rostral aspect, a site of convergence of branchial arches and chondral and membranous cranium, give rise to the formation of basal encephaloceles.

Encephaloceles have been regarded as NTD, and it has been suggested that their origin consists of a primary defect in cranial neurulation [7]. If this were the case, important skin and neural structural anomalies would be expected in all encephaloceles [7]. Current hypotheses consider encephalocele as a post-neural closure defect based on the findings of distorted but relatively well-preserved cerebral cytoarchitecture [7]. Most authors believe that the primary anomaly in the development of the majority of encephaloceles consists of a defective interposition of mesoderm between the neuroectoderm and the cutaneous ectoderm [1, 4, 7].

The cause of most encephaloceles is unknown [1, 4, 7]. They may be of sporadic, familial, environmental or genetic origin. Encephaloceles have been produced experimentally by exposure to irradiation, trypan-blue, an excess of vitamin A, folic acid antagonists and malnutrition. In humans, encephaloceles have been reported after exposure to antiepileptic drugs (phenytoin, primidone, valproate, and carbamazepine), warfarin, hyperthermia, viral infections and maternal diabetes mellitus [1, 4, 7]. Several syndromes such as those of Meckel-Gruber, Knobloch, Walker-Warburg, Joubert, Voss, dyssegmental dwarfism, cryptophthalmos and the amniotic band syndrome may be associated with encephaloceles [1, 4, 7].

Epidemiology and Incidence. The world incidence of encephalocele ranges from 0.8 to 4 per 10,000 births, with no sex predominance [1, 4, 7]. The spina bifida to cranium bifidum ratio is 10:1. There are considerable geographic variations in encephalocele [1, 4, 7]. Occipital encephaloceles account for 85% of the cases in Europe and the USA, while sincipital and basal encephaloceles are more frequent in Africa, Asia and Australia [1, 4, 7]. The incidence of anencephaly and encephalocele seems to be decreasing due to (a) prenatal diagnosis and termination of pregnancy and (b) periconceptional folic acid intake.

Classification and Clinical Forms of Encephalocele. Encephaloceles are classified according to the bone in which the bone defect is situated. From a practical point of view, we prefer Rutka et al.’s classification [7] in which the lesions are grouped according to their two main locations: convexity (posterior) and anterior cranial fossa encephaloceles (Table 7.1.3).

1. Convexity (Posterior) Encephaloceles. These arise at any point from the nasion to the foramen magnum.
   a) Occipital encephaloceles constitute, by far, the most frequent location of encephaloceles [1, 4, 7]. Their size does not always reflect the amount of herniated cerebral tissue (Figs. 7.1.1 and 7.1.2). The skin can be thinned, but intact, or ulcerated with CSF leak. Lesions situated above the torcular (Fig. 7.1.1c) contain one or both occipital lobes and sometimes...
Encephaloceles and Related Malformations

7.1.1 Encephaloceles and Related Malformations

a) Encephaloceles are herniations of intracranial contents through a bony defect in the skull. They are classified into posterior (convexity) and anterior cranial fossa encephaloceles.

b) Posterior (convexity) encephaloceles are further divided into occipital, occipitocervical, parietal, and temporal.

b) Occipitocervical encephaloceles extend from the posterior fossa to the upper cervical spine [1, 7].

c) Parietal encephaloceles are usually located midline and contain only one of the cerebral hemispheres [4, 7, 10].

d) Temporal encephaloceles arise at the antero- and posterolateral (Fig. 7.1.4a) fontanels are usually meningoceles and contain CSF and neuroglial rests [4].

2. Anterior Cranial Fossa Encephaloceles. These malformations are present at birth, but they may not manifest until adult life [1, 3, 4, 7]. These encephaloceles may vary in composition and contain dysplastic brain or only CSF [1, 3, 4, 7]. They may associate with other facial anomalies such as cleft lip or palate, microphthalmia, coloboma, cataracts and defects of the corpus callosum [1, 3, 7]. Encephaloceles of the anterior cranial fossa can be classified into two main groups [1, 3, 7]:

a) Sincipital encephaloceles (Fig. 7.1.2) arise from a skull defect in the foramen cecum placed anterior to the cribriform plate.

b) Basal encephaloceles are located more posteriorly and protrude through the cribriform plate or body of the sphenoid (Fig. 7.1.3). They may contain portions of brain, pituitary gland or hypothalamus, optic nerve and chiasm and the anterior cerebral arteries. They are grouped into several subtypes:

- Transethmoidal
- Transsphenoidal
- Sphenethmoidal
- Spheno-orbital
- Sphenomaxillary
- Basioccipital

Table 7.1.3 Classification of encephaloceles (adapted from [7])

<table>
<thead>
<tr>
<th>Posterior (convexity) encephaloceles</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital (70–85%)</td>
<td>Supratentorial</td>
<td>Infratentorial</td>
</tr>
<tr>
<td>Occipitocervical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal (10–15%)</td>
<td>Interfrontal</td>
<td>Interparietal</td>
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<tr>
<td>Temporal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cranial fossa encephaloceles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sincipital (5–15%)</td>
<td>Frontoethmoidal</td>
<td>Nasofrontal</td>
</tr>
<tr>
<td>Basal encephaloceles (1.5%)</td>
<td>Sphenopharyngeal</td>
<td>Sphenoorbital</td>
</tr>
</tbody>
</table>

Fig. 7.1.1a–c Photographs of two typical cases of occipital encephalocele (a,b). Angiography depicting the amount of cerebral tissue herniated into the cephalocele sac (c). Reprinted with permission from [4], Springer-Verlag.
Clinically, basal encephaloceles may present with nasal obstruction causing respiratory or feeding difficulty, spontaneous rhinorrhea, meningitis and even with endocrine disturbances [1, 3, 4, 7]. They often associate with palatal clefts. Basal encephaloceles constitute one of the causes of recurrent meningitis [1, 3, 4, 7]. Differential diagnosis of intranasal masses includes nasal polyps, but these are almost inexistent in pediatric patients. Nasal polyps do not tense up with Valsalva maneuvers while intranasal encephaloceles do (Furstenberg sign) [7].

Associated Anomalies. Approximately 50% of patients with encephaloceles are born with, or develop, hydrocephalus, especially those situated posteriorly [4, 7]. Reported intracranial anomalies include corpus callosum agenesis or hypoplasia, arachnoid and porencephalic cysts, absence of the septum pellucidum, cerebellar dysplasia or atrophy, disorders of the neuronal migration (neuronal heterotopias, lissencephaly, polymicrogyria and pachygyria), cerebral or brain stem atrophy, Chiari and Dandy-Walker malformation, white matter anomalies, etc. [1, 3, 4, 7]. They may also course with venous sinus and torcular anomalies [1, 3, 4, 7]. Parietal cephaloceles may contain dorsal interhemispheric cysts and duplication of the sagittal sinus [4, 7, 10]. Associated extracranial malformations are present in about 50% of cases and comprise ocular, cardiac, renal, digestive tract, skeletal, pulmonary and muscle defects [4].
Diagnosis of Encephalocele. Prenatal diagnosis can be achieved by maternal AFP screening and by antenatal ultrasonography and MR [1, 4, 7]. Evaluation of the baby's clinical condition by the pediatrician is mandatory to assess children's vitality and to search for extracranial anomalies [4]. Diagnosis of most convexity and sincipital encephaloceles is readily made by inspection. The presence of a skull defect is a necessary requisite to confirm the diagnosis [4]. The main diagnostic tool in the assessment of cephaloceles is MR (Figs. 7.1.2b, 7.1.3a, 7.1.4b) that depicts the structures involved in the malformation [1, 4, 7]. At present, MR angiography and MR venography are deemed necessary for planning the operation. Skull radiographs and helical CT with 3-D reconstruction (Fig. 7.1.3b) are very valuable, especially in cases of basal encephalocele [1, 4, 7].

Treatment of Encephaloceles. Surgical treatment requires (a) a general pediatric evaluation and (b) a complete neuroimaging study, including cranial MR, MR angiography and bone-window CT [1, 4, 7]. Surgery is withheld in cases with a prognosis incompatible with life [4, 7]. Children with a dismal prognosis who have hydrocephalus can be given a CSF shunt as a palliative measure [4]. Urgent surgery is considered in cases with: (a) absence of skin covering, (b) hemorrhage, (c) CSF leak, (d) airway obstruction and (e) impairment of vision [1, 4, 7]. Elective surgery is indicated to: (a) protect the brain, (b) prevent infection, (c) facilitate nursing, (d) improve function (airway, vision, etc.) and (e) restore cranial contour (cosmesis) [1, 4, 7].

Techniques for Encephalocele Repair. The following techniques can be used for the various types of encephalocele repair:

1. **Convexity and Simple Sincipital Encephaloceles.** In convexity encephaloceles and in some minimal forms of sincipital cephaloceles, a direct surgical approach to the malformation is performed [1, 4, 7]. The child is anesthetized, intubated and placed in an optimal position for exposure. The sac and an ample zone of surrounding skin are thoroughly cleaned and prepared with Betadine. The cutaneous incision is made, and the skin and meningeal coverings are dissected free. An attempt should be made to replace most cerebral tissue within the cranial cavity, a task that proves impossible in the majority of cases. However, necrotic or devitalized tissue can be sacrificed [1, 4, 7]. The dura mater is usually large enough to accomplish a primary watertight meningeal closure. If this is not possible, a duraplasty, with autologous or heterologous grafts, can be performed. The margins of the bone defect may be rongeured, placing pieces of the removed bone on the dura mater to stimulate spontaneous osseous healing [4]. Generally, there is an adequate amount of skin, and there is no need to make skin transpositions or grafts. If needed, collaboration with the plastic surgeon is requested.

2. **Complex Sincipital and Basal Encephaloceles.** Complex sincipital encephaloceles and most basal lesions are best treated by a multidisciplinary team that includes a maxillofacial and a plastic surgeon [3, 7]. In this way, associated facial anomalies and clefts can be appropriately approached [3, 7]. These lesions often require an intra- and an extracranial approach. The intracranial approach is the preferred procedure for management of these lesions, as it permits replacement of vital structures within the cranial cavity and dural repair.

![Photograph of a child with a meningocele of the posterolateral fontanel (a) (reprinted with permission from Child's Brain, Karger AG, Basel). MR of a vertex meningocele (b)](image)
Cranial and Spinal Dysraphisms

with pericranium [3, 7]. Current approaches include bifrontal craniotomy (for most lesions) or pterional or subtemporal approaches for encephaloceles extending to the orbit or the infratemporal fossa. Small basal cephaloceles are now being treated with endoscopic techniques, but these methods are restricted to encephaloceles with small cranial defects and to centers with experience in these approaches.

3. Advances in Encephalocele Repair. In addition to the use of neuroendoscopic procedures and craniofacial remodeling in sincipital and basal cephaloceles, there is a growing interest in brain preservation and in techniques aimed at increasing the skull capacity to accommodate the herniated tissues [4].

Complications of Encephalocele Repair. Surgical mortality has decreased notably with modern methods of anesthesia and neurosurgery [1, 4, 7]. Reported intraoperative complications include hemorrhage and cerebral infarction. Complications after operation include wound dehiscence or necrosis, CSF leaks, meningitis, superficial or deep infection, development of hydrocephalus and epilepsy [1, 4, 7].

Prognosis of Encephaloceles. Neurological and intellectual results are better in anterior and basal cephaloceles than in convexity lesions [1, 4, 7]. The outlook for children with encephalocele depends on the amount of herniated brain, the presence of microcephaly and hydrocephalus [1, 4, 7]. Only 20–30% of posterior encephaloceles achieve normal intellectual development [4]. In the absence of hydrocephalus, this increases to 40%; however, many will have some physical disability [4]. Atretic cephaloceles and cranial meningoceles, because of their lack of functional brain tissue, carry a much better prognosis than true encephaloceles [4].

7.1.1.4 Cranial Meningocele

Cranial meningocele is unfortunately a very rare variant of encephalocele (Fig. 7.1.4a, b). The sac of the malformation is composed of intact skin lined interiorly by arachnoid and contains only CSF [1, 4, 7]. Some instances, known as glioceles, also contain neuroglial remnants. Clinically, cranial meningocele resembles an encephalocele, but they can easily be differentiated by ultrasonography and MR [4, 7]. Principles of surgical treatment in meningocele are similar to those used in encephalocele repair. The prognosis of cranial meningocele is usually very good in terms of outcome, morbidity, and mortality [4]. Obviously, outcome is related to the absence of associated cerebral and extracranial abnormalities [4].

7.1.1.5 Atretic Cephalocele

Atretic cephalocele is a midline subscalp tumor (Fig. 7.1.5a) from 0.5 to 3 cm in diameter, cystic or nodular, that locates on the parietal or occipital regions [5, 10]. It is formed by meninges, neuroglial rests and fetal vessels [5]. Abortive cephaloceles occur in two main locations: parietal and occipital [5, 10]. Typically, the lesion’s stalk communicates with the intracranial cavity through a small osseous orifice. The term abortive, atretic or rudimentary cephalocele refers to the hypothesis that this anomaly represents an arrested or involuted meningoencephalocele. The origin of atretic cephalocele is related to Ingalls’ theory of persistence of the nuchal bleb [5]. This cystic formation is found on the dorsal aspect of 2-month-old embryos’ heads, connected with the anterior rhombencephalon. When it becomes isolated by growth of the surrounding mesoderm, it may give rise to an atretic cephalocele.

Fig. 7.1.5 a Photograph of a nodular parietal atretic cephalocele. b MR depicting the appearance of the lesion (arrowhead) and fetal position of the so-called falcine sinus (arrow)
The prevalence of atretic cephalocele is unknown, although it accounted for 50% of our cases of encephalocele and affected to both sexes equally [5]. The presenting symptoms are related to the subscalp lesion, as a firm or cystic nodule, covered by normal, thinned or angiomatous skin, which sometimes is surrounded by a hairy collar [5, 10]. The lesions are usually detected at birth or may manifest with pain later in life [5]. The neurological examination is often normal. Atretic cephaloceles are usually of sporadic occurrence, but they may show a familial predominance or form part of a known syndrome.

CT and MR studies are required to ascertain the presence of associated brain anomalies that occur in approximately 50% of the cases [5, 10]. In parietal atretic cephaloceles, there is a cigar-shaped arachnoid cyst that goes from the malformation's dome to the dorsal mesencephalon [5]. MR angiography is essential for ascertaining the relationship of the cephalocele with the sagittal sinus [5]. There is usually an abnormal vertically positioned falcine sinus (Fig. 7.1.5b) [5]. Atretic cephaloceles can be diagnosed by prenatal MR [4, 10]. Differential diagnosis is established against sinus pericranii and dermoid cysts [5]. In atretic cephalocele, the bone defect is oval or elongated and narrows from inside outward, while dermoid cysts have a round and sclerotic margin that narrows from the outside inward [5]. Atretic cephalocele enhances after contrast infusion in CT, but the dermoid cyst does not [5].

Surgical treatment is indicated (a) in painful lesions, (b) for esthetics and (c) to establish a histological diagnosis [5]. Surgery consists of performing an elliptical incision around the malformation followed by removal of the lesion and its stalk that is sectioned at the level of the dura mater [5]. Opening the meninges offer no additional benefit and entails risks of hemorrhage. The margins of the skull defect are rongeured to promote osseous closure. As expected, the prognosis of this apparently inoffensive lesion depends exclusively on the eventually associated occult cerebral anomalies, which mainly occur in children affected by a known syndrome [5, 10].

### 7.1.1.6 Scalp Defects

Aplasia cutis congenita (ACC) consists of a focal defect of skin present at birth [2, 8]. It may involve any part of the body, but it preferentially locates at the cranial vertex. Most cases of ACC are sporadic, although some reports indicate a familial trait, some with autosomal dominant or recessive inheritance [2, 8]. Certain cases of ACC occur within the spectrum of anomalies of a recognized syndrome. Adams–Oliver syndrome consists of scalp ACC associated with terminal transverse defects of the limbs [2, 8]. One in four cases of trisomy 13-15 presents lesions of ACC.

The prevalence of ACC is presently unknown, although it has been estimated in 3/10,000 births [2, 8]. In about 60% of the cases, the scalp defect is restricted to the scalp, while in the remaining 40%, the lesions may appear scattered through the trunk or limbs. Combined lesions of the scalp and the rest of the body are found in 25% of patients. Some 80% of scalp defects are midline, mainly on the cranial vertex, although they may occupy a lateral position. Approximately 20% of instances of scalp ACC are associated with an underlying skull defect.

The origin of scalp ACC remains unknown [2, 8]:
1. Some authors consider this condition as part of the spectrum of NTDs and hypothesize that it represents an arrested form of a neural tube closure defect similar to encephalocele and meningocele.
2. Others attribute scalp ACC to a faulty fusion of the mesoderm that is essential for the normal development of the ectoderm.
3. ACC has also been attributed to defective blood flow at the cranial vertex (a critical zone for scalp vascularization) due to a scarce vascular development or to impaired flow by overdystension of the fetal scalp.
4. ACC has as well been ascribed to ischemic or thrombotic episodes in placental infarction.
5. Others relate these scalp defects to focal pressure necrosis as happens in amniotic band syndrome or in cephalopelvic disproportion.
6. ACC and skull defects have also been reported in association with teratogens (misoprostol, methimazole, aminopterin, methotrexate, and benzodiazepines), intrauterine infection (varicella-zoster or herpes simplex virus) and cocaine abuse.

The diagnosis of scalp ACC is readily made by inspection (Fig. 7.1.6a,b); we recommend using good lighting and magnifying loupes [2, 8]. Macroscopically the lesions are well-circumscribed, oval or irregular in shape and 0.5–10 cm in size, resembling an ulcer of variable depth [2, 8]. When the lesions heal before birth, they look like a congenital scar. Microscopically, the lesions are composed of atrophic cutaneous elements devoid of skin adnexae. A thorough neonatal examination is mandatory to rule out other cutaneous or systemic anomalies. Cases with multiple malformations are submitted to the appropriate genetic studies. Those instances that are brought for neurosurgical consultation usually require neuroimaging studies [2, 8]. Cranial MR allows assessing the condition of the underlying brain (Fig. 7.1.6c). MR angiography and venography are used to depict the condition of the affluent vessels and the sagittal sinus. CT with 3-D reformatted images is used to assess the underlying skull defect.

Differential diagnosis is established against atretic cephalocele, sinus pericranii and heterotopic scalp tissues. Some lesions can be erroneously attributed to trauma caused by vacuum extraction, forceps or fetal scalp monitoring electrodes.
Sinus pericranii is a rare vascular anomaly of the cranial vault that mainly occurs in children or adolescents [6, 9]. It consists of a round, soft, fluctuant, pseudotumoral subscalp lesion, non-pulsatile, collapsible on pressure, that deflates with head elevation and that refills when the patient lies down, bends forwards or with Valsalva maneuvers [6, 9]. Generally, the lesion is situated at, or close to, the cranial midline, along the superior sagittal sinus, and rarely in a lateral position. Sinus pericranii preferentially occurs in a frontal location, followed by the parietal, occipital and temporal regions [6, 9]. The prevalence of sinus pericranii is presently unknown, and it usually affects children of all races and both sexes.

The origin of sinus pericranii is unclear [6, 9]:
1. Most cases are of congenital origin, a hypothesis supported by the coexistence of sinus pericranii with systemic angiomas, cavernomas and aneurysmal venous malformations.
2. Trauma has been reported in acquired cases.
3. Some instances are related to conditions with raised intracranial venous pressure as occur in children with craniosynostosis or with brain tumors.

Microscopically, congenital sinus pericranii is lined by endothelium and by fibrous tissues in traumatic instances.

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and MR angiography delineates the venous nature of the lesion (Fig. 7.1.7). Sometimes, phlebography or sinography are utilized that demonstrate the vascular nature of the anomaly, its flow and its drainage. Differential diagnosis is made against other vascular malformations of the scalp (cavernoma, cirsoid aneurysm, arteriovenous fistula, telangiectasia and other hemangiomas) and against atretic cephaloceles of the anterior cranial fossa: management and outcome. Pediatr Neurosurg 23:148–158


7.1.1.8 Conclusions

Congenital true encephaloceles are becoming rarer and rarer lesions in the industrialized world. Cranial meningoceles and atretic and basal encephaloceles constitute the most frequent forms that we will face in future clinical practice. The majority of these lesions are amenable at surgical treatment and deserve careful planning. Some sincipital and all basal encephaloceles, given their low incidence and complexity, should preferentially be managed at reference centers. Conservative or surgical treatment of scalp aplasia cutis and sinus pericranii requires an individual evaluation. Further knowledge on the origin and genetics of all these congenital cranial malformations will probably lead to the adoption of better preventive measures that will decrease their incidence.

7.1.2 Spinal Anomalies

7.1.2.1 Spina Bifida Aperta

Aperta means “open,” which designates that the neural placode is not covered with skin in this type of spina bifida. The presence of an uncovered placode is caused by a local failure of primary neurulation, which refers to the formation of the neural tube. Spina bifida aperta is synonymous with myelomeningocele. The further distinction between myelomeningocele and myeloschisis is questionable from its embryologic origin, and it has been suggested to consider all open lesions as myelomeningoceles.

Nearly all myelomeningocele patients have an associated Chiari II malformation, which is thought to arise due to a constant loss of cerebrospinal fluid (CSF) from the open neural tube. This CSF leakage might result in a
disproportionally small posterior fossa in relation to its contents, creating the Chiari II malformation. Reports about intrauterine repair of myelomeningoceles show the potential reversal of pre-existing hindbrain herniation. Between 20 and 30% of the children develop symptoms related to Chiari II, and up to one third of the symptomatic children do not survive. The Chiari II malformation probably plays an important role in the origin of hydrocephalus in myelomeningocele patients. Hydrocephalus is present at birth in about 15% of these infants, but after closure of the myelomeningocele, more than 90% of the patients require a shunt. Consequently, hydrocephalus and Chiari II should be considered as integral aspects of spina bifida aperta.

7.1.2.1.1 Myelomeningoceles (MMC)
The incidence of MMC is 0.7–0.8 per 1,000 live births, but it varies from region to region. The recurrence risk with one previously affected child rises to about 1–2%, and with two affected offspring even to 10%. The etiology is probably polygenic, and consequently the affected fetus is more susceptible to environmental teratogens. Periconceptual folic acid (0.4 mg) prevents 60–70% of cases of neural tube defects. Ingestion of these higher doses of folate may overcome relative deficiencies in either maternal or fetal methionine synthetase reductase that is an important element in various metabolic pathways. Antenatal screening for MMC can be done by determining the maternal alfa-fetoprotein (AFP) at 17 weeks’ gestation with a detection rate of 72% and a 1.9% false-positive rate. If maternal serum AFP is raised, an ultrasonography (US) should be performed. US at 18–20 weeks’ gestation has an 83% detection rate without false positives. Indirect signs of MMC, such as the “banana” and “lemon” signs seen on cranial imaging, are highly predictive even when the spinal anomaly cannot be detected directly. The banana sign represents an elongated appearance of the cerebellum due to Chiari malformation, and the lemon sign designates the concave inward appearance of the frontal bones. These signs have a detection rate of 93 and 80% respectively. A final method of prenatal identification of MMC is to measure the AFP and acetylcholinesterase levels in the amniotic fluid.

Post-natal Management. If an MMC has been identified prenatally, one may choose either for a caesarean section or a normal delivery. The issue of the risk of potential secondary damage to the placode during vaginal delivery has not been settled. After birth, the child requires a thorough neurological examination. The sensory level of the neurological deficit is determined using a pin, moving from caudal to rostral. The sphincter function is assessed, observing the anal tone and watching urine dribbling out of the urethra. Lower limb deformities must be inspected. The head circumference is measured, and the presence of sunsetting eye posture is checked. Associated anomalies of other than the nervous system are exceptional. The anomaly itself should be inspected carefully for location and size in order to anticipate the indication for combined plastic surgical treatment. Additional US is required to assess the ventricular size and the presence of hindbrain hernia. MRI is invaluable in patients with large MMCs at the thoracolumbar level in order to judge the extent of a Chiari II malformation, the shape of the ventricles and the presence of additional intracranial and intraspinal anomalies. Depending on all of these examinations and in consensus with the parents, one may decide what treatment strategy to choose.

Surgical Strategy. The aim of the operation is to create a watertight closure of dura, to provide good skin cover, and to prevent secondary tethering. MMCs do not have to be closed emergently since a delay in repair of a few days does not increase the incidence of CNS infection. The patient is operated under general anesthesia in prone position. Perioperative blood loss should be limited using bipolar coagulation. First, the placode should be identified (Fig. 7.1.8).

Subsequently, the sac is opened directly into the subarachnoid space at the edge of the normal skin. The neural placode is mobilized by dissecting the arachnoid membranes circumferentially. Care must be taken not to damage the dorsal nerve roots that arise along the ventral side of the placode. All cutaneous tissue must be removed from the edges of the neural placode in order to prevent an inclusion dermoid. The lateral edges of the neural placode are approximated with sutures in order to prevent tethering by creating a neural tube (Fig. 7.1.9).

Caudal to the placode, an intact filum terminale should be looked for and, if present, be sectioned in order to prevent tethering. Subsequently, the surrounding dura

Fig. 7.1.8 Typical example of a myelomeningocele. The central placode, which is continuous with the elevated and stretched skin, can be recognized
can be mobilized from the underlying fascia, and the dural sac should be closed as capacious as possible and in a watertight fashion. An additional fascial layer may be mobilized in order to create an extra layer covering the dural sack. Finally, the skin is closed. In the case of a large skin defect, a musculocutaneous flap technique (gluteus maximus or latissimus dorsi) may be used.

**Hydrocephalus.** The vast majority of children affected with MMC (90%) will need surgical treatment of hydrocephalus. The most common treatment is ventriculoperitoneal (VP) shunt placement. If hydrocephalus is present immediately after birth (25%), shunt insertion and closure of the MMC can be combined. In the remaining patients, symptomatic hydrocephalus can be expected shortly after closure of the MMC, and a second operation is required in order to put in a shunt. The issue of optimal timing of shunt insertion in MMC patients has not been settled. Simultaneous repair and shunt insertion creates the advantage of improved wound healing of the back without CSF leakage and prevention of potential brain damage due to ventricular dilatation. However, the early shunt insertion might also increase the risk of shunt infection because of the reversal of CSF flow from the spine to the shunt in combination with the presence of a compromised immune system in these newborns. This expected increased infection rate could not be confirmed by other authors. The presence of MMC itself has also been identified as a risk factor for shunt infection. The alternative treatment of hydrocephalus by endoscopic third ventriculostomy (ETV) appears to be particularly effective in children who were previously shunted and older than 6 months of age, but familiarity with the abnormal ventricular anatomy in MMC patients is essential in order to perform ETV safely.

**Chiari II.** The surgical treatment of a symptomatic Chiari II malformation should always start with evaluation of the hydrocephalus or the shunt function. In the case of persistent progressive symptoms after treating the hydrocephalus, one may decide to decompress the Chiari II. In the case of mild symptoms, the treatment strategy remains controversial.

**Tethered Cord Syndrome.** Most children with a repaired MMC will have a tethered cord almost by definition. The development of tethered cord syndrome (TCS) takes place in only 10–30% of patients. The most common symptoms are increased weakness and progressive gait disturbances. Surgical detethering may result in improvement or stabilization of symptoms.

**Outcome.** The natural history of untreated patients is 30% one-year survival and 20% two-year survival. The leading cause of death is symptomatic Chiari II. The sensory level of the neurological deficit relates to the prognosis of mobility. The mental outcome is influenced by the presence of hydrocephalus and by shunt complications, especially infections. Approximately 70% have IQs greater than 80. Late complications may be due to a symptomatic tethered cord syndrome in 10–30% of children.

**7.1.2.2 Spina Bifida Occulta**

Occulta means “closed/hidden,” which designates that these spinal dysraphic lesions are always covered with skin. Consequently, the neural tube must have closed at least initially. Therefore, these anomalies should be considered post-neurulation disorders. Characteristically, hydrocephalus and hindbrain hernia are not concomitants of closed dysraphic states. The presence of an occult spinal lesion may be recognized by cutaneous stigmata. The symptoms may often be classified as a tethered cord syndrome. Various abnormal morphologies can be distinguished: lipomyelomeningocele (LMC), dermal sinus, split cord malformation (SCM), thickened filum terminale, meningocele and some rare malformations.

**Tethered Cord Syndrome.** Symptoms related to a tethered spinal cord may create a TCS. The pathophysiology has been extensively elaborated by Yamada. The clinical signs are considered to be caused by stretch-induced neuronal dysfunction. The strain typically exists between the caudal end of the spinal cord and the lowest pair of dentate ligaments at the Th12–L1 cord level. TCS is characterized by neurological and/or urological and/or orthopedic symptoms. Typical are motor and sensory deficits in the lower limbs, incontinence and scoliosis. The anatomy of a tethered spinal cord can also be present without any symptoms. The development of symptoms and consequently the creation of a TCS cannot be predicted and may occur later in life. The occurrence of late-onset symptoms in spina bifida occulta, creating an adult TCS,
may not always be recognized. The predominant symptom is pain in the low back, but its extension into the legs is not quite dermatomal. The pain is usually accentuated by physical exercises, particularly flexion and extension of the lumbar spine. The surgical treatment of adult TCS has been reported to be effective. The indication of prophylactic treatment of an asymptomatic tethered cord has not been settled in all cases and depends partly on the type of the congenital anomaly involved.

### 7.1.2.2.1 Lipomyelomeningocele
LMC, or congenital lumbosacral lipoma, is the most important type of spina bifida occulta. The incidence is uncertain since most series reflect institutional recruitment, but an estimated incidence of 4–8 per 100,000 was reported. The pathogenesis has been related to a disturbed differentiation within the dorsal mesoderm. An alternative explanation refers to a local re-opening of the neural tube underneath the skin. Various types of lipomas can be distinguished according to the interface localization on the cord: caudal, dorsal or dorsolateral and caudolateral lipomas. Although LMCs are covered with skin, the presence of a subcutaneous lipoma or typical cutaneous stigmata warrants additional MRI investigation. Most LMCs create the anatomy of a tethered spinal cord, but some of these lipomas are asymptomatic at birth. The development of a TCS cannot be predicted, and controversy exists about the indication of prophylactic detethering in asymptomatic patients. The discussion started with the publication of the long-term results of surgical treatment in spinal lipomas. It was found that in spite of prophylactic detethering in asymptomatic patients, neurological symptoms developed in nearly 60% of patients in 12 years. Consequently, it was postulated that the development of symptoms in lipoma patients might not only be due to spinal cord tethering, but myelodysplasia might also contribute. The latter would not be influenced by surgery.

In order to learn about the characteristics of the natural history of LMCs, a protocol was designed to follow asymptomatic patients. Interim analysis after a mean follow-up of 4.4 years showed neurological deterioration in 25% of asymptomatic patients, creating a similar pattern of progression as in surgically treated symptomatic patients. Others advocate that repetitive surgical detethering may prevent progression of symptoms in TCS patients, and prophylactic treatment should be recommended in asymptomatic patients.

**Surgical Strategy.** The aims of surgical treatment in LMC patients are to disconnect the spinal cord from its subcutaneous lipoma, to create a dural sack dorsally and to prevent retethering of the cord within the spinal canal. Since the spine is bifid, part of the subcutaneous lipoma may be left in order to protect the cord within the open spinal canal. First, the subcutaneous lipoma is dissected down to the level of the defect within the lumbosacral fascia. Subsequently, the most caudal lamina, which may be bifid, is taken off in order to expose the dural sack. The dorsal defect of the dural sack is exposed, and the extension of the lipoma into the dural sack is defined. The next step is to open the dura and to expose the attachment of the lipoma to the cord. Attention must be paid to save the dorsal nerve rootlets. Especially in dorsolateral or caudolateral lipomas, distortion of the cord may be present. Perioperative electrical stimulation can be very helpful to distinguish between functional nerve roots and fibrous bands. The lipoma should not be separated from its attachment to the cord, but a small remnant can be left (Fig. 7.1.10).

If an effective detethering has been accomplished and the cord can move freely within the spinal canal, the dura should be closed as spacious as possible. Sometimes a dural substitute must be used. Local complications like infection, pseudomeningocele and CSF leak are relatively common (20–25%), and permanent neurologic deficits occur in 0–4% of patients. Surgical detethering in symptomatic LMC patients has been shown to be effective, causing relief of symptoms or stabilization of complaints in the majority of cases. In adult TCS, pain, especially, is improved after surgery, and multiple repeated untethering operations may offer symptomatic relief to well-selected patients.

### 7.1.2.2.2 Dermal Sinus
Dermal sinus tracts are remnants of dermis that failed to separate from the neur ectoderm after closure of the neural tube. Collection of skin products within the sinus may cause a dermoid cyst. Secondary infection of the dermoid sinus tract may cause meningitis and extensive scar formation of the caudal nerve roots. The extension of the sinus tract may ascend within the spinal canal up to the level of the conus. The intradural dermoid cyst may cause...
a tethered cord. The prevention of a secondary infection and the potential occurrence of a tethered cord indicate surgical extirpation. One should anticipate on sufficient surgical exposure along the ascending sinus tract.

7.1.2.2.3 Split Cord Malformation

The term “split cord malformation” (SCM) has been proposed by Pang and Dias, and two types can be distinguished. Type I SCM refers to the presence of two hemicords within two separate dural sheaths divided by a median bony or fibrocartilaginous spur. Type II SCM delineates two hemicords separated with a fibrous midline septum within a single dural sheath. The alternative terminology of “diastematomyelia,” designating splitting of the cord into two hemicords, or “diplomyelia,” describing a complete duplication of a segment of the spinal cord, is more difficult to assess properly. Different theories about the pathogenesis can be found, but most of them refer to an early disturbance in the fusion of the notochordal anlagen into a single notochord during the third gestational week. The impaired fusion of the notochord will induce two hemicords. Subsequently, displaced somitic tissue may result in associated abnormal vertebral segmentation. Associated congenital anomalies are numerous like LMC, filum lipomas or dermoid sinus. Many children with SCM appear to be asymptomatic at birth. Subtle skin stigmata may be present. Hypertrichosis, especially, is strongly correlated with SCM (50%). Urinary tract dysfunction has been reported in 75% of tested patients. Neurological decline can be insidious, and therefore early surgical detethering is recommended.

Surgical Strategy. Since SCM are strongly associated with concomitant congenital anomalies that may contribute to a TCS, preoperative imaging of the complete spine with MRI is essential. All aspects that may contribute to a TCS should be considered in designing the treatment strategy. The presence of a terminal filum lipoma, especially, should be ruled out. Exploration of the spinal canal in SCM patients may be difficult. The abnormal shape of the vertebrae and the distortion of the spinal column may complicate the identification of the spinal canal. First, the dural sack should be visualized. In the case of SCM type I the midline bony spur should be taken out. Subsequently, the dural sacs should be opened in order to perform a detethering of both cords (Fig. 7.1.11).

The medial nerve roots of both hemicords are non-functional and can be transected. The medial parts of the dural sacks can be resected, and the dura at the dorsal side should only be closed in order to create a single dural sack. In the case of SCM type II, one should always explore intradurally in order to detether effectively. The use of intraoperative neuromonitoring may be valuable. The long-term outcome appears to be favorable with stabilization of symptoms.

7.1.2.2.4 Thickened Filum Terminale

A thickened filum terminale or filum lipoma is associated with a TCS due to its supposed tightness. The tightness within the terminal filum and consequently its repetitive strain to the distal spinal cord cannot be visualized. Only circumstantial evidence like a low-lying position of the conus, thickening of the filum (filum lipoma), bifid laminal arches and an enlarged distal dural sack may contribute to the diagnosis of tight terminal filum (Fig. 7.1.12).

Most patients will only be diagnosed after a TCS has developed and an MRI is made. The indication to treat remains controversial as expert opinions illustrate. The surgical treatment of a tight or thickened terminal filum is a straightforward and safe procedure. The outcome of TCS patients is excellent. Retethering is unlikely to occur, and myelodysplasia is absent.

7.1.2.2.5 Meningocele

A meningocele represents a herniation of a meningeal sack filled with cerebrospinal fluid covered with intact skin. Since the spinal cord remains within the spinal canal, neurological symptoms are often absent or mild. An MRI scan is essential to diagnose a meningocele and to identify additional anomalies. Anterior meningoceles are associated with anorectal deformities. The surgical closure is straightforward, but the cord should be inspected in order to exclude a tethered cord. Secondary retethering is unlikely to occur.

Fig. 7.1.11a,b Example of a type 1 split cord malformation. The separate dural bags and the bony spur can be appreciated on the transverse T2-MRI (a). Perioperatively, two cords are found to be separated by a bony spur which is covered with a dural layer (b)
7.1.2.2.6 Myelocystoceles
A distinction can be made between terminal and non-terminal myelocystoceles. Terminal myelocystoceles constitute a skin-covered lumbosacral mass in which a meningocele is present containing a herniating, low-lying hydromyelic cord. The pathogenesis is considered to be related to a disturbance in the differentiation of the caudal cell mass (secondary neurulation). Most patients have a neurological deficit, and concomitant associated anomalies are common. The surgical treatment is aimed at release of the tethered cord herniation and creation of free communication between the hydromyelic cord and the arachnoid space. Non-terminal myelocystoceles are rare, skin-covered lesions in the cervical or thoracic region. A fibroneurovascular stalk present within the meningocele may create a tethered cord. The pathogenesis is thought to be a post primary neurulation disturbance due to a local non-separation between skin and cord. The treatment consists of detachment of the fibroneurovascular stalk from the cord and opening the syringocele to drain the CSF. Associated anomalies are less common, and late deterioration may occur due to retethering.

7.1.2.2.7 Miscellaneous
Various lower spinal cord malformations are associated with anorectal or urogenital anomalies like the caudal regression syndrome or the Currarino triad. This relation is thought to be due to an early disturbance in the caudal eminence. The VATER association (vertebral anomalies, tracheoesophageal fistula, radial or renal anomalies) is an example of a particular combination of congenital anomalies including the spine. Extensive diagnostics and multidisciplinary consulting are required in these complicated patients.

Suggested Reading
7.2 Craniosynostosis

7.2.1 Non-syndromic Craniosynostosis

Marie Lise C. van Veelen-Vincent, Irene Mathijssen, Eric Arnaud, and Dominique Renier

7.2.1.1 Introduction

Craniosynostosis refers to the abnormal closure of one or more sutures. The resultant head shape occurs due to the restricted growth perpendicular to the affected suture and the compensatory growth parallel to the unaffected sutures. The type of craniosynostosis is usually named by the specific resulting head shape. For example, scaphocephaly, or boat-shaped skull, results from a sagittal synostosis, and trigonocephaly, or triangular skull, results from metopic synostosis. Further classification differentiates between primary and secondary craniosynostosis, syndromic or non-syndromic cases and simple or complex craniosynostosis (Table 7.2.1).

Most cases are primary or idiopathic. Secondary craniosynostosis is due to a known underlying disorder. Among those disorders are metabolic diseases like Hurler’s, nutritional deficiencies like rickets and exposure to teratogens, for example sodium valproate [67] or thyroid hormone. Mechanical factors like foetal head constraint in utero, over-shunted hydrocephalus but also lack of primary brain growth in microcephaly are well-known causes of secondary craniosynostosis (Table 7.2.2).

Craniosynostosis can be syndromic, occurring in the context of other dysmorphisms, or non-syndromic. More than a hundred syndromes have been described in which craniosynostosis represents one of the features. Among them, Crouzon’s and Apert’s syndromes are the most frequently occurring. Non-syndromic craniosynostosis usually involves a single suture, while syndromic craniosynostosis more frequently affects multiple sutures. The terms simple and complex synostosis refer to the number of sutures involved.

This chapter will address the non-syndromic craniosynostosis.

7.2.1.2 Classification

Craniosynostosis is the premature fusion of cranial sutures leading to an abnormal skull shape. Abnormal skull shapes were described by Hippocrates and Galen. Virchow [126], however, was the first to relate the abnormal skull shape to the premature fusion of cranial sutures. The extent of morphological and functional problems varies with the amount of sutures affected and is most pronounced in syndromic cases. Single-suture craniosynostosis is generally considered a purely cosmetic problem. However, increasing attention has been drawn to the occurrence of functional problems in single-suture synostosis. Raised intracranial pressure (ICP) is reported in up to 33% of patients [123, 105, 122]. Cognitive dysfunction, particularly affecting speech and learning abilities, is found to various degrees in all types of single-suture synostosis (Table 7.2.4). Problems with self-esteem occur in up to 10% [9].

Surgery for craniosynostosis was first reported by Marie-Lannelongue in 1890. Since then, a myriad of operating techniques have been reported. In the past, these interventions were associated with a high morbidity and mortality. This led to debate as to whether these interventions were justified, especially in single-suture craniosynostosis. The multidisciplinary approach by craniofacial teams greatly improved the treatment of these disorders. Surgical and especially anaesthetic techniques progressed, reducing morbidity and mortality to minimal figures. At present, surgery for single-suture synostosis is fully accepted, not only because morbidity has decreased but also because functional problems in these cases are being recognised. The current discussions revolve around the optimal timing and surgical techniques necessary to improve morphologic as well as functional outcomes in patients with craniosynostosis.

7.2.1.3 Prevalence

The prevalence of craniosynostosis in general is around 1:2,500. In the population seen by a craniofacial centre, syndromic cases account for about 15–20%, whereas the non-syndromic cases account for 80–85%. Among the non-syndromic craniosynosostes, sagittal synostosis is
7.2.1.4 Pathogenesis

During foetal development of the cranial vault, bone centres develop within the membranous “anlagen” of the skull at a specific time and position for each skull bone through membranous ossification. From these bone centres, ossification spreads in a radial pattern. This pattern is visible on the skull of infants. The centre of this radiating pattern indicates the starting point of ossification of that particu-
lar bone. The first onset of the coronal suture is seen at as early as 16 weeks of gestation and at a constant site, the midpoint of the future suture, where the two parietal en frontal bones meet first. Subsequently, the suture develops in both the cranial and caudal direction. Synostosis of the coronal suture can also be traced back to about 16 weeks of development, with the fusion of the two calvarial bones starting at the same site as suture initiation in normal development. Fusion of the bones spreads similar to suture formation. This fusion in fact means agenesis of the suture [82, 83].

The occipital bones are not formed by membranous ossification but by endochondral ossification, just like the sphenoid wings, temporal bones and skull base.

Skull growth is most important in the first 3 years of life. Most of the growth takes place in the sutures between the bone plates. Within the centre of the sutural area, a population of proliferating osteoprogenitor cells is maintained. A number of these cells enter the pathway of osteogenic differentiation. While moving away from the proliferating population and with ongoing differentiation, these bone-matrix-secreting osteoblasts approach the bone edges and contribute to the expansion of the bone [89]. A disturbance in the balance between proliferation, differentiation and apoptosis [16] causes premature ossification within the suture and thereby its synostosis. Some factors that affect this balance have been recognized, such as the underlying dura and the pressure that is exerted on that dura by growing brain and cerebrospinal fluid pressure. Without direct contact to dural cells, a suture will fuse [96]. In experiments in which sutures were rotated and moved to other locations on the dura, the suture took over the closing rate of the suture that used to overly that specific location of the dura [70, 17]. In rat experiments, dura mater shows regional differences in expression of osteogenic cytokines and activation of osteoblasts associated to the overlying suture [40, 128].

The signalling pathway by which the dura influences growth at the suture site becomes more and more elucidated. For example, fibroblast growth factors (FGF) play an important role. Binding to fibroblast growth factor receptor 2 (FGFR2), one of the four FGF receptors, by the ligand FGF4 causes fusion in embryologic sutures. Mutation in the gene encoding for FGFR2 causes continuous activation of the receptor, independently of the presence of the FGF ligand. This mutation thereby up-regulates the signalling pathway. Mutations in FGFR genes are found in Crouzon’s and Apert’s but also in some patients with apparent isolated single-suture synostosis. Other types of mutation affect the TWIST and MSX2 homeobox genes and can be found in Saethre-Chotzen syndrome, Boston-type craniosynostosis and in a small percentage of non-syndromic synostosis. Those genes are all involved in proliferation and maturation of mesenchymal and bone cells [129].

Experiments by Kirschner [58] illustrate how environmental factors may play a role. By the application of a constraining cerclage to the pregnant rat uterus, he was able to apply a pressure to the underlying foetal rat skull. This induced altered patterns of foetal TGF-beta expression in bone and underlying dura at the level of the suture. In the constrained foetuses, TGF-beta1 immunoreactivity was increased while TGF-beta3 immunoreactivity was decreased when compared to non-constrained foetuses.

Bone differentiation does occur in other areas besides the suture. This growth also seems to be dura dependant. The osteogenic properties of immature dura are more extensive than those of mature dura [40, 127]. This explains the fact that young children below the age of two are capable of repairing calvarial defects in contrast to older ones. It is interesting that this potential for calvarial healing is most pronounced during the period of important brain development and active intracranial expansion. This led the group of Longaker to the hypothesis that mechanical strain generated by the growing brain may induce the immature dura to express osteogenic factors. They found up-regulation of TGF-beta1 mRNA and FGF-2 protein levels in rat immature dural cells when exposed to mechanical strain [35]. That dura plays an important role in bone growth and calvarial defects can also be concluded from the finding that growing skull fractures are invariably associated with a dural tear.

From the age of 6 years on, skull growth is mainly achieved through resorption of bone at the inner surface of the skull and apposition at the outer surface. The role of the sutures appears to be of minimal importance from this time on, although most sutures remain patent much longer. The metopic suture is the only suture to close within the first year of life.

7.2.1.5 Functional Problems in Non-syndromic Craniosynostosis

Functional problems associated with craniosynostosis are raised intracranial pressure, developmental delay and visual disturbances.

Intracranial hypertension does occur in non-syndromic and also in single-suture craniosynostosis (Table 7.2.1). Systematic invasive measurements (Table 7.2.3) have shown raised ICP (mean ICP above 15 mmHg) in around 15–20% of patients and borderline ICP (mean ICP between 10 and 15 mmHg) in up to 38% of patients [122].

Raised ICP is related to the number of affected sutures [120, 103, 105, 122]. The frequency of raised ICP is as high as 30–60% in patients with brachycephaly and complex synostosis. The development of raised ICP is a progressive event since the incidence increases with age.
Craniosynostosis

from 5 to 20 minutes, minimal ICP level varies from 20 to 40 mmHg and the frequency should be at least 4 per nocturnal recording.

Hydrocephalus, which is a more frequent aetiology of raised ICP in syndromic craniosynostosis, is rarely observed in non-syndromic craniosynostosis. In these cases, hydrocephalus is usually attributed to coincidental disorders [21].

Delay in cognitive development is well recognized in syndromic craniosynostosis. Increasing evidence suggests that non-syndromic craniosynostosis is also associated with developmental problems (Table 7.2.4). Several studies have shown a mild but significant developmental delay for all types of single-suture synostosis [55, 19]. In older children, especially, learning and language disorders are reported [72, 115]. Most studies fail to show a relationship between affected suture, surgical aspects and developmental delay [54, 117]. In series that did find a relationship, a lower incidence of developmental delay and learning disorders is found in patients with scaphocephaly (39%) than in patients with trigonocephaly (57%) or plagiocephaly (51–61%) [12, 106].

Without surgery, the frequency doubles after one year of age. Among patients with an uncorrected scaphocephaly, the frequency even increases 4-fold after one year of age. Renier found a statistically significant relationship between preoperative elevated ICP and decreased IQ level [103]. This relationship was more evident in older patients, leading to the conclusion that the longer the duration of craniosynostosis and its associated ICP, the greater the effect on intellectual function.

Some, but not all, of these patients have papillary oedema and radiological signs of raised ICP. The presence of papillary oedema reliably indicates elevated ICP, but its absence does not rule out elevated ICP, at least in children under the age of eight [123]. Radiological signs of raised ICP, for example the typical beaten-copper pattern, have a low sensitivity as well [124]. Invasive ICP measurements are helpful in cases where the indication for surgery or repeated surgery is debatable. The analysis of plateau waves may help interpret the findings in children with borderline ICP values [28, 120]. However, it is not completely clear what criteria one should use to define abnormal plateau waves. Reported duration varies from 5 to 20 minutes, minimal ICP level varies from 20 to 40 mmHg and the frequency should be at least 4 per nocturnal recording.

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### Table 7.2.3 ICP measurements

<table>
<thead>
<tr>
<th>Author</th>
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<th>Normal (%)</th>
<th>Borderline (%)</th>
<th>Raised (%)</th>
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<tr>
<td></td>
<td>Trigonocephaly</td>
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<td></td>
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<tr>
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<td>Plagiocephaly</td>
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<td>Multiple sutures: Brachycephaly</td>
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<td>38</td>
<td>17</td>
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<tr>
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<td>16.6*</td>
<td>33.0*</td>
<td>5.7*</td>
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<td>Multiple sutures: Brachycephaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Multiple sutures: Complex</td>
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<td>63.6*</td>
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<tr>
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<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Tuite (1996) n= 122</td>
<td>Single suture</td>
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</tr>
<tr>
<td>Tuite (1996) n= 122</td>
<td>Multiple sutures</td>
<td>34</td>
<td></td>
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</table>

* Percentages have been computed by van Veelen-Vincent
Not only cognitive delay but also motor delay is reported in single-suture synostosis [19, 55, 13]. The proportion of children with developmental and behavioural problems at first consultation increases with age [106]. This may be due to the deleterious effect of persisting craniosynostosis. However, several authors have reported an increase with age of the proportion of children with developmental problems in the same cohort irrespective of surgery [54, 12]. This finding might suggest that the cause of developmental delay is rather primary instead of secondary to the craniosynostosis itself. Raybaud and Di Rocco propose the hypothesis that in syndromic craniosynostosis, besides mechanical distortion of the brain caused by skull deformity, white matter disorders, especially, may occur as a result of the same gene mutation causing the synostosed suture. L1CAM is an adhesion molecule involved in white matter development, and mutations are associated with white matter disorders. It has been shown that L1CAM cannot play its role without close interaction with FGFRs [102].

Most authors do not find any beneficial effect of surgery on these developmental delays, although Bellew [13] and Cohen [19] found that motor delay improved. Shimizu [114] describes a postoperative improvement in behavioural problems after surgery for mild trigonocephaly operated at older age. However, patients who are operated

### Table 7.2.4 Cognitive development

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Outcome</th>
<th>Influencing factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-syndromic or single suture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker</td>
<td>6 yr, 4 mo</td>
<td>49% speech, cognitive and behavioural abnormalities</td>
<td>Age +; surgery –</td>
</tr>
<tr>
<td>Da Costa</td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Cohen</td>
<td>T1 = preop</td>
<td>Mild mental and motor delay</td>
<td>Surgery + (only on motor score)</td>
</tr>
<tr>
<td></td>
<td>T2 = 1 yr postop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapp-Simon</td>
<td>T1 = 8 mo</td>
<td>47% learning disorders at T2 and T3</td>
<td>Age +; surgery –</td>
</tr>
<tr>
<td></td>
<td>T2 = 21 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3 = 50 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kapp-Simon</td>
<td>T = at dx</td>
<td>Statistically significant delay</td>
<td></td>
</tr>
<tr>
<td>Scaphocephaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnaud</td>
<td>&gt;6 mo</td>
<td>IQ (or DQ) &lt; 90</td>
<td>Age at presentation +; surgery –</td>
</tr>
<tr>
<td>Bellew</td>
<td>8 yr</td>
<td>Poor gross loco motor function</td>
<td>Surgery +</td>
</tr>
<tr>
<td>Magge</td>
<td>6–16 yr</td>
<td>50% reading and spelling disorders</td>
<td>Surgery –</td>
</tr>
<tr>
<td>Shipster</td>
<td>9 mo to 15 yr, 7 mo</td>
<td>37% speech and language disorders</td>
<td>Surgery –</td>
</tr>
<tr>
<td>Trigonocephaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelleher</td>
<td></td>
<td>34% speech and language disorders</td>
<td></td>
</tr>
<tr>
<td>Bottero</td>
<td></td>
<td>Mental delay</td>
<td>Surgery &gt; 1 yr +; severe deformity +; other extracranial deformities +</td>
</tr>
<tr>
<td>Plagiocephaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathijssen</td>
<td>&gt;6 mo</td>
<td>IQ (or DQ) &lt; 90</td>
<td>Surgery &lt; 1 yr –</td>
</tr>
<tr>
<td>Brachycephaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnaud</td>
<td>&gt;6 mo</td>
<td>IQ (or DQ) &lt; 90</td>
<td>Age preop +; surgery &lt; 1 yr +</td>
</tr>
</tbody>
</table>

IQ intelligence quotient, DQ developmental quotient
Craniosynostosis

Primary synostosis has to be differentiated from postural plagiocephaly and secondary synostosis. Details are described further in this chapter in the paragraphs concerning the specific types of craniosynostosis.

In all children, a careful medical history should be taken with special attention to causes of secondary craniosynostosis, familial occurrence, signs of raised intracranial pressure and neurological development. A careful clinical and neurological examination is mandatory. Head circumference, the presence of a torticollis, additional dysmorphisms of the face, orbits and limbs are noted. Ophthalmologic examination may show astigmatism, strabismus or papillary oedema.

Laboratory investigations include genetic testing in all cases except in scaphocephaly with a negative family history and may include research for secondary causes. Plain radiographs (anteroposterior, lateral and Town) can show either the absence of a suture or the concomitant stenotic ridge. More important are the additional signs showing the type of compensatory growth or deformity. In trigonocephaly, the upper margin of the orbit is moved upwards and inwards giving the orbits the aspect of a “surprised racoon” (Fig. 7.2.3c). In anterior plagiocephaly and in brachycephaly, the upper margin is moved upwards and outwards with upward displacement of the sphenoid wing, which results in a “harlequin” or “Mephistophelean” look of the orbits (Fig. 7.2.4c). The temporal fossa bulges outwards in brachycephaly, especially in case of underlying genetic disorders. Additionally, radiographs may show exaggerated digital impressions, suggesting increased ICP. CT scan and especially 3D reconstructions confirm the absence of the synostotic suture with a greater certainty than plain radiographs. Deformities of the skull base are best demonstrated on CT. Brain windows usually show an enlarged subarachnoid space in the areas of compensatory growth, a feature that disappears after the age of 18 months in operated as well as non-operated cases. In non-syndromic craniosynostosis, MRI is only indicated in trigonocephaly because of its association with additional cerebral deformations.

It is important that children are taken care of in the setting of a multidisciplinary craniofacial team. Patients with non-syndromic craniosynostosis may present or develop problems in different specialty areas and evolve into complex cases later in life.

7.2.1.6 Diagnosis

The morphological changes in each form of craniosynostosis are so specific that the diagnosis is essentially clinical (Table 7.2.1). Radiological examinations serve to confirm the diagnosis. Primary synostosis has to be differentiated from postural plagiocephaly and secondary synostosis.

Indication, Timing and Extent. Surgery was first described by Marie-Lannelongue in 1890. Initial interventions include simple strip craniectomies, followed by extended strip craniectomies. Today, total calvarial and supraorbital remodeling are the most frequently used tech-

### Table 7.2.5 Proportion of children with normal mental level by age at first presentation (taken from [105])

<table>
<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>&lt; 1 year</th>
<th>&gt; 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaphocephaly</td>
<td>426</td>
<td>94%</td>
<td>74%</td>
</tr>
<tr>
<td>Trigonocephaly</td>
<td>210</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Plagiocephaly</td>
<td>156</td>
<td>91%</td>
<td>79%</td>
</tr>
<tr>
<td>Brachycephaly</td>
<td>56</td>
<td>89%</td>
<td>50%</td>
</tr>
<tr>
<td>Complex</td>
<td>40</td>
<td>88%</td>
<td>56%</td>
</tr>
</tbody>
</table>

### Table 7.2.6 Proportion of children with normal mental outcome after treatment, by age at operation (taken from [105])

<table>
<thead>
<tr>
<th>Type</th>
<th>Operation at &lt; 1 year</th>
<th>Operation at &gt; 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaphocephaly</td>
<td>91%</td>
<td>81%</td>
</tr>
<tr>
<td>Trigonocephaly</td>
<td>88%</td>
<td>79%</td>
</tr>
<tr>
<td>Plagiocephaly</td>
<td>90%</td>
<td>84%</td>
</tr>
<tr>
<td>Brachycephaly</td>
<td>90%</td>
<td>43%</td>
</tr>
<tr>
<td>Complex</td>
<td>76%</td>
<td>70%</td>
</tr>
</tbody>
</table>
niques. The most recent techniques, however, are going back to strip craniectomies using endoscopic procedures and bone distractors. Major debates concerning surgery concentrate on three elements: the extent of surgery, the timing of surgery and the indications for surgery.

The indication for surgery is to prevent raised intracranial pressure and mental retardation and to reduce the impact of dysmorphisms on psychological behaviour. If half of patients can be expected to develop functional impairments, the other half de facto receives surgery for cosmetic reasons. It is, however, not possible to predict at an early age which patients are going to develop these impairments, while on the other hand, strong evidence exists that early surgery prevents further developmental deterioration. These considerations impose an indication for surgery, irrespective of the important value of a cosmetic intervention in this type of morphological changes [9].

Timing remains an issue of debate. Arguments for early surgery, before 6 months of age, include that the procedure can be more restricted. Early surgery prevents the dysmorphism from worsening, and early surgery might benefit from passive postoperative remodelling due to the important growth of the brain in the first 6 months of life. Further arguments for early surgery are the likelihood of reossification of calvarial defects, the malleability of calvarial bone and the favourable effect on the facial dysmorphisms [77, 76, 79]. Arguments for late surgery, after 9 months of age, are that the definite skull shape can be obtained and that the chances of regrowth and renewed constriction are smaller [101]. Inquiries by the International Society of Craniofacial Surgery (ISCFS) among their members showed that most surgeons choose to operate before the age of one. Patients with scaphocephaly are preferably operated before the age of 6 months but delayed until the age of 9 months in the case of late referral [81].

Over the last century, surgery has moved from strip craniectomy of the affected suture via extended strip craniectomy towards total calvarial remodelling. Strip craniectomy has a high risk of regrowth and renewed restriction. Extended strip has improved these results in scaphocephaly, but especially when combined with outfracturing of the shortened parietal bone flaps and when performed in young children. In older scaphocephalic patients, with more extensive frontal bossing, remodelling of the forehead is necessary. In craniosynostosis which involve the superior orbital rim strip, craniectomy does not seem to be satisfactory. "Autocorrection" of the skull base deformity and the orbits does occur [99, 107, 26] but is not sufficient [79, 125, 110]. In those types, the forehead, as well as the superior orbital rim, needs to be remodelled.

**Minimally Invasive Techniques.** Endoscopic techniques entail a strip craniectomy by a minimally invasive procedure (Fig. 7.2.1). Access is gained through two small incisions at the level of the bregma and the lambda, depending on which suture is to be removed. After making two burr holes, an endoscope is introduced which permits controlled stripping of the dura from the calvarial bone and haemostasis. A bone strip along the affected suture is removed using mayo scissors. In scaphocephaly, the procedure may be extended with two lateral strips. After the intervention, a moulding helmet is applied to compensate for the lack of remodelling. A helmet might, however, restrict growth by itself and does not seem a logical treatment tool in craniosynostosis. The authors of the first reports on this technique emphasize the minimal blood loss and short hospital stay [50, 51, 8, 94, 118, 113]. Randomized studies are not available but should be performed in order to demonstrate the long-term results of endoscopic techniques.

The use of springs combined with strip craniectomy was described by Lauritzen [69]. This technique aims at increasing intracranial volume at the level of the restricted suture by introducing metal springs. However, it relies on spontaneous correction of the additional dysmorphisms that have occurred due to compensatory growth. This technique has incidentally been used in non-synos-
totic occipital flatness [3] and to correct hypotelorism in trigonocephaly [73]. David [23] described a prospective series of 15 patients with sagittal synostosis treated with strip craniectomy and springs. The cranial index (CI = skull width / skull length × 100) was corrected from a preoperative mean of 64.3 to 77.6 after surgery. A study of Guimaraes-Ferreira [41] compared 10 patients with sagittal synostosis operated by spring-mediated cranioplasty to match historical controls that were operated by an extended strip craniectomy. Morphological outcome, the duration of surgery and the need for blood replacement were significantly better in the spring-corrected study group. However, no randomised studies have been reported to further evaluate this technique. The rate of distraction might be variable and unpredictable. Another drawback is the necessity of a second intervention to remove the springs.

General Aspects. In the following paragraphs, each type of craniosynostosis will be discussed separately. First, a few general comments must be made.

The parents must be extensively informed. Their full consent is imperative, since this concerns major surgery with potential complications and is in the majority of cases performed for cosmetic reasons.

Preoperative laboratory testing should include haemoglobin, haematocrit and blood typing. The presence of irregular antibodies should be excluded since blood may be necessary at short notice. The clotting status should only be screened if clotting abnormalities are suspected on clinical or family history.

The patient can be operated in either the prone or supine position according to the area that has to be most accessible for remodellation. Preventive antibiotics are routinely administered. More than a single shot or 24 hours postoperatively does not seem to further decrease the percentage of postoperative infections [81]. The scalp is infiltrated with adrenaline 1:200,000 and Marcaine 0.25% at the site of the planned incision. Scalp clips are used to further minimise blood loss. The incision is usually bicoronal and may end either above or behind the ear. A zigzag configuration on the temporal sides makes the incision easier to hide beneath the hair. For young scaphocephalic patients, in whom the forehead does not need to be remodelled, the incision may be brought back to the level of the lambdoid sutures where it will remain hidden beneath the hair even after male pattern hair loss.

The scalp can be easily detached from the periost by its anatomical plane. It is advisable to leave the periost on the bone and to remove it only just before the craniotomy and on removing the bone flap, because removing the periost will unavoidably increase blood loss even with the use of bone wax.

The dura should be very carefully detached from the open fontanel. The sagittal sinus might be displaced in anterior plagioccephaly. Any dural tear has to be sutured in order to avoid leakage and infection. Venous bleeding is stopped by using bipolar coagulation and haemostatic agents.

The remodelled bone flaps can be fixed with wire, sutures or microplates and screws. Reabsorbable material is preferred since metal has the tendency of migrating into the dura and even the brain [34, 36, 61, 30]. Reabsorbable plates are thicker than titanium plates and therefore more visible under the skin and more likely to cause pressure points. To avoid these problems, the reabsorbable plates can be placed at the interior of the skull whenever possible [111].

Before closing, a wound drain is left in place for 48 hours.

Anaesthesia. The major anaesthetic problem is the presence of continual blood loss and the risk of sudden massive blood loss. All patients should have adequate venous access and an arterial line. The need for a central line in older patients is debatable. In younger patients, the central venous pressure serves as an extra guide to blood volume. Cross-matched blood should be readily available. Temperature control is essential, particularly in patients under a year where the head constitutes a relatively high percentage of the body surface area. Since it is difficult to assess the blood loss with any accuracy and blood loss can be rapid and massive should a sinus inadvertently be disrupted, it is essential that the surgeon and anaesthesiologist communicate any abnormal blood loss or adverse events immediately.

The avoidance of hypercapnia can prevent a rise in intracranial pressure and subsequent venous bleeding. Movement of the head during surgery may result in kinking and displacement of the endotracheal tube and cause hypoventilation. Excessive rotation or flexion of the head can cause obstruction to the internal jugular vein, causing a rise in venous pressure, intracranial pressure and extensive bleeding and should be avoided.

Various methods have been used to decrease blood loss. A slight head-up position of the operating table may decrease venous bleeding but should not be exaggerated in order to prevent air embolisms from occurring. The use of controlled hypotension may decrease arterial or capillary bleeding but has little influence on venous bleeding or bleeding from the bone [88].

Haemostasis should be investigated after replacement of more than 50% of total blood volume and corrected if necessary. A single study has investigated the influence of tranexamic acid on blood loss during and after surgery. The study observed a decrease in blood loss by one third of normal blood loss with the use of tranexamic acid compared to the control group [27]. A prospectively randomized study concerning the effect of immediate preoperative haemodilution on the need for transfusion showed no significant reduction of the incidence or of the amount of transfused blood [43].
7.2.1.8 Postoperative Management

Patients are observed clinically and neurologically in a high care or intensive care unit for 24 hours after surgery. Blood haemoglobin and haematocrit should be followed closely as blood loss may continue after the intervention. The haematocrit of blood collected from the wound drains can be useful in estimating the exact blood loss. Comfort scores will help to determine whether the child has pain and needs extra medication. Fever is to be expected following the first days after surgery and does not need any treatment.

If surgery involved reconstruction of the forehead and superior orbital rim, the eyes will be oedematous and impossible to open for one or two days.

Most patients are ready to leave the hospital around day four or five after surgery.

Follow-up will be frequent in the first year after surgery, then every two years until the age of six and finally every three years until adulthood. Attention should be paid to the occurrence of any clinical signs of increased intracranial pressure, especially slowing development and school performances, headache and visual disturbances. Head circumference measurements should confirm adequate growth. Radiographs are routinely made to look for exaggerated digital impressions. Ophthalmologic examination is conducted to rule out papillary oedema at every follow-up visit.

7.2.1.9 Scaphocephaly

Scaphocephaly, Greek for boat skull, describes the head shape that results from fusion of the sagittal suture (Fig. 7.2.2). The impaired growth of the skull width is compensated by excessive skull length. Frontal bossing is a common sign, which tends to progress during the first year of life. Occipital bossing, also called the bullet, is somewhat less frequent and may be more pronounced in cases where fusion starts at the posterior end of the

Fig. 7.2.2a–c Picture of patient with sagittal synostosis, before (a) and after (b) surgery. Radiographs of patient with sagittal synostosis (c). c see next page
suture. Severe forms show a "saddle", a depression of a few centimetres in length at the level of the sagittal suture, presumably where the fusion first started.

Scaphocephaly is the most frequent type of craniosynostosis. It has a strong male preponderance. Familial cases occur in up to 6% [63]. Genetic disorders are seldom found [112]. Scaphocephaly, as well as trigonocephaly, is more likely to develop in twins compared with singletons. It occurs both in monozygotic and dizygotic twins, although the risk is somewhat higher in monozygotic twins. This suggests the presence of an environmental as well as a genetic component [68].

The diagnosis can be made at birth. Skull shape may resemble the shape after breech position. However, in the case of synostosis, a ridge can be palpated at the site of the sagittal suture. In normal neonates, the parietal bones are mobile with respect to each other. The skull shape after breech position normalises in a few weeks while the dysmorphisms of a true scaphocephaly progress.

Clinical and neurological examination in infants is typically normal. Signs of raised ICP are rare and occur in older children. Preoperative invasive ICP measurements show raised ICP in 10–17% of cases and borderline ICP in 20–40%. Children may present with headache. Papillary oedema is extremely rare (0.4% [106]). When children present at an older age, the decision to proceed to surgery may be difficult. The morphological changes are usually less severe in these children. In the absence of any signs of raised ICP, an expectant course may be followed. However, if the morphological changes are important, e.g. CI < 66, surgery might be considered, accepting a higher operative morbidity and mortality.

Morphological results seem to be better after more extensive procedures than with strip craniectomy. Several studies compared postoperative cranial indexes between different techniques [52, 78, 86, 98]. Strip craniectomy resulted in a CI of 71–73; different variants of the extended strip, including the total vertex craniectomy described by Epstein [31], resulted in a CI of 73–79, and total calvarial remodelling resulted in 74–77. In our centre, we used to perform a fronto-biparietal remodellation at 9 months of age. The postoperative cranial index was 73. We now perform an H-extended strip craniectomy with outfracturing and remodelling of the parietal bone flaps at 3–6 months of age (Fig. 7.2.2c). The mean postoperative cranial index is 76.

We will describe the technique used at our institution. The patient is in supine position with the head slightly flexed on a headrest. Incision starts above the ear and runs towards the lambda. The scalp is reflected to the extent that the coronal and lambdoid sutures can be identified. The periost is left in place. A 4-cm-wide strip of bone is removed at the level of the sagittal suture, extending from the coronal sutures to the lambdoid sutures. Just behind the coronal sutures and just before the lambdoid sutures, a triangle of bone is removed to create two parietal flaps. The parietal flaps are outfractured at the level of the squamosal suture. Barrel stave cuts are added to mould the parietal flaps. The frontal and posterior corner ends of the parietal flap are rounded in order to prevent parts from protruding or causing pressure wounds.

Postoperatively, the parents are advised to maintain the head in midline position during sleep as long as possible. This reduces the occipital prominence and may even help to reduce the length of the skull [2].

In older children, important occipital bossing (bullet) may be addressed surgically. This should always be weighted against the increased risk of this procedure. In scaphocephaly, we would not extent the intervention beyond the transverse sinuses. The dura can be detached from the bone at the lambdoid sutures until the level just above the transverse sinus. Longitudinal cuts at 1-cm intervals are made, and the resulting fingers are bent outwards. This flattens the bullet but does not add to the anteroposterior shortening. If correction of the frontal bossing is necessary, the frontal bone is removed 1 cm above the superior margin of the orbit. The forehead is shortened, and the bossing is lowered by removing a strip at the inferior margin of the bone flap. The flap is tilted to the back by gradually increasing the widths of the removed strip on the lateral sides of the frontal bone flap.
7.2.1.10 Trigonocephaly

The incidence of metopic synostosis seems to be on the rise. It used to be the third most frequent occurring single-suture synostosis after sagittal synostosis and unilateral coronal synostosis. Several authors [10, 125, 108] have reported an increasing incidence. In the series of Renier [108], trigonocephaly used to represent 10% of the non-syndromic craniosynostosis but has now increased to 21.6%. It is not clear whether this represents a recruitment bias or a real augmentation.

The condition shows a male predominance of 75%; 2–6% of cases are familial, and some cases are syndromic. Among the non-syndromic craniosynostoses, trigonocephaly is most associated with other malformations, karyotype anomalies and cognitive and behavioural dysfunction [12, 20, 64, 116, 108, 57]. Intracranial hypertension occurs in a minority of cases (7.7%, [105]) and is usually mild.

Metopic synostosis is easily recognized by the triangular shape of the forehead (trigonocephaly) when viewed from above (Fig. 7.2.3a). The forehead is narrow and keel-shaped. Hypotelorism, recessed lateral orbital rims and a diminished bi-temporal distance are additional findings [108]. An isolated frontal ridge without the accompanying dysmorphisms of the orbit and temporal bone should not be considered for surgery; those ridges will remodel spontaneously during the first years of life [79].

More severe cases are usually operated. Shimoji [114] describes surgery in mild trigonocephaly without a keel-shaped forehead but with depressed temples and slight hypotelorism. Surgery was performed, even at an older age, for reasons of symptoms like hyperactivity, language developmental delay and motor dysfunctions. The study reports an increase in frontal cerebral blood flow on single photon emission computed tomography (SPECT) studies and improvement of behavioural problems and developmental delay. These findings are in contrast with most studies concerning the effect of surgery on developmental delay in trigonocephaly. Perhaps the older age at which surgery was performed in Shimoji’s study explains this difference.

Several operative techniques have been described, all aiming to improve the triangular forehead, the recessed lateral orbital rim and the temporal narrowing. Most involve fronto-orbital remodelling. After bifrontal craniotomy, a new forehead is reconstructed by using frontal or fronto-parietal bone. The lateral parts of the orbital rim are brought forwards and outwards. The midline angle of the orbital rim is flattened either by breaking or by sectioning and refixing the midline with reabsorbable sutures and plates or a bone graft (Fig. 7.2.4b). Discussion concentrates on the necessity of correcting the hypotelorism. The hypotelorism will correct itself over time after removing the synostosed suture, apparently due to plasticity of the endocranial base [99, 107, 26]. However,
some state that this autocorrection is not sufficient and that better results are obtained if a bony graft is placed between the two halves of the superior orbital rim [79, 125, 110]. This technique is in fact only a cosmetic correction of the hypotelorism in the sense that the interorbital distance is not enlarged.

The new forehead is fixed to the orbital rim. The lateral parts of the forehead have to be reconstructed in such a way that the bi-temporal diameter is enlarged and even overcorrected [6, 110]. In this region, no bony defects should be left, and the temporal muscle should be reinserted meticulously in order to prevent the temporal depressions so often seen after correction of trigonocephaly [105, 125, 110].

Morphological outcomes are generally good to excellent [7, 107, 26, 20], although recently, temporal depressions are reported more frequently as an adverse event [46, 110, 125, 107]. Cognitive function is not improved by surgery [45]. However, early surgery, before one year of age, seems to prevent further deterioration [105, 107, 15].

Fig. 7.2.4 a Operating technique for sagittal synostosis. b Operating technique for metopic synostosis. c Operating technique for unicoronal synostosis. d Operating technique for bicoronal synostosis.
7.2.1.11 Plagiocephaly

Plagiocephaly literally means twisted head. Anterior plagiocephaly is used to describe the resulting skull shape of unicoronal synostosis. It has to be differentiated from postural plagiocephaly and from synostosis of the frontosphenoidal suture [24, 85]. Frontosphenoidal suture synostosis may either accompany unicoronal synostosis or occur isolated. The latter case is difficult to diagnose and requires 3D CT.

Unicoronal synostosis is the third most frequently occurring single suture synostosis. The dominance of females over males is 69%. In 61% of cases, the right coronal suture is affected; in 39% it is the left [108]. Coronal synostosis can present as an isolated sporadic form, as part of a syndrome or as a familial inherited condition. Familial cases range from 8.4 to 9.5% [62]. In some of these families, unicoronal as well as bicoronal synostosis are observed. Gene mutations can be found in up to 20% of patients, including changes in FGFR2, FGFR3 [66] and TWIST [93].

Unicoronal synostosis is accompanied by significant and, if left untreated, progressive facial deformity (Fig. 7.2.5a). The forehead and orbital rim ipsilateral to the affected suture are retruded and flattened, the orbit is elevated and the nose root may be displaced to the ipsilateral side. The forehead on the contralateral side may protrude, thus accentuating the asymmetry. The resultant effect on the lower face can be best described as longitudinal expansion of the ipsilateral hemiface and compression of the contralateral hemiface [79]. Children with mutations more often present hypertelorism and asymmetric brachycephaly with bilateral retrusion of the orbital rim [93]. Bulging of the temporal fossa on the affected side is a strong indicator of the presence of the FGFR3 P250R mutation [66].

Surgical intervention aims to correct the frontal and orbital asymmetry (Fig. 7.2.4c). In general, a bifrontal bone flap is removed in one piece. A bilateral correction of the orbital rim seems necessary in almost all cases, especially in cases with severe protrusion of the contralateral side [74, 11] and in patients with genetic mutations [93]. The superior orbital rim is lifted, uni- or bilaterally, and corrected in the midline. The lateral canthus of the orbit is brought forwards. This can be achieved by cutting the orbital rim inferiorly through a wide segment of the frontozygomatic suture just above the zygoma. The rim can then be advanced by placing a “mortise and tenon” bone graft or using reabsorbable plates [44]. Alternatively, the lateral canthus can be advanced by cutting vertically down

Fig. 7.2.5a–c Picture of patient with unicoronal synostosis, before (a) and after (b) surgery. Radiographs of patient with unicoronal synostosis (c)
the lateral orbital wall after removal of the orbital rim at a higher point above the frontozygomatic suture. The canthus is then advanced by placing a small triangular bone spur in the vertical cut [6]. Finally, the frontal bone is remodelled and fixed to the orbital rim. If the temporal region is bulging, this should be corrected as well by moving the posterior margin of the frontal bone flap backwards.

Morphological results are generally good to excellent in most patients [44, 87, 104, 47], especially concerning the shape of the forehead. Facial deformity tends to correct spontaneously after intervention. Vertical orbital dystopia is corrected or improved in a large proportion of cases ranging up to 81% [87, 47]. The optimal timing of surgery is unclear. Renier reported a higher proportion of bad morphological results in cases operated after the age of one year. On the contrary, Hilling found no relationship between postoperative appearance and age at surgery between 6 and 15 months. The risk of poor results necessitating re-operation is shown to be higher in the presence of genetic disorders [93, 18].

**7.2.1.12 Brachycephaly**

Brachycephaly, or “short head”, results from synostosis of both coronal sutures. It occurs more often in the context of a syndrome but can also occur isolated. The majority are female (66–79%) [108, 92, 66]. The risk of raised ICP is high (31.3%), as can be expected with fusion of two sutures. A frequently identified genetic disorder is the FGFR3 P250R mutation or Lajeunie-Muenke type craniosynostosis. Additional disorders may be identified in some of these patients, including brachydactyly, abnormalities on radiographs of hands and feet, sensorineural hearing loss and developmental delay [90].

The skull is short, high and broad (Fig. 7.2.6). The forehead is retruded and flattened or even concave in the inferior part; the superior part is bossing or growing vertically (turricephaly). The supraorbital rim is retruded. The infraorbital rim is normal, unlike in syndromic cases with midface hypoplasia. The nasal dorsum is low. Hypertelorism may be present. Especially in Lajeunie-
Muenke type craniosynostosis, temporal bossing may be prominent [66].

Surgical correction consists of a bifrontal craniotomy with remodelation of the forehead and advancement of the supraorbital rim of about 1.5 cm (Fig. 7.2.4d). The bandeau is fixed to the temporal bone with a tenon and mortise principle or reabsorbable plates. A bone graft is used to fill up the space between the bandeau and the nasion. Secondary nasal dorsum augmentation is usually unnecessary in non-syndromic cases [79]. Grade I hypertelorism may be corrected cosmetically by redressing the midline of the bandeau to a width of 20 mm at the level of the nasal root. More severe hypertelorism needs orbital correction around the age of 5 years [79, 6]. Remodeling of the forehead aims at correction of the concavity or inferior flattening. Several techniques have been described [74, 105, 60, 6]. The "new" forehead is fixed to the bandeau. Temporal bossing is corrected by taking the craniotomy further backwards.

In cases with the FGFR3 P250R mutation, the morphological and functional outcome may be suboptimal [5]. The risk of reoperation increased from 4.3% in cases without to 20.7% in cases with this mutation in a series described by Thomas [121].

### 7.2.1.13 Non-syndromic Occipital Plagiocephaly and Lambdoid Synostosis

Non-syndromic posterior plagiocephaly arises from a postural preference, most frequently a rotation of the head to the right side. About 30% of cases are associated with a torticollis or tight sternocleidomastoid muscle. A prospective cohort study of 200 patients identified limited head rotation, lower activity levels, male gender, first-born and supine sleep position as risk factors [48]. The incidence has increased following the advice of putting infants to sleep in the supine position in order to avoid sudden infant death. Incidence was as high as 1 in 68 infants in a series reported by Littlefield in 2004 [71].

The differential diagnosis of posterior lambdoid synostosis can be made on clinical signs [29]. Viewed from above, the head shows a trapezoid form in the case of a synostotic defect with the ear moved to posterior on the affected side. In the case of a postural flattening, the view from above shows a parallelogram with the ear moved to anterior on the affected side. From a posterior point of view, the ear is moved downwards at the affected side in lambdoid synostosis (Fig. 7.2.7), while in non-synostotic plagiocephaly, the ears remain at the same height. Non-synostotic posterior plagiocephaly may have an important impact on the face and forehead. It should then be differentiated from anterior plagiocephaly due to unicoronal synostosis. In the postural form, the eyebrow will be moved downwards on the flattened and retruded side of the forehead. In the synostotic form, on the contrary, the eyebrow is moved upwards on the flattened side of the forehead. In typical cases, radiographs are unnecessary. However, radiographs may show sclerosis along the open lambdoid suture on the flattened side. This is not a sign of synostosis but confirms the diagnosis of positional deformity [25].

Treatment of the non-synostotic form, when presented before the age of 6 months, consists in giving postural advice combined with physical therapy in the case of constrained neck movements or asymmetric neurological development [100]. Helmet therapy is recommended if
There is no improvement or even progression of the deformity with repositioning after 2–3 months. Graham [39] recommends helmet therapy if the CI is larger than 90 or with a diagonal diameter difference of more than 1 cm at the age of 6 months. A moulding helmet is most effective between the ages of 4 and 12 months [100]. A helmet successfully reduces posterior flattening and asymmetry but has little effect on changes of the face and forehead. Review of the literature did not permit conclusions as to the relative effectiveness of helmet therapy compared to repositioning, although both helped to reduce the deformity [91, 49, 14]. Some advocate surgery in extreme cases, but only on the posterior side. However, subcutaneous implants might be as effective in correcting the posterior aspect of the skull. Until the age of 12 months, effects from postural changes or redressing helmets can be expected. After 12 months, the deformity will remain unchanged but become less obvious due to covering hair and the growth of the face later in life.

Posterior plagiocephaly due to synostosis of the lambdoid suture is rare. Most cases are unilateral, but bilateral lambdoid synostosis does occur. It presents more often in males. Many surgical techniques have been described, varying from strip craniectomy to distraction by springs with or without craniotomy and occipital craniotomy with remodeling of the occipital contour. Techniques to create a larger intracranial volume are interdigitation expansion [6], switch cranioplasty or “tiara” reconstruction [37], in which the occipital bone flap is moved backwards either by using multiple mortise and groove interdigitations or by tipping a coronal bandeau or tiara over to the occipital region and fixing the occipital bone to this tiara.

Multiple Sutures. Multiple-suture synostosis is most commonly associated with syndromic cases but may occur as an isolated form. Different combinations of affected sutures are described, all giving rise to different skull shapes. Oxyccephaly for example occurs with coronal and sagittal synostosis. Pansynostosis refers to fusion of all sutures. The constrained brain will push to compensatory enlargement, thus forming an abnormal skull shape. However, when pansynostosis is accompanied by a microcephalic but otherwise normal head shape, the brain is apparently not expanding, most probably due to a primary cerebral condition. In those cases, there is no indication for surgery.

Surgical technique depends on the sutures affected and may combine several of previously described techniques. Frequently, two interventions are necessary – one anteriorly and one posteriorly.

Outcome: Morphological Results and Adverse Events. Morphological outcome is good to excellent in the majority of cases for all non-syndromic craniosynostosis: 44–81% in unicoronal synostosis, 65–96% in metopic synostosis. The accompanying facial dysmorphisms tend to correct progressively with age. This is not the case in syndromic synostosis. However, the determination of a good morphological result remains subjective. Different grading systems have been derived. For example, Renier graded the results from 1 to 4: 1 – perfect result; 2 – imperfect result, additional surgery optional; 3 – mediocre result, additional surgery necessary; 4 – failure, complete revision indicated. Others have used the re-operation rates as a measure of outcome [130].

Anthropometric analysis may provide a more objective measure. The cranial index (biparietal diameter / anteroposterior diameter × 100) can be used and has the advantage that normative values by age are known [32]. At 1 year of age, the normal CI ranges from 77 to 81. CT and radiographs provide objective information but involve an additional exposure to radiation. However, many details like temporal depressions or bulging are not picked up by CT or anthropometry and are best appreciated by an independent observer, justifying the additional value of clinical grading systems.

Adverse events are relatively rare. The most common intraoperative complication is a dural tear, which occurred in 6.5% (range 0–25%) of a total of 1,190 procedures reported by the responders to the ISCFs questionnaire for benchmarking [81]. More severe complications included sinus haemorrhage and cortical damage, which were reported in 0.6% (range 0–7%) and 0.2% (range 0–2%), respectively. In this series, no operative deaths were noted, but two patients died within the period of 30 days postoperatively.

Infection rate is usually low. Postoperative wound infections occurred in 0.7–1.4% of simple synostosis and in 3.2–10.4% of complex cases. Among factors influencing the occurrence of wound infections are duration of surgery, the combination of intracranial and extracranial intervention, age of the child and number of surgeons present in the operation theatre [119, 131]. Cranial defects persist more frequently if surgery is performed after the age of 1 year [97]. Postoperative infection is associated with bone reabsorption and persistent defects.

The risk of recurrence is low, varying from 0.6% for trigonocephaly and plagiocephaly to 6.9% for Apert’s [107]. The chance of re-operation is increased for non-syndromic coronal craniosynostosis if the FGFR3 P250R mutation is present.

Recurrence refers to recurrence of the abnormal skull shape, not to the recurrent fusion of the synostosed suture. In fact, reformation of the suture following surgery is a very rare event [1]. Sagittal synostosis may show “evolving” craniosynostosis with additional synostosis of the coronal sutures in up to 10.5% of cases. This may be associated with raised ICP. The frequency of raised ICP in operated non-syndromic craniosynostosis is not known but is probably very low. A peculiar adverse event in sag-
ittal synostosis constitutes the progressive forming of a bulge at the site of the earlier anterior fontanel (Fig. 7.2.8) after extended strip craniectomy [80]. Marucci describes 7 cases in a cohort of 89 patients. CT scanning demonstrated new synostosis involving other sutures in five patients. All patients underwent genetic screening. Two of them had FGFR mutations (one FGFR2 and one FGFR3). Five patients underwent ICP monitoring, which was elevated in four. All patients required re-operation.

Several authors reported that cognitive functions did not improve after decompressive surgery. However, Renier showed that the percentage of children with a normal development is higher in children operated before the age of one than in children operated after the age of one. This appears to be true for all types of craniosynostosis except plagiocephaly [107, 84]. Therefore, one may conclude that decompressive surgery cannot improve cognitive development but does prevent further deterioration.

**Suggested Reading**

32. Farkas LG, Munro IR (1981) Anthropometric facial proportion in medicine. Thomas, Springfield
Non-syndromic Craniosynostosis


7.2.2 Syndromic Craniosynostoses


7.2.2.1 Introduction

Syndromic craniosynostoses constitute a heterogeneous group of pathological conditions characterized by the association of the early fusion of several cranial sutures and various congenital malformations, especially of the face and the limbs. The hallmark of syndromic craniofacial dysostoses is the involvement of both the neurocranium (calvarium and skull base) and the viscerocranium (orbital and midfacial skeleton) (Fig. 7.2.9). The calvarium is characterized by multiple suture synostoses and the face by a maxillary hypoplasia. It is still unknown whether the often associated maldevelopmental anomalies of the brain and cerebrospinal fluid (CSF) dynamics found in many of these conditions should be regarded as primary or secondary events. Probably, however, the number and the time of fusion of the affected sutures might exert a direct role on the phenotype of at least some of these pathological entities, as demonstrated by the more common occurrence of a caudal herniation of the cerebellar tonsils in Crouzon syndrome than in Apert syndrome, the latter being characterized by a later fusion of the lambdoid suture as compared to the former.

Venous drainage from the cranial cavity is often impaired in these malformations (Fig. 7.2.10) secondarily to a hypoplastic posterior cranial fossa leading to various degree of increased CSF pressure and enlargement of the subarachnoid or ventricular spaces. Several hypotheses have been raised to explain these findings: the venous obstruction could be secondary to the abnormalities of the bone growth affecting the skull; the disorder could be primarily resulting from dysplastic growth of the basicranium or due to the persistence of a foetal pattern of venous drainage and failure of normal maturation of the posterior fossa drainage.

Moreover, in several of these conditions, an associated developmental failure of the middle third of the face results in ocular proptosis with the risk of corneal damage following even trivial traumas. Furthermore, the under-development of the airways may lead in several cases to alterations of respiratory function (Fig. 7.2.11), of which nocturnal apnoeas are the most dreadful. The multifactorial involvement of various craniofacial structures and functions justifies the common utilized term of “faciocraniostenoses”, which points to the specific association of bone anomalies of the skull and facial skeleton and emphasizes the difficulties experienced in their management.

Fig. 7.2.9 Three generations of patients with Crouzon syndrome

Fig. 7.2.10 Left: sagittal brain MR of a child with Crouzon syndrome. Note the acrocephalic shape of the skull and the associated deformations and distortions of the cerebral structures, ventricular enlargement and the caudal descent of the cerebellar tonsils (Chiari type I malformation). Right: Venous angiography. Note the compression of the venous outflow associated to collateral drainage (arrows)
7.2.2 Syndromic Craniosynostoses

7.2.2.2 Genetics

Several mutations implicated in syndromic craniosynostosis have been found (Table 7.2.7). They involve mostly three of the four fibroblast growth factors and are mostly autosomal dominant. In syndromic synostosis, a single gene defect generates different clinical phenotypes. A difference in the interactions with extracellular matrix constituents has been suggested to explain the variability in phenotypes in spite of common gene defects.

7.2.2.3 Main Syndromes

A synopsis of the main syndromic craniosynostoses can be found in Table 7.2.8.

7.2.2.3.1 Crouzon Syndrome

(Craniofacial Dysostosis)

Crouzon syndrome is an autosomal dominant syndrome first described by Crouzon in 1912. Crouzon syndrome represents approximately 4.8% of cases of craniosynostosis at birth. The birth prevalence has been estimated to be 1:25,000 births. The syndrome associates craniosynostosis and facial hypoplasia. The craniosynostosis phenotype varies in the different subjects, but in most of the cases, both coronal sutures are involved. The facial phenotype is characteristic and includes a hypertelorism with exorbitism, a short upper lip and a relative mandibular prognathism with an inverted bite (Fig. 7.2.9). The exorbitism is due to the retrusion of both the forehead and the maxilla. These features can be seen at birth but usually appear at 2 years of age and worsen progressively. However, some congenital forms exist in which the maxillary hypoplasia is more marked. The affected subjects suffer from breathing difficulties and show a major exorbitism that can impair the occlusion of the eyelids. Ventriculomegaly is common and sometimes progressive. Chiari type I malformation is also quite common in this syndrome, found in approximately 70% of the cases, and may be associated with a syrinx and complicate the surgical management (Fig. 7.2.10). The Chiari type I malformation may be related to the small size of the posterior cranial fossa, the shortness of the clivus and the premature fusion of the lambdoid sutures during the first two years of life.

The gene responsible for Crouzon syndrome has been located on the long arm of chromosome 10 (Table 7.2.7). More than 30 mutations have been identified in the FGFR2 gene (exon IIIa and IIIc), and they can be found in around 60% of the patients.

Table 7.2.7 Mutations in syndromic craniosynostosis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Chromosome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apert</td>
<td>10q25.3-q26</td>
<td>FGFR2</td>
</tr>
<tr>
<td>Crouzon</td>
<td>10q25.3-q26</td>
<td>FGFR2</td>
</tr>
<tr>
<td>Pfeiffer</td>
<td>10q25.3-q26</td>
<td>FGFR2</td>
</tr>
<tr>
<td></td>
<td>8p11.2-p12</td>
<td>FGFR1</td>
</tr>
<tr>
<td>Saethre–Chotzen</td>
<td>7p21</td>
<td>TWIST</td>
</tr>
<tr>
<td></td>
<td>10q25.3-q26</td>
<td>FGFR2</td>
</tr>
<tr>
<td></td>
<td>4p16</td>
<td>FGFR3</td>
</tr>
<tr>
<td>Jackson–Weiss</td>
<td>10q25.3-q26</td>
<td>FGFR2</td>
</tr>
<tr>
<td>Beare–Stevenson cutis gyrata</td>
<td>10q25.3-q26</td>
<td>FGFR2</td>
</tr>
<tr>
<td></td>
<td>4p16</td>
<td>FGFR3</td>
</tr>
<tr>
<td>Crouzon syndrome with acanthosis nigricans</td>
<td>4p16</td>
<td>FGFR3</td>
</tr>
<tr>
<td>Lajeunie–Muenke syndrome</td>
<td>4p16</td>
<td>FGFR3</td>
</tr>
<tr>
<td>Boston-type craniosynostosis</td>
<td>5q34-q35</td>
<td>MSX2</td>
</tr>
</tbody>
</table>
Craniosynostosis complete penetrance and variable expression. Pfeiffer syndrome associates brachycephaly to membranous syndactyly of hands and feet with enlarged and deviated thumbs and great toes. Brachydactyly, ankylosis of the elbows and various visceral malformations can also be found.

Currently, the syndrome is divided into three subtypes. Subtype 1 is the classical and mildest form, with bicoronal synchondrosis leading to brachycephaly and flat face, hypertelorism and mild syndactyly with broad thumbs and great toes. Brachydactyly, ankylosis of the elbows and various visceral malformations can also be found.

Mutations in FGFR2 can also lead to Jackson–Weiss syndrome (Table 7.2.7), which shares several features with Crouzon syndrome. However, the affected subjects also present enlarged great toes and a tarsometatarsic fusion.

Mutations in FGFR3 (Table 7.2.7) may lead to a particular form of Crouzon syndrome associated with dermal anomalies (acanthosis nigricans).

### 7.2.3.2 Pfeiffer Syndrome (Acrocephalosyndactyly Type V)

Pfeiffer syndrome was described in 1964 by Pfeiffer. The frequency of Pfeiffer syndrome has been estimated at 1:200,000. Its transmission is autosomal dominant with complete penetrance and variable expression. Pfeiffer syndrome associates brachycephaly to membranous syndactyly of hands and feet with enlarged and deviated thumbs and great toes. Brachycephaly, ankylosis of the face, and poor survivals. Cloverleaf skull characterizes, although not exclusively, subtype 2 with hydrocepha-
lus and small posterior cranial fossa and a Chiari type I anomaly. Cloverleaf skull (Fig. 7.2.13) is associated with a very poor prognosis.

Pfeiffer syndrome is genetically heterogeneous. It can be due to a mutation in the FGFR1 gene or due to several types of mutations in FGFR2 (Table 7.2.7). Mutations in the same gene, FGFR2, may thus lead to three types of faciocraniosynostosis, i.e. Crouzon, Jackson–Weiss and Pfeiffer, thus suggesting that other factors also play a role in the pathogenesis of such syndromes.

7.2.2.3.3 Apert Syndrome (Acrocephalosyndactyly Type I)
Apert syndrome is a congenital syndrome described in 1906 associating faciocraniosynostosis to syndactyly of the extremities. The incidence is approximately 1:50,000 live births. Most cases are sporadic due to a paternal de novo mutation in the exon IIIa of the FGFR2 gene (Table 7.2.7). Autosomal dominant inheritance has also been reported.

The craniostenosis is bicoronal and spares the longitudinal sutures. The face is large with hypertelorism and exorbitism, parrot-beaked nose and inverted bite. The syndactyly may be complete or sparing the thumb and/or the last finger (Fig. 7.2.14). Fusion of cervical vertebrae is also commonly observed. Cerebral malformations mainly involving the corpus callosum and the limbic structures may also be demonstrated with MRI (Fig. 7.2.15). Abnormal gyration of the temporal lobe with dysgenesis of the parahippocampal area has also been found upon neuropathological analysis. The size of the ventricles is often increased, but this ventriculomegaly is not progressive in almost all cases. Varying degrees of mental deficiency have been associated with Apert syndrome, with about
one fifth of the affected subjects with an intelligence quotient below 50; however, individuals with normal intelligence have also been reported. This high rate of mental impairment is related to the common incidence of brain anomalies, including the olfactory-limbic-septal-callosal structures, white matter hypoplasia, pyramidal tract abnormalities and non-progressive “distortion” ventriculomegaly.

### 7.2.2.3.4 Saethre–Chotzen Syndrome (Acrocephalosyndactyly Type III)
The first cases were reported by Saethre in 1931 and Chotzen in 1932. More than 40% of the cases are familial. The transmission is autosomal dominant. The penetrance is incomplete and the expression variable. The most typical phenotype associates brachycephaly and maxillary hypoplasia. The premature fusion of the cranial sutures typically involves both coronal sutures. However, any suture may be implicated with an asymmetry of the face, an unusually shaped ear with prominent crus and partial soft tissue syndactyly of fingers and toes (second and third fingers, third and fourth toes, with small distal phalanges). The great toe is usually enlarged, but it is not deviated. A ptosis, symmetrical or not, is observed in almost all cases. The syndrome may be extremely variable in its clinical expression; thus, examination of the family members is of paramount importance to detect potential carriers. The gene responsible for Saethre–Chotzen syndrome is TWIST, located on chromosome 7 (Table 7.2.7). Mental deficiency is uncommon.

### 7.2.2.3.5 Carpenter Syndrome (Acrocephalopolysyndactyly Type II)
This syndrome, autosomal recessive, is extremely uncommon and characterized by acrocephalus, soft tissue syndactyly of the hands, syndactyly and polydactyly of the feet. Some subjects present with obesity and hypogonadism.

### 7.2.2.3.6 Lajeunie–Muenke Syndrome
This syndrome is characterized by uni- or bilateral coronal synostosis, mild maxillary hypoplasia, hypertelorism and ptosis. The transmission is autosomal dominant. In some patients, it is associated with skeletal abnormalities such as thimble-like middle phalanges, coned epiphysis and/or neurological impairment, namely sensorineural hearing loss or mental retardation. In spite of a variable phenotype, this syndrome has been related to a unique mutation on the FGFR3 gene, Pro 250 to Arg, which is characteristic of this disease.

### 7.2.2.4 Functional Aspects
The fusion of several sutures that is found in syndromic synostosis results in a worse prognosis in terms of intellectual development, visual deterioration and raised intracranial pressure than is found in monosutural synostosis. Moreover, the anomalies in facial morphology and facial growth of craniofaciosynostosis may also lead to insufficient eye protection, respiratory obstruction, dental malocclusion and crowding of teeth, which often require specific treatments.

Increased intracranial pressure (ICP) is, in fact, frequent in syndromic craniosynostosis. The elevated ICP is not only secondary to the synostosis but also to presence of associated hydrocephalus and venous anomalies. Visual impairment may follow a long-standing elevated ICP, but it can also be secondary to the exophthalmus that is commonly found in these syndromes. It is worth noting that optic atrophy and visual loss are observed mainly in Crouzon syndrome.

Mental delay has also a variable incidence according to the syndrome type and to the associated brain malformations (mainly septum pellucidum abnormalities). Mental retardation is commonly found in Apert syndrome, which appears to be the most serious condition, and in some patients with Pfeiffer syndrome, especially those with cloverleaf skull deformity. On the other hand, mental retardation is rare in Crouzon syndrome. In general terms, cognitive outcomes are better after an early surgical correction and in cases of a good psychosocial environment of the child (Table 7.2.9).

### 7.2.2.5 Management Principles
The goals of craniofacial surgery are functional and esthetic. The first year of life is of paramount importance

### Table 7.2.9 Mental retardation in children with syndromic craniosynostosis according to the age at surgery

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mental retardation in children operated on before 1 year of age</th>
<th>Mental retardation in children operated on after 1 year of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apert</td>
<td>56%</td>
<td>95%</td>
</tr>
<tr>
<td>Crouzon</td>
<td>12%</td>
<td>41%</td>
</tr>
<tr>
<td>Saethre–Chotzen</td>
<td>10%</td>
<td>47%</td>
</tr>
</tbody>
</table>
for the treatment of the cranial vault in order to reduce the abnormally increased intracranial pressure and eventually normalize the CSF flow. In fact, in the first year, the brain has a rapid growth, and the outcome in terms of intellectual development has been proven to be better in patients operated on early (Table 7.2.9). Further advantages of the early surgical repair include easier bone remodelling and the higher potential for bone growth, which allows the “physiological” filling of possible bone defects that follow the surgical correction.

The classical management of faciocraniosynostosis includes anterior skull remodelling as a first step and a facial advancement as a second step. Iterative facial surgeries are often required.

The anterior procedure allows one to address both the problem of the abnormal ICP and the supraorbital recession consequently protecting the eyes and the visual function. The fronto-orbital advancement can be performed using the floating forehead technique or a horizontal tongue-in-groove advancement in children over 6 months of age. The facial advancement can be obtained by carrying out a Le Fort III osteotomy. In selected cases, a frontofacial monobloc advancement with simultaneous mobilization of the orbits and face can be performed. Currently, the use of internal or external distractors is preferred in order to obtain important facial advancements (Fig. 7.2.16). As a rule, the facial advancement should be delayed until final dentition is in place and stable occlusion can be achieved. However, in selected cases, especially in the case of breathing impairment, an early facial advancement may be necessary. In other cases, a tracheostomy should be undertaken prior to craniofacial surgery.

An early posterior cranial vault expansion may also be performed as an initial step to reduce the intracranial pressure, withholding the frontofacial correction until the child is older. This can be achieved, in particular, when the occipital flattening is evident and the posterior fossa is excessively small. The procedure usually results in a progressive improvement of venous outflow from the skull. An early posterior expansion can be obtained, either by elevating a large parieto-occipital bone flap, or using a spring-mediated cranioplasty in children with patent lambdoid sutures. Enlargement of the foramen magnum may also be necessary in some cases with symptomatic Chiari type I malformation.

The ventricular dilatation that may be found in syndromic craniosynostosis (Table 7.2.10) may also require a treatment. Often it is associated with tonsillar herniation of varying degrees, and an enlargement of the foramen magnum may be necessary. In others with a mechanical CSF obstruction, an endoscopic ventriculocisternostomy may allow for control of the intracranial pressure. However, in several cases of syndromic craniosynostosis, the venous outflow is impaired. The progressive opening of the venous collateral channel may lead to the absence of overt hydrocephalus. Nevertheless, some patients may require a ventriculoperitoneal CSF shunt.

Table 7.2.10  Reported prevalence of non-progressive ventriculomegaly and hydrocephalus in syndromic craniosynostosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Normal ventricles</th>
<th>Non-progressive ventriculomegaly</th>
<th>Hydrocephalus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crouzon</td>
<td>49.5%</td>
<td>31.6%</td>
<td>18.9%</td>
</tr>
<tr>
<td>Apert</td>
<td>32%</td>
<td>60%</td>
<td>8%</td>
</tr>
<tr>
<td>Pfeiffer</td>
<td>20%</td>
<td>12.2%</td>
<td>46.8%</td>
</tr>
</tbody>
</table>

Fig. 7.2.16 Left: Pre-op 3D head CT scan in a child with Crouzon syndrome. Note the facial retrusion and inverted bite. Right: Same child, during distraction after a frontofacial advancement. Note the correction of the facial retrusion
In all cases, several types of surgery are required (Table 7.2.11). A close collaboration between plastic surgeon and neurosurgeon as well as paediatric neuroanaesthetist is mandatory in order to improve both functional and cosmetic outcome.

**Suggested Reading**


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**Table 7.2.11 Types of surgeries in syndromic faciocraniosynostoses**

<table>
<thead>
<tr>
<th>Operation</th>
<th>Age</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranioplasty (skull expansion</td>
<td>Infancy</td>
<td>Prevent ICP hypertension; cosmetic benefit</td>
</tr>
<tr>
<td>and remodelling)</td>
<td></td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Foramen magnum opening</td>
<td>Infancy</td>
<td>Relieve tonsillar herniation and associated syringomyelia</td>
</tr>
<tr>
<td>CSF shunt or endoscopic third</td>
<td>Childhood</td>
<td>Reduce ICP</td>
</tr>
<tr>
<td>ventriculostomy</td>
<td></td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Facial advancement</td>
<td>Infancy, childhood, adolescence</td>
<td>Protect the eyes; protect against breathing difficulties; provide cosmetic improvement</td>
</tr>
<tr>
<td>ENT procedures (choanal dilation,</td>
<td>Infancy, childhood</td>
<td>Improve the airways; protect against breathing difficulties</td>
</tr>
<tr>
<td>grommet insertion, tracheostomy, etc.)</td>
<td></td>
<td>Aid hearing; treat chronic ear infection</td>
</tr>
<tr>
<td>Squint surgery</td>
<td>Childhood</td>
<td>Correct squint; improve vision</td>
</tr>
<tr>
<td>Mandibular and oral surgery</td>
<td>Adolescence</td>
<td>Improve the occlusion; cosmetic benefit</td>
</tr>
</tbody>
</table>
7.3 Neurocutaneous Syndromes

GIANPIERO TAMBUURINI AND CONCEZIO DI ROCCO

Syndonym. Also known as phakomatoses, a term derived from the Greek root phakos (birthmark) pointing out the common, visible dermatologic manifestations characteristic of these syndromes.

Definition. The neurocutaneous syndromes consist of several heterogeneous disorders, grouped together because of their common manifestation with neurologic, cutaneous and ocular signs. Disorders classified in this group of pathologies include neurofibromatosis (types 1 and 2), tuberous sclerosis complex, von Hippel–Lindau disease, Sturge–Weber syndrome and Rendu–Osler–Weber disease. Less common diseases also categorized as phakomatic syndromes are: Wyburn-Mason disease, nevoid basal cell carcinoma syndrome, proteus syndrome, encephalocraniocutaneous lipomatosis, Cowden's disease, Bannayan–Riley–Ruvalcaba syndrome, Cowden's disease, multiple endocrine neoplasia. Due to their extremely rare occurrence in the neurosurgical practice, these last pathologies will not be dealt with in detail.

7.3.1 Neurofibromatoses

The neurofibromatoses are the most common of the neurocutaneous syndromes. There are at least two distinct disorders in this group that share some features but are both clinically and genetically distinct: the neurofibromatosis types 1 (NF1) and 2 (NF2).

7.3.1.1 Neurofibromatosis Type 1

Synonym. NF1 is also known as peripheral NF or von Recklinghausen’s disease.

Epidemiology. It is the most common form of NF accounting for approximately 96% of the cases with an incidence of 1 in every 4,000 live births. Neither sex prevalence nor a particular preference for race has been described.

Etiology. NF1 is inherited in an autosomal dominant fashion, with nearly complete penetrance but variable expression. However, a positive family history is present in only about 50% of the patients; the other 50% of cases are thought to represent new mutations. The involved gene is a tumor suppressor gene located in the pericentric region of the long arm of chromosome 17; it has an extremely high spontaneous mutation rate with more than 200 varieties identified up to now. The gene product, neurofibromin, is a large ubiquitous cytoplasmic protein which exists in multiple forms in different tissues; it is thought to interact with intracellular cytoplasmic microtubules activity.

Diagnosis and Management. No widely accepted genetic test is available for diagnosis, which is based essentially on clinical features. The latter are not all present at birth; they appear in varying degrees at different patient ages (Table 7.3.1).

Table 7.3.1 National Institute of Health (NIH) consensus development conference on neurofibromatosis criteria for the diagnosis of NF1 [1]; usual time of presentation of clinical signs

<table>
<thead>
<tr>
<th>Diagnostic criteria for NF1 (patient must exhibit two or more of the following):</th>
<th>Usual time of presentation of clinical findings:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Six or more café au lait macules (5 mm or larger in prepubertal patients; 15 mm or larger in postpubertal patients)</td>
<td>Birth/infancy</td>
</tr>
<tr>
<td>2. Two or more neurofibromas of any kind or one plexiform neurofibroma</td>
<td>Adolescence/adulthood</td>
</tr>
<tr>
<td>3. Axillary/inguinal freckling</td>
<td>Late childhood/early puberty</td>
</tr>
<tr>
<td>4. Optic pathway glioma</td>
<td>Childhood</td>
</tr>
<tr>
<td>5. Two or more Lisch nodules (iris hamartomas)</td>
<td>Adolescence/adulthood</td>
</tr>
<tr>
<td>6. Distinctive osseous abnormality (sphenoid wing dysplasia, scoliosis, thinning of long-bone cortex*, pseudoarthrosis*)</td>
<td>Adolescence/adulthood/*birth</td>
</tr>
<tr>
<td>7. A first-degree relative with NF1 as per the above criteria</td>
<td>–</td>
</tr>
</tbody>
</table>
Cutaneous Manifestations:
- Café au lait macules: areas of abnormal skin pigmentation, varying in size from a few millimeters to a few centimeters, with regular borders and an even coloration throughout. Often they are present at birth and are almost evident by the time a child is 1 year of age. With increasing age, spots may increase in size and number with 80% of adults with NF1 having at least six. They occur on most areas of the body, excluding palms, soles of the feet and scalp.
- Skin-fold freckling: freckles a few millimeters in diameter usually found in the submammary, axillary or inguinal regions. Unlike café au lait spots, these lesions may not be evident until late childhood or early puberty.

Ocular Manifestations:
- Lisch nodules: raised, pigmented (yellow-brown), iris hamartomas, easily detected by slit-lamp examination. Often absent in childhood, Lisch nodules increase in prevalence with age: they are found in approximately 94% of postpubertal patients. Histopathologically, they consist of masses of melanocytes.
- Other (unusual) ocular manifestations: congenital glaucoma or eyelid, conjunctival and orbital neurofibromas, thickened corneal, conjunctival and ciliary nerves, retinal astrocytomas and sectorial retinitis pigmentosa.

Musculoskeletal Findings:
- Sphenoid wing dysplasia: the most typical bony lesion leading to pulsatile exophthalmos
- Scoliosis: affects between 10 and 20% of patients, often manifesting in adolescence
- Tibial pseudoarthrosis: may be resistant to treatment and require amputation in up to 80% of patients
- Others: thinning of long bone cortex, limb hyperplasia, vertebral scalloping and (rare) rhabdomyosarcoma

Neurologic Manifestations:
- Peripheral neurofibromas: multiple cutaneous, subcutaneous and peripheral lesions, often distributed in the thoracoabdominal region or around the nipple–areola complex. Histologically benign (malignant transformation, rare), they vary in number from a few to thousands. Mainly they pose a primarily cosmetic problem which is somewhat amenable to local surgical treatment under patient’s request.
- Plexiform neurofibroma: often involves a large peripheral nerve or part of the sympathetic chain with potential for disfigurement (arm/leg hemihypertrophy) or impairment of function of the involved area. Though basically benign, they undergo malignant transformation (malignant peripheral nerve sheath tumor: MPNST) in 6% of cases. For asymptomatic lesions a “wait and see” policy has to be preferred; trials of medical treatment with 13-cis-retinoic acid and interferon alfa-2a are under evaluation. In symptomatic subjects, surgical debulking/removal of the tumor may be attempted. However, there is a high risk of recurrence at the surgical site; moreover, large symptomatic lesions often encase several neural bundles, with a high risk of postoperative neurological deficits. For MPNST, biopsy followed by possible limb amputation, radiotherapy and chemotherapy are advised (5 years survival: 40%).
- Paraspinal neurofibroma: the most common tumors that affect the spine in patients with NF1. Paraspinal neurofibromas generally arise from the dorsal roots in the cervical and lumbar regions; they may grow into the spinal canal via the intervertebral foramen, resulting in dumbbell-shaped lesions. Surgical resection is indicated in all symptomatic subjects and on radiological criteria (mass effect) for the cervicothoracic area (risk of myelopathy secondary to long-term spinal cord compression).
- Optic pathways glioma (Fig. 7.3.1): the most common of the central nervous system manifestations of NF1, affecting approximately 15% of patients. This tumor most commonly occurs during childhood with the greatest risk during the first 6 years of life; females are affected twice as often as males. It has the potential to arise at any point along the optic pathways; however, prechiasmal lesions are the most common. Approximately half of all optic pathway gliomas remain asymptomatic, and the majority of them, including symptomatic ones, rarely progress following diagnosis. Ocular signs are the most frequent clinical manifestation in symptomatic subjects, varying in type and degree according to the tumor extension; 39% of children with chiasmal lesions also present hypothalamic–pituitary dysfunction. Recommendations:
  - Asymptomatic children: all should have serial ophthalmological evaluations, yearly in patients younger than 6. Patients with abnormalities at ophthalmological examination should undergo MRI of the brain and orbits.
  - Symptomatic children: careful follow-up is necessary with ophthalmologic and contrast-enhanced MRI scans performed every 3 months for the first 18 months, followed by assessment at increased intervals if the lesion remains stable. Surgery has limited indications: in children with intraorbital and prechiasmal lesions and blind eye (or proptotic eye with severely compromised vision), surgery may be performed for cosmetic purposes and to prevent the spread of the tumor toward the chiasm. In patients with chiasmatic tumors, surgery may be necessary to debulk large tumors, especially those with cystic components. In the child older than 3 years, radia-
tion therapy is an option; up to 80% of patients may show tumor stabilization/shrinkage. However, also in these cases, radiation therapy poses the risks of neurocognitive and neuroendocrine sequelae, in addition to radiation-induced malignancies. Especially in the last 15 years, a number of clinical series have shown evidence that tumor progression can be delayed using both single and multiagent chemotherapy; consequently, chemotherapy is currently proposed as a first-line treatment, especially in younger patients (<3 years) in whom radiotherapy is contraindicated.

Abnormalities of CSF spaces:
- mild degree of ventricular dilation is a relatively common finding in subjects with NF1; its role in the pathogenesis of psychomotor delay is, however, discussed. Indeed, in most of the cases, the enlargement of the ventricular system is not associated to an increased intracranial pressure and it is not progressive. The same applies at the spinal level to the focal enlargement of the subarachnoid pouches that accompany spinal roots. Only exceptionally do these meningeal dilations become symptomatic by compressing or distorting the spinal roots, consequently requiring treatment (generally CSF shunting).
- Other intracranial tumors and unidentified bright objects: Hemispheric gliomas occur in fewer than 0.5% of NF1 patients, and posterior fossa gliomas occur in 1% of the cases. Most of these tumors do not show any tendency to grow. For this reason, as for optic pathway lesions, a serial monitoring (clinical and radiologic) is appropriate in patients who remain asymptomatic, reserving surgery for symptomatic patients and/or tumors with a tendency to grow. Unidentified bright objects (UBO) are a frequent finding in patients with NF1. They are represented by areas of spontaneous hyperintensity in T2-weighted MRI images, most often involving the basal ganglia, the cerebellum, the brainstem and the subcortical white matter. They are thought to represent areas of spongiform myelinopathy and tend to resolve spontaneously.

Neurological developmental delay:
- 30–65% of NF1 patients manifest some degree of learning disability; in general, language skills are better preserved than visuospatial skills. Attention deficit may also be seen, as well as motor incoordination. In selected cases, these deficits have been related to the presence of UBOs at the MRI scan.

Prognosis. Despite the best medical care, the life expectancy of patients with NF1 remains approximately 15 years less than that of the general population. Malignancy is one of the primary reasons for this reduction in life expectancy among adult patients with NF1, with the overall risk of suffering from some malignant complication being approximately 3–15%.

7.3.1.2 Neurofibromatosis Type 2

**Synonym.** NF2 is also known as bilateral acoustic neurofibromatosis or central neurofibromatosis.

**Epidemiology.** NF2 is a relatively uncommon neurocutaneous syndrome, affecting approximately 1/40,000 live births. Like NF1, it shows no regard for sex or race.

**Etiology.** NF2 is an autosomal dominantly inherited disorder with the causative gene located at the 22q11 locus on the long arm of chromosome 22. The protein product, merlin (also named schwannomin), is believed to function as a cytoskeletal protein. Mutations leading to premature termination of protein translation result in a more severe phenotype.
Neurocutaneous Syndromes

canal are the standard of care for neuroimaging. The management of bilateral vestibular schwannomas in NF2 patients is controversial. Large tumors causing significant brainstem compression should be surgically removed. For smaller and/or asymptomatic tumors, some authors consider early surgery as the best opportunity, in order to achieve total resection and preserve hearing; however, the risk of iatrogenic hearing loss in the patient with functional hearing has led others to advocate conservative management, deferring surgery until tumor growth and/or clinical symptoms occur. Stereotactic fractionated radiation therapy and stereotactic radiosurgery are an alternative; good rates of hearing preservation and tumor control rates up to 98% have been reported. However, long-term follow-up is still lacking; in addition, one must consider the radiation-related risk of inducing malignant tumor transformation or secondary malignancies in the irradiated field.

• Meningiomas: the next most common intracranial pathology. They may be single or multiple and may occur in either a synchronous or metachronous fashion. These meningiomas occur earlier in life than sporadic meningiomas but are histologically benign with no increased incidence of malignancy; therefore, they should be managed as their sporadic counterpart.

• Ependymomas: occur in approximately 20% of NF2 patients; 80% of them are spinal with an additional 10% involving the medulla. As meningiomas, they resemble their sporadic counterpart and should be managed similarly.

• Others: Rare lesions are schwannomas of the trigeminal or other cranial nerves, spinal and peripheral nerve schwannomas.

Table 7.3.2  Diagnostic criteria for NF2 according to the National Neurofibromatosis Foundation Clinical Care Advisory Board (revised from [1])

<table>
<thead>
<tr>
<th>Diagnostic criteria for NF2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite NF2</strong></td>
</tr>
<tr>
<td>Bilateral vestibular schwannomas or</td>
</tr>
<tr>
<td>Positive family history plus unilateral vestibular schwannoma before age 30 or</td>
</tr>
<tr>
<td>Two of: meningioma, schwannoma, glioma, juvenile posterior subcapsular lenticular opacity</td>
</tr>
<tr>
<td><strong>Probable NF2</strong></td>
</tr>
<tr>
<td>Unilateral vestibular schwannoma before age 30, plus one or more</td>
</tr>
<tr>
<td>of: meningioma, schwannoma, glioma, juvenile posterior subcapsular lenticular opacity or</td>
</tr>
<tr>
<td>Two or more meningiomas plus unilateral vestibular schwannoma before age 30 or</td>
</tr>
<tr>
<td>One of: glioma, schwannoma, juvenile posterior subcapsular lenticular opacity</td>
</tr>
</tbody>
</table>

Diagnosis and Management. By using linkage analysis, with markers flanking the NF2 gene, a presumptive diagnosis of NF2 can be made in families with two or more affected individuals. However, this test is relatively time consuming and expensive; therefore, the diagnosis of NF2 still remains largely a clinical one. Diagnostic criteria are outlined in Table 7.3.2.

Approximately 11% of patients are identified while asymptomatic; 90% of symptomatic subjects become so in adolescence/adulthood. New signs and symptoms may develop with increasing age, indicating the need of a long-term continued serial assessment.

Ocular Manifestations:

- Juvenile posterior subcapsular lenticular opacities: the most common ocular findings in NF2, presenting in approximately 50% of patients. These lesions have the potential to cause visual impairment and should be surgically removed.
- Retinal hamartomas
- Epiretinal membranes
- Lisch nodules (rare)

Neurologic Manifestations (Fig. 7.3.2):

- Bilateral vestibular schwannomas: the hallmark of NF2, occurring in 95% of cases. Patients usually become symptomatic during adolescence: sensorineural hearing loss is the most common first complaint. Tinnitus, ataxia, headache and facial nerve dysfunction are usually associated. Brainstem auditory evoked potentials (BAEPs) have a 95% predictive diagnostic value for these tumors and should be considered as a primary investigation tool in asymptomatic subjects. Thin slice axial and coronal MRI views, with and without contrast agent, centered on the internal auditory canal are the standard of care for neuroimaging. The management of bilateral vestibular schwannomas in NF2 patients is controversial. Large tumors causing significant brainstem compression should be surgically removed. For smaller and/or asymptomatic tumors, some authors consider early surgery as the best opportunity, in order to achieve total resection and preserve hearing; however, the risk of iatrogenic hearing loss in the patient with functional hearing has led others to advocate conservative management, deferring surgery until tumor growth and/or clinical symptoms occur. Stereotactic fractionated radiation therapy and stereotactic radiosurgery are an alternative; good rates of hearing preservation and tumor control rates up to 98% have been reported. However, long-term follow-up is still lacking; in addition, one must consider the radiation-related risk of inducing malignant tumor transformation or secondary malignancies in the irradiated field.
- Meningiomas: the next most common intracranial pathology. They may be single or multiple and may occur in either a synchronous or metachronous fashion. These meningiomas occur earlier in life than sporadic meningiomas but are histologically benign with no increased incidence of malignancy; therefore, they should be managed as their sporadic counterpart.
- Ependymomas: occur in approximately 20% of NF2 patients; 80% of them are spinal with an additional 10% involving the medulla. As meningiomas, they resemble their sporadic counterpart and should be managed similarly.
- Others: Rare lesions are schwannomas of the trigeminal or other cranial nerves, spinal and peripheral nerve schwannomas.
7.3.2 Tuberous Sclerosis Complex

**Synonym.** Tuberous sclerosis complex (TSC) is also known as Bourneville's disease.

**Epidemiology.** TSC is the second-most common neurocutaneous syndrome, after NF1, with an incidence of approximately 1 in 6,000 live births and a prevalence in the general population of 1 in 10,000. There is no predilection in regard to race or sex.

**Etiology.** TSC is an autosomal dominantly inherited condition with 80–95% penetrance and variable expression. Up to 50% of cases are thought to be due to new mutations. Two responsible genes have been identified (TSC1 and TSC2). Of the sporadic cases, approximately three quarters are secondary to TSC2 mutations. This gene has been localized on chromosome 16 (16p13.3); the protein product (tuberin) is thought to exhibit GTPase activity, being involved in cellular differentiation and proliferation. The TSC1 gene has been found on chromosome 9 (9q34); it encodes for a protein (hamartin) implicated in the organization of actin cytoskeleton and has a main role in neuronal migration.

**Diagnosis and Management.** The diagnosis of TSC is clinical. Diagnostic criteria are outlined in Table 7.3.3.

**Cutaneous Manifestations:**
- **Ash leaf spots:** dull white polygonal hypopigmented macules often present at birth. Though common, they are not pathognomonic of TSC, being found also in normal subjects.
- **Facial angiofibromas:** acne-like lesions, typically found in a malar distribution. They develop in 75% of TSC patients and are composed of vascular and fibrous dermal tissue.

### Table 7.3.3 Diagnostic criteria for TSC according to the National Institute of Health TSC Consensus Conference

<table>
<thead>
<tr>
<th><strong>Major features:</strong></th>
<th><strong>Minor features:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial angiofibroma or forehead plaque</td>
<td>Multiple randomly distributed dental enamel pits</td>
</tr>
<tr>
<td>Atraumatic ungual/periungual fibroma</td>
<td>Hamartomatous rectal polyp</td>
</tr>
<tr>
<td>Hypomelanotic macule (more than 3)</td>
<td>Bone cyst</td>
</tr>
<tr>
<td>Shagreen patch</td>
<td>Cerebral white matter migration lines</td>
</tr>
<tr>
<td>Multiple retinal nodular hamartomas</td>
<td>Gingival fibromas</td>
</tr>
<tr>
<td>Cortical tuber</td>
<td>Nonrenal hamartomas</td>
</tr>
<tr>
<td>Subependymal nodule</td>
<td>Retinal achromic patch</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma (SEGA)</td>
<td>Confetti-like skin lesions</td>
</tr>
<tr>
<td>Cardiac rhabdomyoma</td>
<td>Multiple renal cysts</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td></td>
</tr>
<tr>
<td>Renal angiomyolipoma</td>
<td></td>
</tr>
</tbody>
</table>

**Definite TSC:** 2 major features or 1 major and 2 minor features

**Probable TSC:** 1 major feature plus 1 minor feature

**Possible TSC:** 1 major feature or 2 minor features

Fig. 7.3.2a,b Axial (a) and sagittal (b) T1 MRI sequences after gadolinium injection of a 14-year-old boy with NF2. A bilateral vestibular schwannoma (a) and a frontal convexity meningioma (b) are documented.
Neurocutaneous Syndromes and bilateral and may result in renal failure in up to 40% of cases.

Neurologic Manifestations:
- **Seizures:** develop in up to 85% of TSC patients. These often represent the first sign of the disorder; 69% of the cases become symptomatic by the first birthday, and most will show evidence of seizures within the first 2–3 years of life. Males are typically affected more than females. EEG and clinical hypsarrhythmia is the most frequent pattern at presentation, but seizures may evolve into a psychomotor or general tonic–clonic form. They are refractory to medical treatment in about 20% of patients, who should be considered for epilepsy surgery.
- **Cognitive dysfunction:** seen in approximately 50% of TSC patients. A strong correlation exists between the age of onset of seizure activity, seizure control and cognitive dysfunction.
- **Cortical tubers:** the most common cerebral lesion seen in TSC. Tubers are hamartomas often found along gray–white junctions of the frontal lobes; however, most patients display multiple lesions affecting both hemispheres and multiple lobes asymmetrically. Pathologically, they consist of gliotic plaques with possible calcifications and cystic degeneration. Upon MRI, they appear as hyperintense on T2-weighted images and iso-hypointense on T1-weighted scans, with minimal enhancement after intravenous contrast administration. Surgical treatment is considered only for the control of related medically refractory seizures.
- **Periungual fibromas:** flesh-colored papules specific of TSC found in 19% of TSC patients during adolescence/adulthood.
- **Shagreen patch:** orange-peel hamartoma, affecting 21% of TSC patients. It is most commonly seen in the lumbar region. Like ash leaf spots, it is not a pathognomonic sign.

Ocular Manifestations:
- **Retinal phakomas (astrocytomas):** seen in 50–75% of TSC patients. They are mulberry-like lesions, often diagnosed at birth as an absent red reflex. They do not cause impairment of vision (Fig. 7.3.3c).
- **Achromic retinal patches**

Cardiac and Respiratory Manifestations:
- **Cardiac rhabdomyoma:** occurs in up to one half of TSC patients. In most cases, they do not cause clinical impact. Less commonly, heart failure, arrhythmias or thromboembolic events may occur; medical management is appropriate in most patients, as these lesions tend to disappear as the child ages spontaneously. Surgery should be reserved for acutely presenting cases.
- **Pulmonary lymphangioleiomyomatosis:** occurs in 2–5% of affected females during their fourth decade. May be a fatal complication (dyspnea, hemoptysis, spontaneous pneumothorax).

Renal Manifestations:
- **Benign angiomyolipoma:** affects 70–80% of patients with TSC; occurs bilaterally in about three quarters of the cases, manifesting generally in late childhood. Larger lesions should be considered for surgery.
- **Renal cysts:** the second most common renal lesion affecting 20% of TSC patients. They are often multiple and bilateral and may result in renal failure in up to 40% of cases.

Neurologic Manifestations:
- **Seizures:** develop in up to 85% of TSC patients. These often represent the first sign of the disorder; 69% of the cases become symptomatic by the first birthday, and most will show evidence of seizures within the first 2–3 years of life. Males are typically affected more than females. EEG and clinical hypsarrhythmia is the most frequent pattern at presentation, but seizures may evolve into a psychomotor or general tonic–clonic form. They are refractory to medical treatment in about 20% of patients, who should be considered for epilepsy surgery.
- **Cognitive dysfunction:** seen in approximately 50% of TSC patients. A strong correlation exists between the age of onset of seizure activity, seizure control and cognitive dysfunction.
- **Cortical tubers:** the most common cerebral lesion seen in TSC. Tubers are hamartomas often found along gray–white junctions of the frontal lobes; however, most patients display multiple lesions affecting both hemispheres and multiple lobes asymmetrically. Pathologically, they consist of gliotic plaques with possible calcifications and cystic degeneration. Upon MRI, they appear as hyperintense on T2-weighted images and iso-hypointense on T1-weighted scans, with minimal enhancement after intravenous contrast administration. Surgical treatment is considered only for the control of related medically refractory seizures.
- **Subependymal nodules:** periventricular hamartomas typically located at the level of the caudate nucleus and striothalamic zone of the lateral ventricle; they are composed of glial and vascular tissue and covered

**Fig. 7.3.3a–c** Coronal (a) and axial (b) T1 MRI sequences after gadolinium injection of a 10-year-old boy with tuberous sclerosis and left foramen of Monro subependymal giant astrocytoma (SEGA). The fundus oculi examination (c) shows the presence of retinal phakomas (astrocytomas), a further typical aspect of this syndrome.
by ependymal tissue. Subependymal nodules are considered benign lesions, and no specific treatment for them is needed. They do have, however, the potential for malignant transformation and as such should be followed in time.

- **Subependymal giant cell astrocytomas (SEGAs)** (Fig. 7.3.3a,b): thought to be unique to TSC. SEGAs occur in approximately 6% of patients with TSC, arising along the terminal sulcus near the foramen of Monro. Pathologically, they are believed to arise from transformation of a subependymal nodule. The vast majority is located within the ventricles at the foramen of Monro; occasionally, a similar form may be found within the brain parenchyma, secondary to the degeneration of a cortical tuber. Symptoms of increased intracranial pressure (due to the development of secondary hydrocephalus) or a change in seizure frequency or pattern are the most common manifestations at clinical onset. Radiologically, SEGAs are suggested by a rapidly increasing subependymal nodule showing significant contrast enhancement. The standard of treatment for SEGAs is complete surgical excision, performed through a transcortical or transcallosal approach. For patients in whom complete surgical excision is possible, postoperative shunting for the associated hydrocephalus is generally not required.

**Prognosis.** Long-term outcomes and quality of life for patients with TSC are as variable as the disease expression itself. Patients with mild forms of the disorder can lead full lives without obvious impairment. For others, the degree of disability can be significant with a significant reduction in life expectancy. Long-term survival is mostly conditioned by the wideness of expression of neurologic (epilepsy, SEGAs, hydrocephalus) and renal (renal failure in patients with multiple and/or bilateral kidney cysts) manifestations.

### 7.3.3 Von Hippel–Lindau Disease

**Synonym.** Von Hippel-Lindau disease (VHL) is also named retinocerebellar angiomatosis.

**Epidemiology.** VHL is a relatively uncommon neurocutaneous syndrome, affecting approximately 1 in 40,000 live births.

**Etiology.** VHL is an autosomal dominant inherited disease with high penetrance (70%) and variable expression. The cause of this disorder is thought to involve a tumor suppressor gene, or possibly a linear arrangement of genes on the short arm of chromosome 3 (3p25–26).

- **Ocular Manifestations:**
  - **Retinal hemangioblastomas:** affect 50% of VHL patients. These lesions are often peripherally situated and multiple and tend to occur bilaterally. Diagnosis is aided by the use of fluorescein angiography. Due to the related risk of hemorrhage, retinal hemangioblastomas should be treated also in asymptomatic patients; laser therapy is the mainstay for their management.

**Neurologic Manifestations:**

- **Hemangioblastoma (HB):** the most frequent finding in patients with VHL disease. In this disorder, 75% of all HBs occur in the cerebellum, with most of the remaining lesions occurring in the spinal cord. Hemispheric or brainstem lesions are rare. Patients with cerebellar lesions usually present with symptoms of intracranial hypertension (headache, vomiting), which, in selected cases, may be acute due to tumor hemorrhage. MRI usually shows a T1 hypointense, T2 hyperintense nodule, with an associated cystic component. The nodule usually abuts the pial surface and shows a bright enhancement after contrast administration. For smaller lesions, angiography still provides the most sensitive evaluation. Treatment consists in total surgical removal of the mural nodule; the cyst wall does not need to be completely removed. Spinal HBs are pathologically similar to the cerebellar variety; they are typically intramedullary lesions, although almost all will abut the pial surface of the cord. They may be associated with a syrinx. Surgical excision is the treatment of choice.

**Other Unusual Manifestations.** Uncommon lesions associated with VHL disease include pancreatic cysts, renal cell carcinoma and pheochromocytoma.

### 7.3.4 Sturge–Weber Syndrome

**Synonym.** Sturge–Weber syndrome (SWS) is also known as encephalotrigeminal angiomatosis.

**Epidemiology.** SWS is a relatively uncommon neurocutaneous disorder involving the vasculature of the skin, meninges, eyes and brain. No figures are available regarding the incidence of this disorder in the general population. There does not appear to be any racial or sexual prevalence.

**Etiology.** Little is known regarding the genetics of SWS. No clear pattern of inheritance has been demonstrated, and therefore most investigators believe it to be secondary to new somatic mutations rather than germline mutations.

**Diagnosis and Management.** The primary clinical manifestations of Sturge–Weber syndrome include a congenital unilateral facial nevus, seizures, mental retardation, hemiparesis and impaired vision (glaucoma).
Neurocutaneous Syndromes

in approximately 80% of the patients, most often with an onset during the first year of life. Adequate medical seizure control is possible in approximately 40% of cases. Indications for epilepsy surgery are debated. Some authors recommend early surgery, before any obvious motor deficit occurs, in order to prevent irreversible neurologic damage. Others recommend surgery only for patients with intractable seizures and progressive neurologic deficits. Multiple techniques have been employed, including peri-insular functional hemispherectomy and anatomic hemispherectomy. Following surgery, up to 65% of patients may be seizure-free.

7.3.5 Hereditary Hemorrhagic Telangiectasia

Synonym. Hereditary hemorrhagic telangiectasia (HHT) is also known as Osler–Rendu–Weber disease.

Epidemiology. HHT is a relatively uncommon disease, with a calculated prevalence of 1/39,000 live births.

Etiology. HHT is an autosomal dominant condition. Two genes have been individuated: (1) on chromosome 9 encoding for endoglin, the most abundant growth factor binding protein in endothelial cells and (2) on chromosome 12, encoding for activin receptor-like kinase 1, a protein involved like endoglin in vascular development.

Diagnosis and Management. HHT primarily manifests with the development of angiodysplasias (telangiectasias, arteriovenous malformations) in various organ systems. The respiratory apparatus and the central nervous system are the most frequently involved sites.

Cutaneous Manifestations:

• Facial nevus (port-wine stain): often found in the V1-V2 regions of innervation by the trigeminal nerve. It may be the diagnostic feature of SWS in many patients. The nevus may be a transient, midline salmon patch or a persistent laterally located port-wine stain. Occasionally, it may be bilateral or extended to the lips, neck or trunk. In the unusual forme frustes, it may be absent. Treatment of this cutaneous lesion consists in a laser photothermolysis.

Ocular Manifestations:

• Glaucoma: the most frequent ocular manifestation affecting between 30 and 50% of SWS patients, generally before age 2. This finding is generally unilateral and ipsilateral to the facial nevus. Trabeculotomy may be required for the treatment of this condition.

• Choroidal hemangiomas: unusual; may cause retinal or choroidal detachment with visual loss, necessitating surgical intervention, external beam irradiation or photocoagulation.

Neurologic Manifestations:

• Leptomeningeal venous angiomatosis: prevalently located in the parieto-occipital region and usually ipsilateral to the facial nevus; bilateral in 15% of cases. This leptomeningeal angiomatosis consists of thin-walled veins within the pia mater. As a result, meninges often become thickened and dark red purple colored. Due to steal phenomena, the underlying brain usually shows signs of cortical atrophy. In CT scans, calcifications and reduced volume of the involved hemisphere/s is evident (Fig. 7.3.4a). MRI images are diagnostic, showing the multiple flow void pial signal of the vein's angiomatosis (Fig. 7.3.4b). Reported associated neurologic symptoms include hemiparesis, visual field defects, intellectual impairment and seizures. The latter occur in approximately 80% of the patients, most often with an onset during the first year of life. Adequate medical seizure control is possible in approximately 40% of cases. Indications for epilepsy surgery are debated. Some authors recommend early surgery, before any obvious motor deficit occurs, in order to prevent irreversible neurologic damage. Others recommend surgery only for patients with intractable seizures and progressive neurologic deficits. Multiple techniques have been employed, including peri-insular functional hemispherectomy and anatomic hemispherectomy. Following surgery, up to 65% of patients may be seizure-free.

7.3.5 Hereditary Hemorrhagic Telangiectasia

Synonym. Hereditary hemorrhagic telangiectasia (HHT) is also known as Osler–Rendu–Weber disease.

Epidemiology. HHT is a relatively uncommon disease, with a calculated prevalence of 1/39,000 live births.

Etiology. HHT is an autosomal dominant condition. Two genes have been individuated: (1) on chromosome 9 encoding for endoglin, the most abundant growth factor binding protein in endothelial cells and (2) on chromosome 12, encoding for activin receptor-like kinase 1, a protein involved like endoglin in vascular development.

Diagnosis and Management. HHT primarily manifests with the development of angiodysplasias (telangiectasias, arteriovenous malformations) in various organ systems. The respiratory apparatus and the central nervous system are the most frequently involved sites.

Cutaneous Manifestations:

• Telangiectasias: usually occur in the second and third decade of life; the sites most frequently involved are
the lips and tongue in over two thirds of the patients and fingers and nails with a similar frequency. Cutaneous telangiectasias are usually of no medical importance, but they might be helpful in the diagnosis.

**Respiratory Apparatus Manifestations:**
- *Nasal mucosa telangiectasias*: considered the hallmark of this condition, occurring in 90% of the patients. Their clinical manifestation is with frequent nosebleeds. Cauterization, laser ablation and transcatheter embolotherapy have been proposed for their management.
- *Pulmonary arteriovenous malformations*: affect 5–15% of patients with HHT. Lesions are often multiple and affect both lungs. Due to the high risk of spontaneous bleeding with consequent hemothorax, treatment through transcatheter embolization is indicated also in asymptomatic patients.

**Neurologic Manifestations:**
- *Ischemic stroke*: the most frequent neurologic manifestation. It is related to emboli coming from a coexistent pulmonary vascular malformation.
- *Cerebral vascular malformations*: occur in 5–15% of HHT patients. Telangiectasias, saccular aneurysms, parenchymal arteriovenous malformations and carotid-cavernous fistulas have all been described. They tend to be multiple; a multidisciplinary treatment (surgery, radiosurgery, endovascular treatment) is often required.

**Suggested Reading**
7.4 Hydrocephalus

**Federico Di Rocco, Matthew Garnett, Thomas Roujeau, Stephanie Puget, Dominique Renier, Michel Zerah and Christian Sainte-Rose**

### 7.4.1 Definitions

Hydrocephalus is defined as the abnormal accumulation of cerebrospinal fluid (CSF), within all or part of the ventricular system, which is currently, or has been, at an abnormally high pressure.

The increased CSF volume in hydrocephalus is not the result of brain atrophy or dysgenesis of the brain.

The following terms are used in neurosurgery:

- **Communicating/non-communicating hydrocephalus:** Historically, these terms come from the injection of a contrast material into the ventricles. The hydrocephalus is divided into the two types according to the visualisation of the contrast at the level of the lumbar thecal sac by a lumbar puncture (LP). This term remains in favour because it is useful to distinguish patients who can be treated by an endoscopic third ventriculostomy and those who will likely require a ventriculoperitoneal shunt.

- **Normal pressure hydrocephalus:** usually used to describe chronic hydrocephalus in adults in which the baseline intracranial pressure (ICP) is within normal limits, manifesting itself by a syndrome described by Hakim.

- **Benign external hydrocephalus:** describes enlarged subarachnoid spaces with an associated enlarged head circumference. It is a self-limiting condition, observed during the first few months of life, usually in boys, and resolves within 1–2 years. It has been hypothesised that it could be related to a delayed maturation of the arachnoid villi. This is not a pathological condition requiring treatment.

- **Arrested hydrocephalus:** a condition in which there are asymptomatically enlarged ventricles.

- **Hydrocephalus ex vacuo:** a misnomer. Cerebral atrophy results in a vacant space that is passively filled with CSF.

### 7.4.2 Pathophysiology

Normal CSF production is 0.20–0.35 ml/min (360–500 ml/day) (Gaussian distribution as with any other biological parameter). Production is an active phenomenon. It is independent of pressure. Most CSF production is from the choroid plexus (70–90%); some is from the ependymal lining of the ventricles and some from the endothelium of the brain capillaries.

CSF flows through the ventricular system and into the sub-arachnoid space via the foramina of the fourth ventricle. The CSF is then absorbed at the arachnoid villi into the venous system (essentially at the level of the dural sinuses). Absorption is a passive phenomenon. The rate of CSF resorption depends on CSF pressure.

Total adult CSF volume is 120 ml; normal lateral and third ventricle volume is 25 ml. Childhood CSF volumes are variable, with approximately 50 ml in the neonate.

ICP (defined as the CSF hydrostatic pressure) is the result of the balance that exists between CSF production, CSF flow resistance and CSF reabsorption into the venous compartment. It varies according to the vasoreactivity in the arterial system (e.g. increased during activity and REM sleep) and the venous pressure (e.g. reduced in the upright position).

Hydrocephalus can occur in three different conditions:

1. Increased resistance to CSF circulation at any point from its production at the choroid plexus to its reabsorption at the arachnoid villi (this accounts for more than 95% of the cases).
2. Overproduction of CSF in a patient with normal resistances.
3. Increased venous pressure in the sinuses (increased back pressure) may cause hydrocephalus or pseudo tumour cerebri depending upon the degree of cranial compliance.

### 7.4.3 Aetiology

Hydrocephalus comprises a highly heterogeneous group of conditions which have little in common aside from the dilatation of CSF spaces. The aetiological diagnosis of hydrocephalus is essential, as the prognosis depends largely on the causal mechanism. However, in 14% of the cases, the cause cannot be identified.
The following aetiological factors are present in infants, children and adults:

1. Congenital
   a) Genetic (e.g. X-linked hydrocephalus)
   b) Infection (e.g. toxoplasmosis)
   c) Malformations (e.g. Dandy–Walker, Chiari, stenosis of the aqueduct of Sylvius) (Fig. 7.4.1)

2. Acquired
   a) Increased resistance to CSF circulation
      - Infection (e.g. meningitis) (Fig. 7.4.2)
      - Intraventricular haemorrhage (IVH) (e.g. related to prematurity, SAH) (Fig. 7.4.3)
   b) Increased CSF production (e.g. choroid plexus tumour) (Fig. 7.4.5)
   c) Increased venous sinus pressure (e.g. venous sinus thrombosis, achondroplasia)
   d) Iatrogenesis (e.g. excess vitamin A, posterior fossa surgery)
   e) Idiopathic

The causes of the chronic hydrocephalus of adults include mainly sub-arachnoid haemorrhage (SAH), head injury and meningitis. Many cases are idiopathic.
The frequency of congenital or early onset hydrocephalus is 3/1,000 births (Fig. 7.4.6). The frequency of acquired hydrocephalus is unclear, though for example it occurs in about 10% of patients following an SAH. There are no sex differences except for X-linked hydrocephalus.

Bimodal age distribution has been found, one in infancy (0–10 years) related to congenital and early childhood pathology and the second in adulthood (40–70 years) related to secondary communicating hydrocephalus and chronic hydrocephalus in adults.

Clinical symptoms based on age range include:
- **Infants**: poor feeding, vomiting, irritability, enlarged head circumference, delay in developmental milestones
- **Children**: headaches, vomiting, visual disturbance, neck pain, poor scholarly performance, unsteady gait, drowsiness; can be asymptomatic
- **Adults**: headaches, vomiting, visual disturbance, neck pain, drowsiness, cognitive decline, unsteady gait, incontinence

The classic triad of Hakim for chronic hydrocephalus in adults is cognitive decline, unsteady gait and incontinence.

Clinical signs based on age range include:
- **Infants**: enlarged head circumference, tense anterior fontanelle, dilated scalp veins, suture disjunction, transilluminable skull, sun-setting eyes, increased limb tone
- **Children**: papilloedema, failure of upward gaze, VI nerve palsy, Macewen’s sign (cracked pot sound on skull percussion), unsteady gait, reduced level of consciousness, epileptic seizures, bobble-head-doll syndrome
- **Adults**: papilloedema, failure of upward gaze, VI nerve palsy, unsteady gait, brisk lower limb reflexes, reduced level of consciousness

In chronic adult hydrocephalus, patients often have difficulty walking, ranging from a mild imbalance to inability to stand or walk in addition to urinary incontinence and cognitive decline.

1. **Imaging**: ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) to assess ventricular size, the hydrocephalus aetiology or type and exclude other pathologies (e.g. Chiari malformation, IV ventricle tumours, venous sinus thrombosis)
   a) Acute hydrocephalus
      - Both temporal horns greater than 2 mm with no visible Sylvian or interhemispheric fissures
      - Frontal horn width/biparietal width > 30% (Evans ratio)
      - Transependymal absorption of CSF (Fig. 7.4.2)
   b) Chronic hydrocephalus
      - Erosion of sella turcica from III ventricle herniation
      - Macrocrania
      - Atrophied corpus callosum (Fig. 7.4.4)

2. **Lab tests**: of limited value except:
   a) To confirm if X-linked hydrocephalus and to use in genetic counselling
   b) To assess for infection and protein content in the CSF in post-infectious and/or post-haemorrhagic hydrocephalus

Surgical treatment is the main therapeutic option. Repeat LPs may be used:
1. In infants with intraventricular haemorrhage to allow the condition to resolve spontaneously
2. In chronic hydrocephalus of adults to assist with the diagnosis and to temporise the clinical decline
7.4.8.1 Surgical Options

The surgical treatment of hydrocephalus has been radically modified by the development of endoscopic procedures. Such technique may also be indicated in case of CSF shunt failure. In some cases, both internal and CSF diversion techniques may be used (e.g. multiloculated postmeningitic hydrocephalus).

1. Alternatives to shunts:
   a) Endoscopic third ventriculostomy: used in obstructive hydrocephalus where the level of obstruction is distal to the III ventricle (e.g. pineal region tumour, aqueduct stenosis)
   b) Aqueductoplasty: endoscopic or open disruption of an obstacle within the aqueduct (e.g. a membrane) and placement of a stent; allows the obstruction to be bypassed
   c) Choroid plexotomy or coagulation: unlikely to be successful if used as the only method of treatment except for the treatment of choroid plexus hypertrophy

2. CSF shunts:
   a) Ventriculo-peritoneal: the most commonly used
   b) Ventriculo-atrial: useful if the patient has significant abdominal abnormalities (e.g. previous peritonitis) or patients with hydrocephalus secondary to optic-chiasmatic or hypothalamic tumours
   c) Lumbo-peritoneal: occasionally used in communicating hydrocephalus
   d) Torkildsen: rarely used; shunts CSF from the ventricles to the cisternal space
   e) Ventriculo-pleural: used as a last resort because of the risk of development of a pleural effusion
   f) Ventriculo-gallbladder: used as a last resort in cases of failure of ventriculo-pleural and ventriculo-atrial shunt
   g) Ventriculo-transverse sinus: as above
   h) Extrathecal: may be used temporarily

7.4.8.2 Shunt Valves

There is a large choice of shunt valves. Essentially, either a pressure or flow-controlled valve can be used. Additional considerations are whether to use an anti-syphon device or externally adjustable valve. All ventriculo-peritoneal shunts have a 25% failure rate by 6 months, related to surgical technique and proximal occlusion. Most ventriculo-peritoneal shunts have an actuarial probability of failure of 40–50% by 5 years. The only published exception to this is the Orbis-Sigma valve (flow regulated) that has a reported probability of survival at 5 years of 75%.

7.4.8.3 Medical Treatment

The following medical treatments are occasionally used as a temporising measure (e.g. in infants with IVH, pseudo tumour cerebri):

1. Acetazolamide: a carbonic anhydrase inhibitor; reduces the CSF production at the choroid plexus and may cause hypokalaemia and hyperchloraemic acidosis
2. Furosemide: a Henle’s loop diuretic; lowers cerebral sodium uptake and increases renal water excretion.

7.4.9 Complications

The following complications can arise:

1. Hydrocephalus progression:
   a) Visual changes due to optic atrophy from chronic papilloedema, optic chiasm compression from III ventricle dilatation, transtentorial herniation compressing posterior cerebral arteries
   b) Cognitive dysfunction
   c) Incontinence
   d) Gait disturbance

2. Surgical:
   a) Endoscopic third ventriculostomy:
      – Rare but life threatening intraoperative complications
      – Early failure to control hydrocephalus (depending mostly on age and aetiology)
      – Late failure; may be life threatening in the case of acute hydrocephalus recurrence (secondary closure of the stonia)
   b) Shunt complications:
      – Infection: 2.5% in the best series; higher in most units
      – Shunt failure: obstruction or disconnection; 30% failure by 1 year, 90% failure by 10 years (for most valves)
      – Subdural haematoma: from acute overshunting

Less common complications include seizures, hardware erosion through the skin or visera, septicaemia, shunt nephritis and cor pulmonare from a ventriculo-atrial shunt. Chronic shunt overdrainage and slit ventricle syndrome may occur, especially in patients shunted at a young age. These complications are likely to be reduced, if not avoided, by the use of a flow-controlled valve.

7.4.10 Prognosis

Prognosis is related to the cause of hydrocephalus. Hydrocephalus present at birth (congenital or secondary...
Ongoing care includes patient education regarding the symptoms and signs of shunt malfunction/infection. Education of children should be frequent. Regular clinical reviews (including neurosurgical, ophthalmological and imaging) are advised.

Suggested Reading


foetal hydrocephalus) has a poor prognosis with a 60% survival at 10 years, and less than 20% have a normal IQ. Of the infants with an IVH, 50% will require a shunt. Of the children with a posterior fossa tumour, 20% will require a permanent CSF diversion. Of the adults with chronic hydrocephalus, 60% have improvement in their gait – if the gait disturbance was the initial and predominant symptom.
8.1 Epilepsy

8.1.1 Outcome and Long-Term Perspectives in Epilepsy Surgery

ULRICH SURE AND DOROTHEA MILLER

8.1.1.1 Objective

This section describes the long-term outcome of the following resective epilepsy surgery techniques:
- **Type 1:** temporal epilepsy without focal lesions
- **Type 2:** extratemporal epilepsy without focal lesions
- **Type 3:** lesionectomy for:
  - (a) Vascular lesion
  - (b) Non-vascular lesion

When the outcome of epilepsy surgery is assessed, it is usually evaluated whether the patient is either suffering no more or rarely disabling seizures, or experiences at least a worthwhile improvement. A classification addressing these criteria was introduced into the literature by Engel et al. in 1993:
- **Class I:** free of disabling seizures
  - a) Completely seizure free since surgery
  - b) Non-disabling simple partial seizures only since surgery
  - c) Some disabling seizures after surgery, but free of disabling seizures for the last 2 years
  - d) Generalized convulsions only with antiepileptic drug (AED) discontinuation
- **Class II:** rare disabling seizures (“almost seizure free”)
  - a) Initially free of disabling seizures but has rare seizures now
  - b) Rare disabling seizures since surgery
  - c) More than rare disabling seizures since surgery, but rare seizures for the last 2 years
  - d) Nocturnal seizures only
- **Class III:** worthwhile improvement
  - a) Worthwhile seizure reduction
  - b) Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years
- **Class IV:** no worthwhile improvement
  - a) Significant seizure reduction
  - b) No appreciable change
  - c) Seizures worse

The outcome for patients operated upon for neoplastic lesions (type 3b) should not only be assessed for the outcome of the epilepsy syndrome but also for the tumor-dependant overall survival.

8.1.1.2 Modern Literature Review

The outcome of epilepsy surgery is critically dependant on the underlying pathology and location of the lesion. Therefore, the various outcome data are presented below according to the above-mentioned types of resective epilepsy surgery.

8.1.1.2.1 Type 1

In a randomized, controlled trial, temporal lobe epilepsy surgery (type 1) was found to be superior to prolonged medical therapy. At one year, the cumulative proportion of patients who were free of seizures impairing awareness was 58% in the surgical category compared to 8% in the nonsurgical group [20]. It has also been shown that the outcome of temporal lobe epilepsy surgery is negatively influenced by left-sided surgery and the MRI presence of focal cortical dysplasias (FCD) [10]. The best results are achieved when a hippocampal sclerosis is diagnosed preoperatively, with a 70–90% Engel Class I outcome [2, 3, 14]. The most important factor in achieving the long-term success (Engel Class I outcome) of temporal lobe epilepsy surgery is response within the first follow-up year [3]. An older age and a longer epilepsy duration seem to be negative parameters when the outcome of temporal lobe epilepsy is investigated [10], thus implying that surgery should be performed in these cases as early as possible.

8.1.1.2.2 Type 2

Although patients with extratemporal surgery might also have a good seizure control in up to 60% of the cases [13, 15], the results are usually not as excellent as for temporal lobe surgery (type 1) [18]. The outcome is usually more favorable when a focal lesion is diagnosed by preoperative MRI [7, 12, 22]. In extratemporal epilepsy patients with a “negative” (normal or non-localizing) MRI, subdural grid electrodes are an effective method to uncover the epileptogenic cortex.
8.1.1.2.3 Type 3a
In cavernomas, a seizure control can be reached in about 70% of patients [8], whereas the success numbers might be smaller for patients suffering from an arteriovenous malformation (AVM) and epilepsy, particularly when the AVM had already caused a hemorrhage prior to surgery [16].

8.1.1.2.4 Type 3b
Patients treated for low-grade gliomas and epilepsy by pure lesionectomy may have good long-term seizure control [9]. However, when epilepsy patients with high-grade gliomas are analyzed, their outcome is mainly influenced by their specific tumor biology.

8.1.1.2.5 General
Regardless of the underlying pathology, Janszky et al. recently stated that one third of the patients who did not become seizure free after surgery may achieve seizure control on long-term follow-up. In another proportion of selected patients, even a resective reoperation may make some sense [17]. There does not seem to be a correlation of long-term seizure control between patients with normal (only operated upon after invasive monitoring) or abnormal neuroimaging [1]. In a recent meta-analysis including all types of surgery [18], on average, 20% of the patients achieved long-term antiepileptic drug discontinuation, while 41% were on monotherapy and 31% remained on polytherapy.

Children achieved better AED outcomes than adults. Non-controlled studies consistently reported improved long-term psychosocial outcomes, but the effect was less clear in controlled studies. Intelligence was unchanged by surgery, but long-term memory outcomes were associated with seizure freedom and side of temporal lobe resection. Few long-term, controlled studies exist. In these, longer follow-up was associated with lower rates of AED discontinuation, reflecting lower seizure-free rates over time. Cognitive and psychosocial outcomes were similar to those of short-term studies, and the results were influenced by the presence of controls [19].

8.1.1.3 Recent Clinical and Research Development
Recently, the Engel-outcome classification was amended and simplified according to the proposal of the International League Against Epilepsy (ILAE). This proposal includes the following classifications:
1. Completely seizure free
2. Only auras, no seizures
3. One to three seizure days per year (additional auras included)
4. Four seizure days per year to 50% reduction of baseline seizures
5. Less than 50% reduction to 100% increase of baseline seizures per year
6. More than 100% increase of baseline seizures per year

However, so far, Engel’s classification is mainly usually used to assess outcomes. Several prospective studies evaluating the effect of resection and outcome are on the way. Moreover, the prospective value of preoperative and advanced neuroimaging [particularly of high-field (3 Tesla) MRI] is evaluated more and more. In addition, more patients with histologically proven (routine imaging negative) FCD are diagnosed, some of which may suffer from dual pathologies [4, 6].

8.1.1.4 Future Questions and Directions
Future topics of neurosurgical interest comprise the various types of intraoperative imaging and resection control, such as MRI or ultrasound. Topics also include the increase in quality of preoperative high-field MR imaging that will show us an increasing amount of pathologic lesions (for example, FCDs) in patients who are so far considered “MRI negative.” Furthermore, functional imaging, tractography and new image processing techniques [4] will help to (1) predict the individual risk and (2) securely operate upon patients suffering from epileptogenic lesions in even highly eloquent brain areas. So far, these individuals might only be considered for an explorative awake craniotomy procedure.

8.1.1.5 Conclusion
The long-term outcome of epilepsy surgery is more effective when compared to conservative treatment of epilepsy. It is usually beneficial for the patients treated and mainly depends on the underlying pathology and localization. Recently, high-field MR imaging has provided preoperative evidence for rarely visualized pathologies that can be treated surgically. A wider distribution of high-field MR scanners and innovative imaging techniques may contribute to a decrease of invasive monitoring procedures such as subdural grid placement.

Suggested Reading

8.1.2 Epilepsy: Specific Aspects in Children

LUCA MASSIMI, DOMENICA I. BATTAGLIA, AND CONCEZIO DI ROCCO

8.1.2.1 Drug-Resistant Epilepsy

Drug-resistant epilepsy (DRE) in children can be defined as “persistence of an average of at least one seizure per month, for at least two (or three) years, in a patient treated with at least three different anti-epileptic drugs (AEDs), either alone or in association” [2], with the failure of AEDs resulting also from their unacceptable side effects. However, there is not a single accepted definition, especially due to possible remission periods. Unlike in adults, the duration of symptoms and the number of...
Epilepsy affects 1% of the pediatric subjects during the first two decades of life [2]. The incidence is about 5–7 cases/10,000 children. Although the real incidence of DRE is unknown, the estimated rate among the epileptic population is 5%. DRE represents a significant social problem, especially when children are involved. Medical and social direct and indirect costs are particularly high due to the early onset. The estimated cost for a drug-resistant patient was calculated around US $136,602 per year in 1994 versus US $4,272 per year for a patient with responsive seizures [1].

Presence of neonatal seizures, early onset, high frequency (more than 20 seizures before AED administration), poor initial response to AEDs, occurrence of status epilepticus, association with severe neurological deficits/mental retardation and less than a 3-year-long seizure-free period are the main risk factors for the development of pediatric DRE. The early age at onset is reported to be the most important prognostic factor. Electroencephalogram (EEG) features do not seem to correlate with the prognosis.

Surgery represents the alternative treatment of DRE. The current trend is to anticipate the surgical treatment to preserve cerebral functions from the adverse effects of refractory seizures and of AEDs. Nevertheless, several selection criteria have to be satisfied (Table 8.1.1).

### 8.1.2.3 Main Etiological Forms

#### 8.1.2.3.1 Malformations of Cortical Development

Malformations of cortical development (MCD), also known as neuronal migration disorders or cortical dysplasias, include a heterogeneous group of lesions resulting from the alteration of three embryological steps occurring between the 8th and 16th week of fetal life: cell proliferation of the germinal layers, neuronal migration and organization of the cells within the cortex. Such an altered corticogenesis may be genetically determined or may result from exogenic injuries (intrauterine and/or even perinatal insults), even though its etiopathogenesis is often obscure. The complex and multifactorial etiopathogenesis of MCD explains their possible association with some neurological syndromes (Table 8.1.3).

MCD are one of the prominent causes of pediatric DRE, with up to 40% of the children with DRE and a half of those undergoing epilepsy surgery being affected by MCD. Even though electrocorticography demonstrates the epileptogenicity of the dysplastic cortex, the intrinsic mechanisms of seizure onset still remain essentially unknown. Recent molecular investigations on animal and human cells point to the role played by the NMDA and AMPA receptors for glutamate.

#### 8.1.2.2 Catastrophic Seizures in Infancy and Childhood

The most severe aspect of DRE in children is the so-called catastrophic epilepsy (CE) that is the occurrence of frequent and invaliding seizures and developmental delay. The risk of developing CE is much higher in symptomatic epilepsies than in idiopathic ones. The main characteristics of CE can be summarized as follows: onset during infancy or childhood, poor response to the common AEDs, poor quality of life, high risk of neuromorbidity and mortality. Premature mortality is reported in up to 30% of the symptomatic catastrophic seizures. CE can result in epileptic encephalopathy, a condition in which cognitive, sensory and/or motor functions are altered by the seizures themselves. Ablative or disconnective surgery is required in the case of unilateral and structural brain damage, while indirect surgery (e.g. vagus nerve stimulation) may be indicated in particular cases.

CE represents a small portion of all epilepsies. In infants and children, it is usually associated to the syndromes reported in Table 8.1.2.

### Table 8.1.1 Selection criteria of candidates for surgery for intractable epilepsy

<table>
<thead>
<tr>
<th>General criteria</th>
<th>Specific criteria</th>
<th>Hemispherectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Verification of seizure occurrence</td>
<td>– Assessment of the localization of the epileptic “lesion”</td>
<td>– Presence of contralateral motor deficit</td>
</tr>
<tr>
<td>– Verification of drug resistance</td>
<td>– Correlation between lesion and epilepsy</td>
<td>– Assessment of homolateral EEG alterations</td>
</tr>
<tr>
<td>– Patient’s and/or family’s motivation</td>
<td>– Favorable anatomical conditions for surgical excision</td>
<td>– Assessment of the integrity of the contralateral hemisphere</td>
</tr>
<tr>
<td>– Patient’s and/or family’s compliance</td>
<td>– Absence of progressive neurological disease</td>
<td>– Ineffectiveness of partial resection</td>
</tr>
<tr>
<td>– Possible clinical and social improvement</td>
<td>– Absence of unfavorable psychological/cognitive conditions</td>
<td></td>
</tr>
</tbody>
</table>

AEDs are not considered as absolute criteria in children, especially in the case of early catastrophic seizures.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset</th>
<th>Etiology/associated lesions</th>
<th>Seizures (sz)</th>
<th>EEG</th>
<th>Evolution</th>
<th>Prognosis</th>
<th>Medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohtahara syndrome (early infantile epileptic encephalopathy with suppression–bursts)</td>
<td>Infancy (first month)</td>
<td>Brain malformations, metabolic disorders</td>
<td>Tonic spasms, partial sz, myoclonic sz</td>
<td>Suppression–bursts°</td>
<td>West syndrome, Lennox–Gastaut syndrome</td>
<td>Severe epilepsy, high mortality rate</td>
<td>Not effective (ACTH, steroids)</td>
</tr>
<tr>
<td>Early myoclonic encephalopathy</td>
<td>Infancy (early)</td>
<td>Cryptogenic, metabolic disorders, familial cases</td>
<td>Myoclonic sz, partial sz, tonic spasms</td>
<td>Suppression–bursts°</td>
<td>Idem</td>
<td>Death in half of the cases</td>
<td>Not effective</td>
</tr>
<tr>
<td>Infantile spasms*</td>
<td>Infancy</td>
<td>MCD, tumors, porencephaly, phakomatoses, other genetic diseases, cryptogenic</td>
<td>Spasms</td>
<td>Hypsarrhythmia#</td>
<td>Lennox–Gastaut syndrome, partial sz.</td>
<td>Cryptogenic and porencephaly better that others, mental delay in 70–80% of cases</td>
<td>Vigabatrin, steroids</td>
</tr>
<tr>
<td>Dravet’s syndrome</td>
<td>Infancy (first year)</td>
<td>SCNA1 mutations, hippocampal sclerosis, often cryptogenic</td>
<td>Unilateral generalized clonic/tonic–clonic sz</td>
<td>Multifocal spikes, generalized spike-waves</td>
<td>Myoclonus, atypical absence, focal sz</td>
<td>Normal within the first year, then progressive deterioration</td>
<td>Poorly effective (topiramate, stiripentol)</td>
</tr>
<tr>
<td>Lennox–Gastaut syndrome</td>
<td>Childhood (3–10 years)</td>
<td>Rarely cryptogenic (brain malformations, genetic diseases, etc.)</td>
<td>Tonic sz, atonic sz, atypical absence</td>
<td>Generalized slow spike-waves (awake), bursts of fast rhythmic waves, slow polyspikes and fast rhythms (sleep)</td>
<td>Persisting (tonic) sz</td>
<td>Severe neurocognitive delay</td>
<td>Valproic acid, clobazam</td>
</tr>
<tr>
<td>Doose syndrome (myoclonic-astatic epilepsy)</td>
<td>Childhood (18–60 months)</td>
<td>Genetically determined, SCNA1 mutation</td>
<td>Massive myoclonus, tonic-clonic sz, absences</td>
<td>Generalized spike-waves, theta activity</td>
<td>Persisting sz but also complete remission</td>
<td>Variable (remission vs. CE)</td>
<td>Valproic acid, lamotrigine, ethosucimide</td>
</tr>
<tr>
<td>Continuous spike-waves during slow sleep</td>
<td>Childhood</td>
<td>Cryptogenic, polymicrogyria, porencephaly</td>
<td>Partial sz</td>
<td>Continuous spike-waves occupying up to 85% of slow sleep</td>
<td>Persisting sz, behavioral disorders</td>
<td>Variable</td>
<td>Valproic acid, benzodiazepines, ethosucimide, steroids</td>
</tr>
</tbody>
</table>
Table 8.1.2 (continued) Main epileptic syndromes associated to pediatric CE

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset</th>
<th>Etiology/associated lesions</th>
<th>Seizures (sz)</th>
<th>EEG</th>
<th>Evolution</th>
<th>Prognosis</th>
<th>Medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landau–Kleffner syndrome</td>
<td>Childhood</td>
<td>Unknown</td>
<td>Absent or sporadic</td>
<td>Temporal spike-waves</td>
<td>Functional disruption of speech (verbal and auditory agnosia)</td>
<td>50% of children with severe mental retardation</td>
<td>Valproic acid, steroids</td>
</tr>
<tr>
<td>Progressive myoclonic epilepsy</td>
<td>Infancy, childhood, adolescence</td>
<td>Heterogeneous group of (genetic) syndromes</td>
<td>Multifocal and generalized myoclonus</td>
<td>Different (according to each syndrome)</td>
<td>Tonic-clonic sz, cerebellar and extrapyramidal signs</td>
<td>Variable</td>
<td>Varying according to the syndrome</td>
</tr>
</tbody>
</table>

*High-voltage paroxysmal activity (burst) alternating with short-duration, low-amplitude activity (suppression)*

*When grouped in clusters and associated to developmental delay and to hypsarrhythmia, they constitute the West syndrome, which is the most frequent pediatric epileptogenic encephalopathy*

# Very-high-voltage, slow-wave pattern irregularly interspersed with spikes and sharp waves occurring randomly in all cortical areas
The various forms of MCD differ in macroscopic aspects but share several microscopic features, involving both gray and white matter. They include:
1. Cortical dyslamination (cortical laminar and columnar disorganization)
2. Poor gray/white matter differentiation
3. Lack of myelination
4. Gliosis
5. Microscopic neuronal heterotopia (clusters of misplaced neurons)
6. Rosenthal fibers (perivascular eosinophilic bodies and fibers as a result of degeneration of astroglia)
7. Balloon cells (abnormal and ambiguous increased-size cells, with glasy and eosinophilic cytoplasm and eccentric nucleus, sometimes positive for glial markers and sometimes for neural ones)
8. Giant neurons (increased-size neurons with central nuclei and normal morphology)
9. Immature neurons (normal size, round-shaped and homogeneous neurons, with large and immature nucleus, small cytoplasm and normal morphology)
10. Dysmorphic neurons (neuronal cells with anomalous size, shape, nucleus, cytoplasm and dendrites, showing Nissl substance and cytoplasmatic neurofilaments)

MCD may involve only some areas of the cortex (focal cortical dysplasia) or multiple lobes (quadrantic dysplasia) up to the whole hemisphere (hemimegalencephaly).

### 8.1.2.3.1.1 Localized Malformations

**Focal Cortical Dysplasia (FCD).** FCD is the localized MCD most frequently associated to DRE in the pediatric age. It encompasses a spectrum of alterations ranging from mild cortical disruption to more severe forms. According to Palmini et al. [5], it can be classified into two types (Table 8.1.4). Type IA/B is not easily detected by MRI; its clinical picture varies from absence of epilepsy to DRE and cognitive impairment. Type IIA/B, usually well recognized upon MRI (see below), is often associated to intractable and catastrophic epilepsy, consequently bearing a worse prognosis.

Seizures and neurological signs vary according to the location of FCD, which is usually extratemporal (and frequently periorbital). Focal motor and generalized status epileptics are reported in 30% of the cases, with childhood and adolescence being the ages more burdened. An earlier onset is recorded in familial cases as if genetic anomalies may influence the presentation. Early seizure onset is associated to worse epileptic outcome and higher incidence of neurological deficits and mental retardation. Sensory-motor deficits are reported in 50–75% of the patients while about half of them show an IQ score below 80.

EEG patterns generally consist of isolated epileptiform discharges and focal slowing, frequently involving brain areas more extensive than the anatomy of the lesion, and/or of runs of repetitive epileptiform discharges (4–10-Hz rhythmic spikes or 2–7-Hz rhythmic sharp waves), usually more confined than the size of the lesion showed by neuroimaging.

FCD appearance upon MRI is characterized by focal thickness of the cortical mantle, shading of the gray/white matter junction, increased signal on T2-weighted and proton density sequences (extending from the sur-
face to the ventricle in the case of transmantle dysplasia), sometimes enhancing after contrast medium administration. In about one third of the cases, MRI is apparently normal.

The complete surgical excision of the dysplastic area is one of the most important prognostic factors. Outcome depends on the correct preoperative neuroimaging-based planning and on the intraoperative surgeon’s view. A 60–75% seizure control rate is expected for FCD. Such a rate tends to decrease in time so that a prolonged follow-up is required.

Schizencephaly. Schizencephaly is a migration disorder characterized by unilateral or bilateral clefts usually extending from the pia mater of the frontal or parietal region to the lateral ventricle and lined with a dyslaminated and polymicrogyric cortex. In the “closed (or fused) lips” variant, the walls of the cleft are juxtaposed, while in the “open lips” form, they are separated with subsequent communication between the ventricular CSF and the subarachnoid spaces. Other abnormalities, such as gray matter heterotopia, hippocampal sclerosis, corpus callosum and/or septum pellucidum agenesis may be present. Epilepsy affects 35–85% of patients with schizencephaly, generally starting from the first two decades of life and usually showing an earlier onset and a worse outcome in the bilateral and/or open lips forms. Mental retardation and motor deficit are often associated. Surgery is poorly effective.

Hippocampal Sclerosis (HS). Hippocampal (50–85%) and amygdalar atrophy (30–60%) are frequently found in children with temporal MCD as well as in those with extratemporal MCD (up to 35%), but they can occur also isolatedly (pure HS). There are not significant differences between pure HS and that associated to MCD as to clinical history, seizures presentation and prognosis, and about 90% of the patients are seizure free after surgery.

Gray Matter Heterotopias. These are misplaced masses of gray matter localized within the periventricular or subcortical white matter, often bilaterally, as a result of a failed migration process. Epileptic features are variable; the best outcome is observed in the isolated forms (typically involving the paratrigonal areas).

8.1.2.3.1.2 Diffuse (Hemispheric) Malformations

Hemimegalencephaly (HME). HME is the prototype of congenital hemispheric MCD, consisting of a dysplastic hyper-growth of one cerebral hemisphere, the contralateral one being usually spared or only mildly involved. Indeed, recent histological, neurophysiologic and neuroimaging studies seem to suggest a constant though silent involvement of the “healthy” hemisphere. In spite of the numerous theories, the etiopathogenesis of HME remains unknown. It could be considered as a complex developmental anomaly resulting from a neuronal proliferation disorder (primary event, 3rd to 4th week of gestation) possibly followed by a migration disorder (secondary event, 12th to 20th week). No specific genes have been identified so far.

HME occurs with a prevalence of 1–3/1,000 epileptic children and represents 1–14% of all the MCD and 30–50% of the abnormalities requiring hemispherectomy [4]. It may present as an isolated anomaly (sporadic and most common) or may be associated with partial or total body hemigigantism and/or neurocutaneous syndromes (e.g. Jadassohn’s nevus syndrome, proteus syndrome, Ito’s hypomelanosis, Klippel–Trénaunay–Weber syndrome). In “total HME” the homolateral posterior cranial fossa structures also are involved. Microscopic features of HME include part or all of those reported for the other MCD (see above). Macroscopically, the enlarged hemisphere exhibits increased consistency, hypervascularization and a wide spectrum of surface anomalies (e.g. agyria, pachygria, polymicrogyria, lissencephaly). Such alterations may involve the whole hemisphere or part of it (usually the posterior lobes), with the temporal lobe often being atrophic and the frontal one even grossly normal.

Asymmetric macrocrania, usually without manifestation of raised intracranial pressure, is the most common external clinical finding.

HME is the most severe form of MCD, and most of the affected subjects develop a CE within a few weeks/months from birth. The typical clinical triad consists of DRE, contralateral slowly progressing hemiparesis and hemianopia, and (severe) psychomotor retardation. Seizures affect about 90% of the patients, and most of the syndromes in Table 8.1.2 can be potentially observed. Epilepsy usually starts in the early postnatal period as mild partial seizures and/or asymmetric spasms and/or lateralized myoclonic jerks, often evolving into Ohtahara or West syndrome. Afterwards, Lennox–Gastaut syndrome or severe motor partial seizures/epilepsia partialis continua appear. The early refractory response to AEDs is almost the rule.

Early interictal EEG typically shows the unilateral suppression–burst pattern that can evolve into or be replaced by hemihypsarrhythmia. Late EEG pattern is composed by an even more disorganized and continuous activity over the affected hemisphere, possibly extending to the contralateral side. The aforementioned macroscopic dysplastic findings, such as hemisphere enlargement, gyration anomalies, dysplastic cortex, poor gray/white matter differentiation and heterotopias, can be demonstrated by MRI. The homolateral ventricular system is usually enlarged, with a straight frontal horn and widely enlarged occipital one, but it can also be normal or small. In the late phases of the disease, the affected hemisphere may become atrophic.

Even though burdened by a relatively high mortality and morbidity, hemispherectomy is the treatment of choice of HME. Actually, even up to 80–90% of the patients undergoing hemispherectomy remain long-term seizure free, reaching almost the same rates of those affected by less severe form of DRE requiring hemispherec-
tomy [4]. Nevertheless, the motor and cognitive outcome may remain poor in a high percentage of the operated-on patients.

**Multilobar MCD.** Multilobar MCD includes the hemispheric MCD that cannot be classified as HME because of less-extended dysplastic areas and quite large normal regions. *Posterior quadrant dysplasia,* according to the definition given by D'Agostino et al. [3], is a peculiar MCD involving the temporal, occipital and parietal lobes (postcentral gyrus excluded). The etiopathogenetic hypothesis would be the same as HME, and the partial hemispheric involvement could be explained by a mosaicism. Histological, clinical and neuroimaging features are similar to HME except for the sparing of the anterior hemispheric structures and a meanly less severe clinical course. Multilobar resection can be performed instead of hemispherectomy, obtaining the same good results with a minor surgical risk, unless a preoperative motor deficit is present and/or the EEG anomalies are not holohemispheric.

### 8.1.2.3.2 Congenital or Perinatal Vascular Occlusion

Congenital or perinatal ischemic accidents usually result from cerebral artery occlusion occurring during late pregnancy or in the perinatal period and resulting in periencephalic cyst (PC) formation. The incidence of such a phenomenon is about 1/4,000 live births or probably higher since some of the late perinatal accidents may be underreported. A female and a left-side prevalence are described. Even though several etiologic factors can lead to congenital vascular occlusion, such as infection, severe arterial hypotension, coagulation disorders or trauma, its etiology often remain uncertain. Perinatal asphyxia is proved to play an important role in the pathogenesis of most perinatal brain strokes.

When the injury occurs early in the intrauterine life, the ischemic damage results in focal cortical tissue loss and architectural disorganization (quite similar to polymicrogyria). However, if it occurs later or perinatally, the ischemic cerebral tissue undergoes an extensive involution/resorption, resulting in brain cavitation and gliosis. The final result of both of these events is the PC formation. The middle cerebral artery (MCA) is the most commonly occluded vessel. MRI or CT scan typically shows a cystic cavity replacing the losses of gray and white matter and seldom reaching the ventricular system (ependymal layer preserved). The MCA is usually markedly hypoplastic.

Clinical features include mild to moderate spastic hemiparesis, cognitive delay (speech and learning disorders), behavioral disturbances and epilepsy. The more extended the cortical and white matter damage and the basal ganglia involvement, the more severe the neurological deficit. However, the clinical findings may be less evident than the anatomical damage.

Seizures affect 30–60% of children with PC. In neonates with silent strokes, they usually represent the first clinical sign. The whole spectrum of infancy and childhood epilepsy may be observed, and the development of severe epileptic syndromes (West, Lennox-Gastaut) is not infrequent. DRE occurs in about 5–10% of the cases and reaches the degree of CE less frequently than MCD. EEG may reveal a single focus (corresponding to the cyst or to adjacent areas but also localized distantly) or diffuse epileptic foci (even extending to the contralateral hemisphere). Surgery is reported to be effective, with a favorable epileptic outcome often in more than 90% of the cases. Hemispherectomy is the most widely used surgical technique. In selected cases, the more conservative cyst “uncapping” (excision only of the atrophic/gliotic tissue) seems to ensure good results as well.

### 8.1.2.3.3 Neurocutaneous Syndromes and Epilepsy

Neurocutaneous syndromes are a heterogeneous group of congenital disorders where characteristic skin lesions are associated to central nervous system (CNS) alterations and possible systemic abnormalities.

**Tuberous Sclerosis (TS).** Epilepsy is reported in 78–96% of TS cases, often being the most relevant clinical problem. Seizures follow an age-dependant pathway, usually starting during infancy/childhood (70%) with the onset becoming rare during adolescence/adulthood (5%). Infantile spasms are the prototype of seizures, followed by partial seizures. Epilepsy can show a focal or multifocal origin at EEG, according to the location of cortical tubers at MRI. Actually, both the tubers that are histologically similar to Taylor-type FCD and the neuronal population adjacent to the tubers are thought to have an intrinsic epileptogenicity. DRE, reported in 40–75% of the cases, is often associated to neurocognitive and behavioral disorders, in particular autism (25% of the patients). Vigabatrin is the most effective AED, followed by topiramate, lamotrigine and levetiracetam. Surgical management is challenging because epileptogenic tubers are often multiple, bilateral and extratemporal, thus limiting the number of possible candidates for surgery. Unifocal epilepsy with concordant EEG and MRI can be managed by a single-step surgical approach (tuberecctomy/lobectomy) with a subsequent favorable epileptic outcome in up to 90% of the cases. In selected patients, multifocal or bilateral foci also can be treated with multistaged surgery.

**Neurofibromatosis Type 1 (NF-1).** The prevalence of seizures in NF-1 is lower than in other neurocutaneous disorders, ranging from 3 to 12%. It is a symptomatic epilepsy caused by characteristic associated lesions such as MCD, hypothalamic glioma or hamartomas, hydrocephalus and HS. Consequently, seizures are well controlled by the AEDs or disappear after removal of the epileptogenic lesion. DRE accounts for less than 30% of
the cases and usually depends on the presence of an associated MCD.

_Sturge–Weber Syndrome (SWS)._ Similarly to TS, SWS is associated to a high rate of epileptic patients (75–90%) presenting early onset seizures (85% < 2 years). Epilepsy typically starts as focal; afterwards, secondary generalized seizures and status epilepticus (observed in up to 50% of the patients) can occur. Learning disabilities are often associated, with severe mental retardation in 15–40% of the cases. The pathogenesis of the epilepsy could be explained by the decreased blood flow due to the pial angiomatosis with subsequent focal hypoxia and altered neuronal metabolism. Carbamazepine, alone or in association with phenobarbital or phenytoin, ensures an adequate control of seizures in 40% of the cases and allows the patients to rely on a following monotherapy with valproic acid or topiramate. Resective surgery is a valid alternative for DRE, especially when hemispherectomy is performed. Indeed, even 70–80% of the hemispherectomized patients are long-term seizure free; up to 60% of them are able to come off therapy.

_Ito's Hypomelanosis._ Epilepsy occurs in 35–55% of Ito's hypomelanosis cases, alone or in association with learning disorders (up to 70%), as a consequence of the presence of CNS malformations (MCD). DRE is observed in 40–60% of patients.

_Incontinentia Pigmenti._ Seizures are described in 5–13% of incontinentia pigmenti cases. The etiopathogenesis is related to periventricular acute microvascular hemorrhagic infarctions, which follow the evolution of the skin lesions, and/or to areas of cerebral atrophy.

Epilepsy in the _epidermal nevus syndrome_ and in the _proteus syndrome_ is linked to MCD, especially hemimegalencephaly, and, consequently, it follows the characteristics and the evolution described for these disorders.

### 8.1.2.3.4 Epileptogenic Tumoral Lesions

Primary brain tumors are a frequent cause of pediatric epilepsy. They account for 10–40% of the lesions surgically treated for DRE. Gliomas, namely low-grade ones, are diagnosed in about two third of the cases. The most common location is the temporal lobe (35–75%).

_Ganglioglioma._ Ganglioglioma represents about 40% of all epileptogenic tumors. Usually located within the temporal lobe (>70% of the cases), it can be associated to a peritumoral dysplastic cortex (50%). Histologically, it consists of neoplastic glial elements mixed with large ganglion cells associated to calcifications, perivascular lymphocytic infiltrates and eosinophilic granular bodies. Partial complex seizures, often unresponsive to AEDs, are the presenting symptom in up to 90% of the children; other neurological deficits are rare. Upon MRI, ganglioglioma is isointense on T1-weighted sequences and hyperintense on T2-weighted sequences and after contrast administration; a mass effect may be present. Epileptiform activity is often localized, but either multifocal or contralateral alterations can be found upon EEG. Although patients often undergo the surgical treatment late (initial response to AEDs, slow-growing tumor), surgery is considered the best treatment option, providing for an 80–90% seizure-free outcome. There is not yet agreement on whether surgical removal should be limited only to the tumor or also include the adjacent cortex.

_Dysembryoplastic Neuroepithelial Tumor (DNT)._ DNTs are polymorphic tumors arising during embryogenesis (maldevelopment of secondary germinal layers) and consisting of multinodular, intracortical lesions (neural and glial cells) associated to dysplastic foci in a half of the cases. They can extend into the white matter. As gangliogliomas, DNTs are prevalently located within the temporal lobe and appear iso-hypointense in T1-weighted and hyperintense in T2-weighted MRI; enhancement may occur after Gadolinium application. The mass effect is usually absent as along with the tumoral edema. Partial seizures, with or without secondary generalization, start during childhood or adolescence and develop into DRE in 75% of the cases. Due to the risk of developing distant epileptic discharges, early surgery is recommended. However, surgery seems to provide good results even after long-lasting DRE. Three fourths of the operated-on patients become seizure free, especially after tumorectomy plus removal of the peritumoral epileptogenic area.

_Hypothalamic Hamartoma (HH)._ HHs are rare sessile tumor lesions arising from the tuber cinereum and the inferior hypothalamus (incidence: 1/50,000–1,000,000). They consist of an indolent cluster of small neurons contained within a neuropil-like stroma and provided with intrinsic epileptogenicity, as seems to be demonstrated by ictal SPECT and ictal PET. Clinical features include gelastic seizures, developmental delay and central precocious puberty. Gelastic seizures begin during infancy/childhood and then evolve into catastrophic seizures such as partial, complex, primary or secondary generalized tonic-clonic, astatic and tonic, with subsequent epileptic encephalopathy. Up to 25% of patients, however, show a benign course characterized by epilepsy remission or gelastic seizures responsive to AEDs.

The diagnosis of HHs may be difficult and delayed. In the early phases, especially in infants, gelastic seizures may be under-recognized. Moreover, unless stereo-EEG is used, scalp ictal EEG fails to demonstrate any epileptic activity because of the deep location of the HHs, and scalp interictal EEG is often “normal” as well. Only with the propagation of the thalami and with lobar involvement does EEG become positive, but the result may be confusing. Upon MRI, HHs appear as a small mass, isointense to the gray matter (hyperintense on thin T2-weighted fast-spin echo sequences) attached to the tuber cinereum or to the mammillary bodies. Surgery of HHs is very challenging, because total resection of the hypothalamus cannot be performed, and even partial resec-
tion of the lesion may result in significant clinical sequelae. More than the pure excision, the disconnection of the hamartoma from the surrounding structures, namely the mammillary bodies, is currently considered the goal of surgery. Such a goal is achieved by traditional approaches (anterior transcallosal, subfrontal tran-lamina terminalis, pterional) but, recently, also by means of endoscopic procedures. The seizure-free rate after surgery ranges from 35 to 70%. Quite similar data are reported by some authors following radiosurgical treatment.

8.1.2.3.5 Rasmussen Encephalitis
First described in 1958 by Rasmussen after his first hemispherectomies, this chronic encephalitis still presents several unexplained aspects. First of all, the etiopathogenesis remains unknown. The viral hypothesis is the most important one, since DNA of the Epstein–Barr virus and cytomegalovirus have been found within the specimens of the excised cerebral hemispheres. Secondly, histopathology is aspecific, showing only the signs of chronic cortical and, less frequently, white matter inflammation. Thirdly, the process almost invariably involves only one hemisphere.

Although an onset during adolescence or adulthood is described, epilepsy usually begins during childhood, typically between 4 and 9 years, as sporadic partial seizures. Seizures follow a three-phase evolution pathway:
1. **Onset phase**: rare seizures, mild neurological deterioration
2. **Acute, or progression, phase**: marked increase in frequency and severity of seizures, often intractable, neuropsychological deficits, brain atrophy
3. **Final, or plateau, phase**: decrease in seizure frequency

The final result is the development of DRE (epilepsia partialis continua) and subsequent CE-related encephalopathy. The worst prognosis is observed in the patients with early onset, because they usually show a short onset phase with a consequent early acute phase.

Early MRI may be negative or may show subtle signs of focal edema; then progressive hemispheric atrophy becomes evident. Hemispherectomy is the most effective treatment.

### Suggested Reading
8.2 Pain

LARS ARENDT-NIELSEN

8.2.1 Introduction

Pain is a multi-dimensional perception involving not only the sensory dimension but also many other factors, including emotions, cognition, muscular movement and physiology [11].

The multidimensionality of pain has become widely accepted [25]. The perceptual aspect – the sensory-discriminative dimension – is hereby thought of as the function of pain, which gives information as to the site, duration and intensity of the pain. This dimension often plays a pivotal role in the experimental measurement of pain, but its significance should not be overestimated, given the complexity of pain [21]. Pain can only be adequately characterized by the relationship between its sensory and affective dimensions. Not only the complexity but also the subjectiveness of pain perception contributes to the difficulty of pain measurement [25, 26]. This has spawned efforts to establish an “objective” algesimetry, which does not require the report of subjective states, but primarily assesses responses to noxious stimuli in the motor, autonomic, endocrine and central nervous systems [15].

Despite the weak correlations between the subjective and objective parameters of pain perception, it seems advisable to view pain as multi-dimensional and not to unnecessarily exclude the subjective dimension [17, 18].

It is therefore necessary to combine different stimulation and assessment approaches to gain advanced differentiated information about the nociceptive system under both normal and pathological conditions. Progress has been made in the development of “tonic pain” perception models in order to more precisely simulate clinical pain in the laboratory. The ultimate goal of advanced human experimental pain measurement (quantitative sensory testing) is to obtain a better understanding of mechanisms involved in pain transduction, transmission and perception under normal and pathophysiological conditions. Hopefully, this can provide a better characterization, prevention and management of pain. Experimental approaches can be applied in the laboratory for basic studies (e.g. central hyperexcitability or pre-clinical screening of drug efficacy) but also in the clinic to characterize patients with sensory dysfunctions and/or pain (e.g. neurogenic pain). In recent years, the use of experimental pain measures to evaluate the efficacy of new potential analgesic compounds has developed significantly [5].

The primary advantages of quantitative pain assessment under normal and pathological conditions are:

- Stimulus intensity, duration and modality that are controlled and not varying over time
- Differentiated responses to different stimulus modalities
- Physiological and psychophysical responses that can be assessed quantitatively and compared over time
- Pain sensitivity that can be compared quantitatively between various normal/affected regions
- Experimental models of pathological conditions (e.g. hyperalgesia) that can be studied

Accordingly, the experimental assessment of pain perception for clinical questions has a promising future.

8.2.2 Origin of Pain and Pain Phenomena

The sensation of acute pain is the result of activation of normal (not sensitized) nociceptors classified as Aδ or C nociceptors, according to the peripheral nerve fibre transmitting the neural impulses. In recent years, several classes of C nociceptors in humans have been identified by the technique of microneurography [27, 28].

Nociceptors in the skin are divided into three main classes: C-mechano-heat, type I Aδ-mechano-heat and type II Aδ-mechano-heat. Type I Aδ-mechano-heat nociceptors exhibit a slowly increasing response with a latency of several seconds to heat stimuli of high intensity and long duration [22]. If the skin is activated by rapid heat stimuli (e.g. from a laser), the type II Aδ-mechano-heat nociceptors are activated [31] together with some activation of warmth receptors (C fibres).

Of special importance for pathophysiological mechanisms may be the finding of silent nociceptors that are not activated by normal noxious stimuli, but become active in a state of injury, in particular following inflammation [27]. In the case of a peripheral nerve injury, the C nociceptors may become sensitized due to the effect of a large number of inflammatory substances released at the site of the injury. Sensitization of C nociceptors produces sen-
sory changes restricted to this site and not in surrounding tissue.

These sensory changes are first and foremost allodynia. Allodynia is defined as pain produced by a non-painful stimulus (e.g. a lowering of the heat pain threshold). Secondly, these sensory changes are hyperalgesia. Hyperalgesia is defined as an increased response to a stimulus that is normally painful.

In the event of acute pain, the incoming stimuli to the spinal cord are processed normally, and the nociceptive impulses are passed over to second-order neurons and transmitted in central projection pathways.

In the case of an injury to a peripheral nerve, an increased amount of nociceptive impulses reaches the dorsal horn of the spinal cord, and central sensitization may occur. This central sensitization includes a complicated series of events in neurons in the dorsal horn.

Wind-up, a cumulative increase of action potentials as a result of nociceptive stimulation, is considered a possible first initial step, mediated by activation of N-methyl-d-aspartate (NMDA) receptors [12]. It may not yet be possible to explain all clinical symptoms, findings and sensory abnormalities in patients with chronic pain by the theory of central sensitization, but the demonstration of central hyperexcitability has had a tremendous impact on the understanding of some of the phenomena observed in patients with chronic pain. For instance, the allodynia to mechanical stimulation, frequently encountered in neuropathic pain patients, has been attributed to central hyperexcitability, as has the increase – over time – of areas of pain. Whether the occurrence of spontaneous and paroxysmal pain may be explained entirely or partly by the same mechanisms is still an unresolved question.

Traditionally, clinical pain syndromes have been treated according to the aetiology of pain (e.g. post-herpetic neuralgia, painful diabetic neuropathy). The existing knowledge of possible common neurophysiologic mechanisms involved in different pain entities has made it suggestible to change this approach. It seems more relevant to assess and treat pain according to the underlying neurophysiologic mechanisms involved – “mechanism-based classification of pain” [5, 33].

This opens new perspectives for future pain management and represents a huge challenge for developing test procedures that enable us to distinguish between different mechanisms in a clinical setting.

8.2.3 Experimental Methods for Pain Evaluation

Numerous methods to induce pain experimentally are available. Correlations between different methods are often low to moderate, indicating that different information can be gathered [19]. The most frequently used pain induction methods are derived from the application of mechanical (tactile and pressure), thermal, electrical or chemical stimuli [2]. Rolke et al. [26] have described a comprehensive clinical pain assessment regime to be used for routine assessment and hence for collecting normative data.

8.2.3.1 Estimation of Tactile Sensibility – von Frey Hair

Quantitative testing of tactile sensibility using von Frey nylon filaments is easy. The von Frey filaments constitute a series of nylon fibres of varying thickness, calibrated according to the force required to make them bend. The hairs primarily stimulate the rapidly adapting cutaneous receptors. With increasing bending force, the von Frey hairs will excite skin nociceptors and may be used to determine tactile pain detection thresholds.

In neuropathic pain, tactile sensibility as measured by von Frey hairs may be reduced in affected skin areas [14]. This finding may be overlooked in a routine neurological examination, where testing for tactile sensibility with a cotton swab may only give a sensation of hyperesthesia (in fact allodynia to light mechanical stimulation) and thereby mask an eventual reduction in tactile sensibility. The von Frey hairs may also be employed for mapping areas of secondary hyperalgesia to punctuate stimuli (due to central sensitization) in a clinical context [30]. It has recently been shown that secondary hyperalgesia to punctuate stimuli is mediated by conduction in A nociceptive fibres, in contrast to the Aβ fibre-mediated secondary hyperalgesia to light brush.

8.2.3.2 Pressure Stimulation

The pressure algometer is used for quantitative determination of thresholds of pressure or pinching tolerance.

The primary application of mechanical stimulation has been to assess tenderness in myofascial tissues and joints [6]. The pressure pain thresholds vary substantially between regions, and methodological studies are necessary for each new location examined [7]. The pressure stimulus is regarded as a natural pain stimulus, which induces sensations familiar from daily experience.

The most distinctive feature of this way of experimentally inducing pain is the induction of deep tissue pain in addition to superficial pain. The outcome measures in pressure algometry are pain detection threshold and/or pain tolerance threshold. Pressure algometry has for instance been used to assess the effect of drugs, different treatment modalities, pain thresholds in children, experimental pain in muscles, pain thresholds in population
studies and head and neck pain [7]. The method seems well suited for determination of pressure hyperalgesia in musculoskeletal disorders.

### 8.2.3.3 Thermal Stimulation

The thermo test (quantitative evaluation of thermal thresholds) allows testing of qualities such as heat, cold, heat-pain and cold-pain sensations (Fig. 8.2.1).

Painful syndromes (mainly neuropathic pain) are often characterized with dysfunctions in sensory qualities. These are mediated by thin nerve fibres, fibres that are not available for investigations through conventional electrophysiological testing such as neurography. It is important that neurography tests dysfunction of peripheral nerve fibres, while the thermo test describes the status of the temperature somatosensory afferents system from the cutaneous receptors to the brain. It is not possible to conclude about the level of injury with thermal testing.

With the Peltier thermode, a precisely controlled application of heat- and cold-pain stimuli can be delivered. It includes a natural quality of sensation through the subsequent active return of the skin temperature to baseline. The advantage of this method is that cold, warm, cold-pain and heat-pain can easily be assessed by the same device [20].

Testing for thermal sensory abnormalities is employed not only in evaluation of pain patients. Patients with thin-fibre neuropathies should also be investigated, and a prominent finding in neuropathic pain conditions is heat and cold hyperalgesia. Testing only for heat and cold functions in patients with neuropathic pain will give inconclusive results, in particular because heat and cold hyperalgesia may occur in the presence of normal heat and cold thresholds. Heat- and cold-pain are often described as sudden perception, with radiation and after-sensations – valuable information in the evaluation of hyperalgesia.

In the evaluation of neuropathic pain patients, all four thermal qualities are a must [32]. It is equally important to ask the patient about the quality of the sensation. Paradox sensations are frequently reported; most often that cold pain is perceived as heat.

Apart from testing a painful skin area, a normal skin area should be included as a control. In recent years, heat stimulation of high intensity by argon [1, 3], CO₂ [23], Nd-YAG, copper vapour lasers and xenon light has been developed for cutaneous and mucosal stimulation. Normally, the laser pulses used are of short duration (20–200 ms) and elicit a distinct pricking pain, which at the highest stimulus intensities is followed by a burning pain.

The reliability of the measurements with contact heat and laser stimulation is deemed to be good [3].

### 8.2.3.4 Electrical Stimulation

The application of electrical skin stimuli has a long tradition in experimental pain research and is still widely used but stimulates all the nerve fibres – not just the nociceptive ones. The use of subcutaneous and muscular sites of stimulation is a way of targeting other types of nociceptor populations, of which the deep tissue nociceptors are of particular interest [2, 5]. The possibility of easily varying the electrical stimuli as far as amplitude and frequency are concerned is a great advantage. This has, however, caused new problems to arise as, up to now, hardly two studies have been carried out with the same stimuli parameter. The reliability of the electrical pain perception tests is regarded as good.

### 8.2.3.5 Chemical Stimulation

Chemical pain stimulation, in which algogenic substances (e.g. hypertonic saline) are injected into the muscles or are applied into or onto the skin (e.g. histamine, bradykinin, capsaicin), is unsuitable for clinical examination of pain perception.

### 8.2.3.6 Temporal Summation

Temporal summation of neural impulses in nociceptive nerve fibres is a physiologically important mechanism by which the sensation of pain can be intensified (Fig. 8.2.2). Repeated stimulation causes an addition of synaptic potentials in the spinal cord neurons that may ultimately lead to an increased neuronal response. Temporal summation can be induced by repeated thermal [25], electric-
Psychophysical determinations can roughly be divided into response-dependent and stimulus-dependent methods (see reviews in [2, 5]). A series of fixed stimulus intensities and a rating of each stimulus construct the response-dependent methods. The rating can be given on a visual analogue scale or a verbal descriptor scale as well as by magnitude estimation or cross-modality matching. The stimulus-dependent methods are based on adjustment of the stimulus intensity until a pre-defined response, typically a threshold, is reached. The stimulus intensity required to reach the threshold is recorded in physical units.

Stimulus–response functions are more informative than a threshold determination, as suprathreshold response characteristics can be derived from the data. All quantitative sensory tests are psychophysical tests, which require awake and alert individuals, who fully understand the instructions given and are fully capable of co-operating during testing.

The choice of a suitable method is therefore dependent both on the precision of a given method and on the given diagnostic or scientific target of an investigation; the latter guides the assessment to the aspect of pain perception of interest.

There are several ways of assessing pain and pain tolerance thresholds: the method of constant stimuli, the method of adjustment, the method of limits, etc. They all look for the least amount of physical energy necessary to elicit pain (pain threshold) or for the most amount of physical energy still tolerable for an individual (pain tolerance threshold) [15, 25]. The thresholds have been criticized because they are said to confound perceptual and motivational as well as emotional dimensions. In fact, they only demonstrate where the pain range starts (pain threshold) and where it ends (pain tolerance thresholds). There is no information about pain perception between these range delimiters.

Pain and pain tolerance thresholds monitoring is of great value because it is reliably, easily and simply assessed. A further advantage results from the limited cognitive demands that are imposed during threshold assessment upon the individuals, who have to judge perceptions only as “painful” or as “non-painful”.

The assessment methods, including for phasic pain simulation, are based on a combination of psychophysical, electrophysiological and imaging techniques.
8.2.5 Rating Scales

There are many variants of pain rating scales, which are classified roughly into verbal and numerical scales as well as methods of direct scaling.

A verbal scale is normally divided into several categories, which are labelled for example with “no pain”, “slight pain”, “moderate pain” and “strong pain”. A subject is asked to express her/his pain perception by use of these categories. The answers are quantified afterwards, for example by assigning a number from 1 to 4 according to the category chosen. The advantage of this approach is that it is easy to be understood by the subject and does not require a skilled investigator. However, the assumed equidistance between categories has not been proven for many of these scales. Therefore, ordinal scale properties ought to be taken for granted instead of interval scale properties [17]. These limitations can be avoided by calibrating the psychometric distance between categories in advance. The verbal descriptor scales are examples of such empirically validated scales. The stability of distances between categories across studies requires a universal pain language, which is not very likely to exist even within a given linguistic area [25].

The numerical scales use verbal anchors such as “no pain” and “worst pain imaginable” to define the scale range. Numbers represent only the categories themselves. It is tempting to assume that the numbers guarantee the equidistance between categories. Since the use of numbers by the patients or the subjects and not the numbers themselves determine the psychometric distances between categories, numerical scales are not a simple solution to this problem. Like verbal scales, numerical scales are easily explained and understood, facts that have determined their frequent application.

Another widely used procedure is the visual analogue scale (VAS), which consists of horizontal or vertical lines of 10- or 15-cm length and scale anchors at the beginning like “no pain” and at the end like “worst pain imaginable”. The subject is required to express the intensity of pain perception by indicating a line length subjectively proportional to the perception [17, 25]. The VAS is said to be highly sensitive to treatment effects. However, the cognitive demands in using a VAS are too high for a good proportion of the patients under investigation.

8.2.6 Conventional Neurophysiologic Techniques

8.2.6.1 Neurography

Neurography includes measurements of conduction velocities, motor and sensory amplitudes, distal delay and latency of late volleys such as the H- and F-wave. Nerve conduction studies play an important role in precisely delineating the extent and distribution of a peripheral nerve lesion and in indicating the nerve–root pathology (by evaluation of late reflexes). Neurography does not evaluate the function of thin nerve fibres such as Aδ mediating cold/sharp pain and C-fibres mediating the sensation of heat, heat pain and some forms of tactile pain. Neurography among pain patients is used to document whether there is a true peripheral nerve lesion or a polyneuropathy affecting large myelinized nerve fibres.

8.2.6.2 Sensory-Evoked Potentials

In routine neurophysiologic practice, sensory-evoked potentials are derived from peripheral electrical stimulation. The electrically evoked potentials project to the dorsal columns and hence assess neural transmission of sensory qualities such as light touch, vibration and pressure. Sensory-evoked potentials following pain application with CO₂ laser stimulation relate to pain and nociceptive impulses projected in the spinothalamic tract (Figs. 8.2.3 and 8.2.4).

The potentials evoked by non-painful and painful electrical stimulation are surprisingly similar. None of the components of the evoked potentials elicited by painful electrical stimuli can be considered as pain specific in the sense that they appear only following stimuli above the pain threshold [13]. The shape of the vertex potential does not change when the intensity of the electrical stimulus exceeds the pain threshold but the amplitude saturates [8, 13]. This has led to the suggestion that vertex potentials evoked by nociceptive electrical stimuli are not reliable correlates for changes within the nociceptive system [19].
The large inter-individual variation in the amplitude of the laser-evoked potentials suggests they may not be suitable for routine examinations in clinical practice. A large set of normative data based on laser-evoked potentials from normal healthy, age/sex-adjusted controls is essential. A statistical criterion of three standard deviations might be used to categorise sensory abnormality associated with laser-evoked potentials. In studies where the patient and control groups serve as their own controls (e.g. comparing the differences in amplitude for potentials evoked from two areas or follow-up after surgery) the laser-evoked potentials are suitable for monitoring. The laser-evoked potentials can provide useful information which is not accessible by conventional electrophysiological techniques.

Laser-evoked potentials have been shown to be of value in assessing impairment of pain and temperature sensation in patients with peripheral neuropathies. Correlation between pain/temperature impairment and changes in the laser potentials has been found in patients with syringomyelia, multiple sclerosis and in neurological patients with various dissociated sensory deficits [9].

Sensory testing and clinical neurophysiology studies have indicated that patients with central pain syndromes occasionally have impairment of the pain and temperature sensation. Central pain syndromes could be caused by disinhibition of spinothalamic excitability or by reduction of the spino-thalamic function due to other central changes or disease in the brain. Central pain patients (cerebral or brainstem infarctions) with normal tactile sensation had significantly smaller laser-evoked potentials on the affected side compared with the non-affected side [10]. This study supports a deficit in spinothalamic tract function but does not suggest excessive central responses to the activation of cutaneous nociceptive pathways.

The laser-evoked potential may also be pathologically exaggerated. Fibromyalgia patients show dramatically exaggerated reaction to muscle stimulation (for summary see [29]), and evoked potentials to cutaneous laser stimulation have indicated substantial larger amplitudes in these patients compared to controls. The major exaggeration of laser-evoked potentials resides only in the late components (N170–P390). These effects suggest the presence of exogenous factors such as reduced cortical and
subcortical inhibition or central hyper-vigilance to the nociception, probably involving the limbic mid-cingulate generator. However, it has been shown that hypnotically induced hyperalgesia can also increase the laser-evoked vertex potentials [1].

8.2.7 Conclusion

The diagnosis of neuropathic (and nociceptive pain) is in most cases based on a thorough interview and a clinical examination of the patient. In many cases, however, there is a need for further classification of the painful syndrome, and the question arises as to which testing procedures are adequate. This chapter describes the different clinical neurophysiologic and sensory tests available and their role in the evaluation of painful syndromes. The conventional clinical neurophysiologic methods like neurography (nerve conduction studies) and somatosensory-evoked potentials using peripheral electrical stimulation are of little value since they assess the function of the fast-conducting Aβ fibre and dorsal column system, not the mediating sensation of pain. Somatosensory potentials following CO2 laser stimulation relate to pain and nociceptive impulses projected in the spinothalamic tract, but the large interindividual variation in the amplitude of the laser-evoked potentials suggests that they may not be suitable for routine examinations in clinical practice.

Neuropathic pain is in most cases characterized by sensory abnormalities due to lesions of sensory nerve fibres or sensory pathways within the central nervous system. Further diagnostic and descriptive characterization of a painful syndrome may be obtained by performing quantitative sensory testing (QST), which allows a quantitative evaluation of sensory thresholds to tactile, vibratory, pressure and temperature stimuli. Since neuropathic pain often is characterized by dysfunctions of sensory qualities mediated by thin Aδ and C fibres, a thermo test (quantitative evaluation of thermal thresholds) allowing the testing of heat, cold, heat pain and cold pain is of special importance. Testing for allodynia/hyperalgesia during tactile and thermal stimulation as well as testing for abnormal temporal summation or “wind-up-like pain” is of great value in the evaluation of neuropathic pain and may be helpful in assessing underlying pathophysiological mechanisms.

Quantitative sensory testing has a role to play in clinical neurophysiology, neurology, neurosurgery, and pain management/research. The challenge for the future is to develop techniques to assess (1) pain pathways, including more details on the various mechanisms involved in pain, and (2) pain origin from deeper structures.

Suggested Reading

8.3 Functional Stereotactic Neurosurgery for Movement Disorders: Deep Brain Stimulation

HANS-HOLGER CAPELLE AND JOACHIM K. KRAUSS

8.3.1 Introduction

Before chronic deep brain stimulation (DBS) became the treatment of choice in movement disorders surgery, lesioning procedures like thalamotomy and pallidotomy were used widely to treat patients with Parkinson's disease (PD), tremor or dystonia. Compared to ablative surgery, DBS offers a non-lesional modulation of basal ganglia output; its effects are principally reversible, and it is possible to adapt the therapy to the course of the disease and the individual needs of the patient [16, 14]. The main advantage, however, is that bilateral surgery can be performed in the same operative session without increased risk for side effects (Table 8.3.1). The renaissance of movement disorders surgery for PD also renewed interest in functional stereotactic surgery for other movement disorders like dystonia [16]. In large prospective randomized studies, DBS has been shown to provide substantial benefit in PD, but also in essential tremor (ET) and generalized dystonia [2, 13, 7, 21, 8, 17, 20, 22].

The mechanisms of DBS are a matter of intensive research, and they are still not fully understood. Based on the observations drawn from microelectrode recordings and the recording of local field potentials from the basal ganglia, DBS seems to inactivate the pathological firing and interfere with oscillations of basal ganglia loops [6].

In the future, DBS may be used in combination with other new therapies and technologies. Promising therapies such as viral vectors, gene therapies, stem cell therapies and the instillation of neurotrophic factors which may aid in the survival of neurons have been or will be explored [24, 18, 19, 10].

8.3.2 Principles of DBS Surgery for Movement Disorders

8.3.2.1 Anatomy and Targets

The common contemporary targets for PD, ET and dystonia are shown and summarized in Fig. 8.3.1 and Table 8.3.2. Other targets of interest include the pedunculopontine nucleus and the intralaminar thalamus. The most beneficial target for treatment of ET is the nucleus ventrointermedius thalami (Vim), based on the nomenclature of Hassler, or, anatomically, the nucleus ventrolateralis posterior (VLp), based on the revised nomenclature of Jones [14].

The dorsolateral part of the subthalamic nucleus (STN) and the posteroverentral lateral part of the internal pallidum (Gpi) are the common anatomic targets in DBS for treatment of PD. The posteroverentral lateral part of the Gpi has been established also as the target of choice in severe dystonia (Fig. 8.3.1, Table 8.3.2). The thalamus was evaluated earlier as a target for DBS in dystonia, but it has become somewhat out of focus. Thalamic DBS has been suggested to be more useful in secondary dystonia [16].

Table 8.3.1 Advantages and disadvantages of DBS

<table>
<thead>
<tr>
<th>Advantages of DBS:</th>
<th>Disadvantages of DBS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesioning</td>
<td>Costs of the hardware components</td>
</tr>
<tr>
<td>Reversible</td>
<td>Operative risks (Infection, hemorrhage)</td>
</tr>
<tr>
<td>Ability to change stimulation variables to minimize side effects, increase efficacy</td>
<td>Need to replace pacemakers</td>
</tr>
<tr>
<td>Ability to perform bilateral procedures with reduced risk of transient and permanent morbidity</td>
<td>Extensive follow-up required to optimize stimulation parameters</td>
</tr>
</tbody>
</table>
8.3.2.3 Operative Technique

Stereotactic surgery allows one to reach a defined target anywhere in the brain with three-dimensional accuracy by guidance of a reference system. The stereotactic reference system is a rectangular or circular frame which is fixed to the patient’s head by pins under local anesthesia. For calculation of the target coordinates, either stereotactic CT scans or stereotactic MR scans (or a fusion of both) are obtained. The target can be identified by direct visualization with the MR or “indirectly” given its spatial relationship to the boundaries of the third ventricle. Based on stereotactic atlases (e.g. the Schaltenbrand–Wahren atlas), AC–PC-based coordinates can be transformed via stereotactic imaging to obtain the corresponding frame coordinates. Tilt of the AC–PC line relative to the stereotactic frame may occur.
Fig. 8.3.2 Hardware for DBS. The quadripolar electrodes and the IPG are connected by extension cables (Medtronic, Minneapolis, with permission)

Fig. 8.3.3 Programmer for the patient to turn the IPG on, off or change the amplitude (Medtronic, Minneapolis, with permission)

Fig. 8.3.4a–d Stereotactic frames. CRW frame (a), Leksell frame (b), Riechert-Mundinger frame (c), Riechert-Mundiger frame with Zamorano-Dujovny arc (d) (from Krauss and Volkman, Tiefen Hirnstimulation, Steinkopff, 2005, page 110, with permission)
Fig. 8.3.5 Stereotactic frame (Riechert-Mundiger frame) mounted to the patient’s head and acquisition of stereotactic images (upper row). Identification of the anterior and posterior commissures in CT imaging with parallel simultaneous reformatted views in the axial, sagittal and coronal planes (lower row) (from Krauss, Jankovic, Grossman, Surgery for Parkinson’s Disease and Movement Disorders, Lippincott Williams and Wilkins, 2001, pages 80 and 87, with permission; Krauss and Volkmann, Tiefe Hirnstimulation, Steinkopff, 2005, page 48, with permission)

Fig. 8.3.6 Tilt of the AC–PC line relative to the stereotactic frame may occur in all three planes (“roll, pitch and yaw”). These deviations have to be corrected by using special alignment algorithms (from Krauss, Jankovic, Grossman, Surgery for Parkinson’s Disease and Movement Disorders, Lippincott Williams and Wilkins, 2001, page 89, with permission)
in all three planes. Such misalignments (“roll, pitch and yaw”) need to be corrected by special alignment algorithms (Fig. 8.3.6) [14].

The usual coordinates of the targets are as follows:

- **Vim**: 11–15 mm lateral to and 0 mm below the intercommissural line, and 4 mm posterior to the midcommissural point
- **STN**: 12 mm lateral to and 4 mm below the intercommissural line, and 3–4 mm posterior to the midcommissural point
- **Gpi**: 20–22 mm lateral to and 4 mm below the intercommissural line, and 2–3 mm anterior to the midcommissural point

Usually, the operation is performed under local anesthesia and anesthesia stand-by to take advantage of intraoperative patient cooperation, in particular testing for thresholds of efficacy in symptom suppression and of side effects upon macrostimulation. Patients with severe generalized dystonia or children are operated under general anesthesia. Several neurophysiological methods are used to further refine the target. The most elegant is microelectrode recording. It allows one to demonstrate specific firing patterns along the trajectory to the target. Furthermore, by manipulation of the extremities, the sensorimotor areas of the target nuclei can be determined. After implantation of the DBS electrode, macrostimulation is performed through the different contacts. The electrode can be externalized for testing of clinical efficacy or for recording of local field potentials [6]. In a second procedure, it is connected via an extension cable with the IPG, placed subcutaneously in the infraclavicular region in general anesthesia. The risk of surgery is comparatively low. In a recent study, serious complications in 319 patients included isolated seizure in four patients (1.2%), intracerebral hemorrhage in two patients (0.6%), intraventricular hemorrhage in two patients (0.6%), and a subdural hematoma in one patient (0.3%) [11].

### 8.3.2.4 Hardware-Related Problems

Hardware-related technical problems may include electrode dislocation due to insufficient fixation at the burr hole, cable fracture (extension cable) and infection of the system (cable or IPG). The overall infection rate was reported to range between 2 and 10% [5, 23]. In a series of 119 patients, 15% had 23 hardware-related complications, which included 8 electrode breakages, 4 electrode migrations, 2 stimulator migrations, 3 erosions, 2 erosions and infections, 2 infections and 2 cases of IPG malfunction [5]. The majority of these complications occurred during the first 4 years postoperatively. In the case of infection, antibiotics should be given first; if this is not successful, the whole system sometimes has to be removed.

Battery depletion in the IPGs requires additional surgery. The time until battery depletion occurs differs depending on the chosen stimulation parameters (amplitude, pulse width and choice of contacts). The need to change the IPG battery is more frequent in patients with dystonia (1–3 years) due to a higher stimulation energy than in PD or ET patients (3–6 years) [16].

### 8.3.3 Patient Selection for Deep Brain Stimulation

To be considered for DBS, patients should have had proper diagnostic studies and pharmacological therapy. Note that DBS surgery is a team approach which includes interdisciplinary selection and follow-up of patients. Contraindications, in general, are dementia, psychopathological alterations and severe depression. Also, old age may be a limiting factor.

#### 8.3.3.1 Tremor

Tremor is defined as involuntary rhythmic oscillations of single or multiple parts of the body. Tremor types are classified by the mode of activation (rest, action or kines-thesia), frequency, heredity and further symptoms which may clarify the etiology of the tremor (other movement disorders symptoms, polyneuropathies, etc.). The prevalence of ET has been estimated to be up to 400/100,000 in the normal population and up to 4.8% in patients aged over 65 years.

Tremor can be very distracting. It may not only lead to disability, but also to great social embarrassment. Conservative treatment of ET includes the application of propranolol, primidone or topiramate. Pharmacological therapy is the first-line treatment in PD tremor and ET, but in many instances, it may not sufficiently improve the tremor. Pharmacological therapy, on the other hand, often is ineffective in multiple sclerosis tremor. It has to be considered, however, that ataxia accompanying a tremor is hardly controlled by DBS [4]. In PD patients, it has to be noted that additional symptoms like postural instability, akinesia or rigidity, which may occur in the progress of the disease, are not influenced by thalamic DBS [14]. Therefore, thalamic DBS is hardly a choice in a young patient with tremor-dominant PD. STN DBS has been shown to suppress tremor to a similar degree in PD. Thalamic DBS may be suited, however, for an old PD patient with monosymptomatic tremor over years [14].
8.3.3.2 Parkinson’s Disease

PD results from degeneration of several specific areas, and in particular from dysfunction of the nigrostriatal pathway due to loss of dopaminergic neurons in the substantia nigra pars compacta. The cardinal motor symptoms – akinesia, rigidity, tremor and postural instability – are accompanied by sensory, vegetative, psychological and cognitive deficits. The prevalence in the general population aged over 55 years has been estimated to be 1.5–2.0%.

DBS is an option for advanced PD patients whose symptoms can no longer be adequately managed pharmacologically. The best surgical candidate is a patient who responds well to dopaminergic therapy but has motor complications which develop after 5–7 years of dopaminergic therapy. Severe on/off fluctuations and dyskinesias, but also the cardinal motor symptoms of PD (tremor, rigidity, akinesia, and postural instability), are improved by pallidal or STN DBS [13, 8].

Another issue to consider is that dopaminergic medication can be reduced after STN stimulation. Depression or anxiety occurring in the off condition and drug-induced psychosis thus may also be influenced by DBS. The age of the patient and the stage of the disease have to be considered. Candidates for surgery in general should not be older than 70 years and not at an end-stage of their disease. The Hoehn and Yahr stage in the off condition may range between III and V. Patients who are in Hoehn and Yahr stage V while on are not good candidates. The degree of postoperative improvement can be predicted by the preoperative response to levodopa. It is of the utmost importance to identify patients with other parkinsonian disorders, such as multiple system atrophy, progressive supranuclear palsy and cortico-basalganglionic degeneration. These patients usually do not achieve valuable benefit from GPI or STN DBS. In PD patients with monosymptomatic PD tremor, thalamic DBS may be an alternative in older patients since it is less prone than STN DBS to evoke psychosocial or cognitive problems.

8.3.3.3 Dystonia

Dystonia is characterized by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. Dystonia may be classified along three different axes: age at onset, anatomical distribution (focal, segmental, generalized, hemidystonia) and etiology (primary or secondary). Spasmodic torticollis or cervical dystonia (CD) is the most common form of focal dystonia. CD has a possible prevalence of 0.39% in the population of the United States.

Focal dystonia mostly can be treated successfully by botulinum toxin injections. Primary and secondary dystonia non-responders, however, compromise about 10%, and in some patients with CD, injections are limited by side effects. In hemidystonia, segmental or generalized dystonia, however, often a surgical approach is necessary due to the widespread involvement of several muscle groups. At this time, patients with primary (genetic or sporadic) generalized and segmental dystonia and patients with complex CD are thought to be the best candidates for pallidal DBS [16]. In general, patients with primary dystonia appear to respond well, patients with secondary dystonia respond less well and poorer results are expected in patients with secondary dystonia and structural lesions [16].

8.3.4 Results of Deep Brain Stimulation for Movement Disorders

8.3.4.1 Tremor

Thalamotomy abates tremor in up to 90% of patients. While it is well tolerated when performed unilaterally, its frequency of side effects is not acceptable anymore with bilateral procedures. Dysarthria is the main limiting factor, occurring in at least 30% of patients [14]. In a prospective randomized trial, it was shown that Vim DBS had a comparable efficacy for tremor as thalamotomy, but it was associated with fewer side effects and greater functional improvement [21].

Studies on thalamic DBS in PD patients that have shown improvement of tremor reach class 2, according to evidence-based medicine (EBM) criteria [21]. In the study of Schuurman et al., about 90% of patients with PD had excellent improvement of tremor. In a long-term evaluation of unilateral and bilateral thalamic DBS, PD patients with unilateral DBS had an 85% improvement in the targeted hand tremor, and those with bilateral DBS had a 100% improvement in the left hand and 90% improvement in the right after 5 years [20]. The potential side effects, many of which are transient, included paresthesia and a higher frequency of dysarthria and disequilibrium with bilateral DBS. Due to the necessity of adaptation of the stimulation parameters, especially in the long-term follow-up after bilateral DBS, overall, a mild dysarthria has to be accepted in about 10% of patients to achieve sufficient reduction of tremor [3].

ET of the upper extremities was improved in up to 90% of patients providing class 2 evidence [21]. Tremor of the head or voice may also be well improved but usually is only satisfactorily controlled by bilateral DBS with a slightly higher rate of side effects. The effect of thalamic DBS in ET also has shown to be maintained in the long term by several studies [3, 20]. After 5 years, unilaterally stimulated patients with ET had a stable 75% improve-
ment of the targeted hand tremor; those with bilateral DBS had a 65% improvement in the left hand and an 86% improvement in the right hand compared with baseline.

Treatment of kinetic tremor in multiple sclerosis turns out to be more difficult because of the associated disability and the subsequent cognitive decline. Symptomatic improvement is noted in up to 70% of patients, which does not translate, however, to the same degree in functional improvement [4]. Thalamic DBS offers the possibility of changing the frequency or amplitude, and the long-term benefit may be more long lasting. Primarily in patients with severe action tremor, little atactic disturbance and preserved function of the upper extremity (no severe paresis), the indication for DBS may be given.

Problems may be the development of tolerance to stimulation by physiological adaptation, especially in patients with action tremor. Those patients can switch stimulation off at night to reduce the effect of adaptation.

### 8.3.4.2 Parkinson’s Disease

Both targets, GPi and STN, were compared in randomized trials evaluating improvement in the Unified Parkinson’s Disease Rating Scale (UPDRS). In a study by Krack et al., the motor subscore was improved by 71% in the STN group ("off" medication), whereas the GPi group showed improvement by 39% due to a less pronounced effect on akinesia [13]. In a small randomized, prospective trial, however, Burchiel et al. did not find a significant difference in the motor subscores in both groups [7]. In a non-randomized prospective trial, patients were evaluated 3 months after STN DBS (96 patients) and GPi DBS (38 patients). Levodopa-induced dyskinesias were improved to the same extent in both groups, whereas the other motor subscores showed a more pronounced improvement in the STN group. After 6 months, however, the reduction of dyskinesias in "on" condition was higher with STN DBS than with GPi DBS (74% vs. 64%). Overall, the data to date seem to show a moderate advantage for motor dysfunction for STN DBS. Furthermore, reduction of medication is possible with STN DBS but not with GPi DBS. The equivalent of levodopa in STN DBS can be reduced by 65% compared to the preoperative dose. Another disadvantage of GPi DBS is the relatively higher energy consumption for effective stimulation [14].

According to EBM criteria, the STN has become the major target for DBS (class 2 evidence). Bilateral implantation of two DBS electrodes connected to a single IPG is the standard procedure [14]. It leads to improvement of all cardinal features of PD. The average improvement in motor subscores in almost all studies ranges between 40 and 70%. After 12 months of STN DBS, compared to preoperative off-medication scores, tremor is improved by 81%, rigidity by 63%, bradykinesia by 52%, gait by 64% and postural instability by 69%. Improvement in the motor subscores is about 10% in the "on" condition. Dyskinesias are improved in patients with STN DBS by about 75%. Dyskinesia reduction probably is related to both reduction of medication and a more delayed direct effect. On/off fluctuations, off-period dystonia and associated pain are also ameliorated by stimulation. Long-term studies of STN DBS have reported a significant and sustained benefit on motor symptoms up to 5 years. STN DBS has been proposed to be neuroprotective – possibly related to suppression of glutamate excitotoxicity and reduced cell death in the substantia nigra [3]. As indicated by data from PET scans, however, the progression of the disease continued in patients with advanced PD, although they received effective stimulation according to improvement in the UPDRS motor subscores.

In a German multicenter study, 156 patients with advanced PD and severe motor impairment were evaluated in two groups, comparing patients with DBS plus medication and medication alone. After 6 months of follow-up, improvement was greater in the group of patients with DBS as assessed by the Parkinson’s Disease Questionnaire (PDQ-39) and the UPDRS motor subscore as compared to baseline. The PDQ-39 subscores for mobility, activities of daily living, emotional well-being, stigma and bodily discomfort were improved by 24–38% [8].

In another study, the influence of age was evaluated. In 52 PD patients, improvement of the UPDRS motor subscore was 62% in patients younger than 60 years, whereas improvement in patients aged 60–70 years was 37%, and only 22% in those over 70 years. Whereas the effect on motor symptoms is marked, in general, there is no significant effect on speech, freezing and psychological symptoms such as depression not related to the "off" condition and dementia.

The effect of STN DBS on cognition in PD patients has been evaluated in several studies. In a Swiss study, out of 57 PD patients who underwent SNT DBS, 24.5% developed dementia, fulfilling the criteria for PD dementia. The remainder was cognitively stable over 3 years based on the dementia (DSM-IV) and UPDRS scores. The incidence of cognitive worsening was similar to that in PD patients treated medically [1]. At least the majority of published data suggests that STN DBS affects only little cognition. Nevertheless, some patient subgroups (older age) may be at a higher risk of developing cognitive and neurobehavioral problems.

The disadvantage of STN DBS is the need for a more complex adjustment of stimulation and levodopa medication for the individual patient in the postoperative period. Most profoundly, in some patients, psychiatric adverse effects may occur after STN DBS. Transient anhedonia is not uncommon. Onset or worsening of depression occurs postoperatively in a small percentage of patients.
Therefore, preoperative neuropsychiatric evaluation is essential, and postoperative follow-up is a critical part of patient care. In most patients, behavioral side effects occurred immediately postoperatively and diminished in the long term without the need of specific therapy. The occurrence of neuropsychiatric side effects is multifactorial. Most importantly, comorbidity of depression and anxiety with PD is common. Also, postoperative motor improvement may result in altered balances in the social arrangement. Unrealistically high expectations for the operation may not be fulfilled, and postoperative reduction of medication may have a negative impact in some patients. In patients with severe depression or anxiety unrelated to the “off” condition, the indication for STN DBS has to be carefully clarified, or GPi DBS may be considered the better alternative.

The PPN has been introduced as a target for severe postural instability only recently [25].

### 8.3.4.3 Dystonia

Until the 1990s, thalamotomy and pallidotomy were used to treat patients with dystonia. The effect of pallidotomy in PD on levodopa-induced dyskinesia indicated that the GPi may be a superior target for DBS rather than the ventrolateral thalamus. Subsequently, after this was proven by several pilot studies, the GPi has become the target of choice for DBS in disabling medically intractable dystonia [16]. Nevertheless, there are still types of dystonia (for example secondary dystonia, dystonic tremor) that may be more improved by thalamic DBS. Mostly, two electrodes are implanted and connected to two IPGs or one dual-channel IPG [16].

A German multicenter study investigated the long term outcome of GPi DBS for primary generalized and segmental dystonia by a randomized double-blind study design [17]. Forty patients with primary generalized or segmental dystonia received bilateral pallidal implantation. After surgery, patients underwent initial programming and then were randomized to real stimulation or sham stimulation for 3 months. As assessed with the Burke–Fahn–Marsden Scale (BFM), movement scores improved by a mean of 39.3% resulting from stimulation versus 4.9% for sham stimulation (class 2 evidence). In the whole group, by the end of the trial, movement scores improved by greater than 75% in 5 patients, greater than 50% in 18 patients and greater than 25% in 30 patients. Differences in efficacy were not correlated with generalized versus segmental dystonia, DYT1 status or other factors. Based on assessment with the Beck Depression Inventory (BDI), GPi DBS also improved depression. Dysarthria was the most common adverse event, occurring in five patients. Further adverse effects in GPi DBS were rare and appeared in the period of parameter adjustment postoperatively.

In the long term, GPi DBS in generalized dystonia has been shown to be maintained up to several years. Recently, the long-term follow-up of the French multicenter study (French SPIDY group) has become available. The improvement in motor function was stable at 3 years postoperatively by 58%, and the positive effect on quality of life was similar to that observed at the 1-year follow-up. Data on GPi DBS and long-term improvement in segmental and generalized dystonia fulfill class 2 EBM criteria [22].

We introduced GPi DBS for CD in the late 1990s [15]. It achieves symptomatic and functional improvement, including marked relief of pain in the long term for patients with complex CD. Its efficacy has been confirmed in several studies providing class 3 evidence. The results from a Canadian prospective, single-blind, multicentre study underline the efficacy of GPi DBS in CD. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity score improved from a mean of 14.7 preoperatively to 8.4 at the 12-month follow-up [12].

Health-related quality of life, an important marker for efficacy of DBS, was also assessed in the French multicenter study before surgery and at the 12-month follow-up with the SF-36. The general health and physical functioning subscores improved significantly, and the effect on quality of life was maintained at follow-up at 3 years. Interestingly, improvements in SF-36 subscores are much more marked when compared to those of PD patients with STN DBS [22].

### 8.3.5 Conclusions and Perspectives

Functional stereotactic surgery has become an important therapeutic option in patients with disabling movement disorders. While the main focus at this time is on DBS, several other methods show promise and are being explored or re-evaluated. A preliminary study with five PD patients showed improvement by 39% of motor symptoms after GDNF was delivered by a infusion system to the striatum [9]. A randomized trial with 34 patients which was conducted thereafter, however, failed to show any difference between patients with GDNF infusion and sham surgery [18]. In the light of the impressive results from animal studies, however, GDNF and other growth factors remain attractive to explore new venues for PD treatment and are the matter of intensive research. In a recent study, giant cell-derived neurotrophic factor (GDNF) has been delivered via viral vectors into the striatum in a mouse model of chorea Huntington with amelioration of behavioral deficits and histomorphological changes [19]. There
is another study in the US with 30 patients evaluating the effect of neurturin, another neurotrophic factor close to GDNF. Other groups are working with adeno-associated virus vectors to deliver key enzymes of dopamine production to the brain. The results of a gene-therapy study using viral vectors recently have become available. In a phase 1 trial with 12 patients, adeno-associated virus was delivered through a catheter into the STN [10]. The virus contained the information for encoding the enzyme glutamic acid decarboxylase (GAD) to increase gamma-aminobutyric acid (GABA) in the STN. After 12 months, the UPDRS showed an improvement by up to 40% in 10 out of the 12 patients. However, these results have to be confirmed by larger randomized trials and have to be evaluated carefully.

In the 1990s, there were high expectations for embryonic neural transplantation into the putamen. After the first positive results, long-term follow-up was rather disappointing. Comparative sham-surgery studies showed that neurotransplantation was effective in a subgroup of younger PD patients, but it was burdened with side effects such as frequent dyskinesias. Although neurotransplantation in PD has become somewhat out of focus, stem cells remain a highly interesting topic.

Another novel approach is the stereotactic-based transplantation of human retinal pigment epithelial (hRPE) cells into the striatum, producing local dopamine. In a pilot study in 6 patients, improvement was found at 48% in the UPDRS items for rigidity, tremor and postural instability after 12 months [24].

Further studies are necessary to learn more about safety and efficacy of these and other new therapeutic strategies. Most likely, in the foreseeable future, DBS will remain the standard surgical procedure for treatment of advanced PD and other movement disorders.

Suggested Reading

8.4 Functional Applications of Radiosurgery

**ANDRAS KEMENY**

### 8.4.1 Introduction

Stereotactic radiosurgery was originally conceived to treat functional conditions; the later widespread use has been the result of expansion of indications for vascular malformations and tumours. Historically, only about 7% of Gamma Knife treatments have been carried out for functional indications [1, 2].

### 8.4.2 Aims

The aims of radiosurgery include lesion making in an anatomical target (as opposed to a pathology) and disruption of functional circuits without necrosis.

### 8.4.3 Technique

Functional radiosurgery is carried out almost exclusively on Gamma Knife. The reason is technical (precision required) and personnel (most Gamma Knife units are run by neurosurgeons, whereas other radiosurgical tools, e.g. LINACs, are run mainly by oncological teams).

#### 8.4.3.1 Indications

Indications for radiosurgery include:
- Pain
- Psychosurgery
- Movement disorders
- Epilepsy

### 8.4.4 Pain

#### 8.4.4.1 Trigeminal Neuralgia

A single 4-mm field, 70 – 90 Gy to target results in greater than 90% pain control with a median three weeks’ delay from treatment. Long-term results are greater than 60% pain free. Facial numbness is reported in 8–10%. The best outcome is in previously untreated typical trigeminal neuralgia. Salvage procedures, MS and atypical pain are poor prognostic factors.

### 8.4.5 Psychosurgery

#### 8.4.5.1 Indications

Indications for psychosurgery include:
- Obsessive-compulsive disorder (OCD)
- Anxiety neurosis
- Severe chronic psychogenic pain

#### 8.4.5.2 Anatomical Targets

Anatomical targets include:
- Anterior internal capsule
- Cingulum
- Subcaudate tract

#### 8.4.5.3 Outcome

About 70% of these surgeries are successful, even with long follow-ups exceeding 7 years. The onset of improvement is 6/12. Complications include rare cerebral swelling, controllable with steroids (dexamethasone, 2 mg tds for 7 days, 2 weeks rest, repeated course if necessary). Limitations of this surgery include ethical issues.

### 8.4.6 Movement Disorders

The main debate regarding movement disorders is lesion making versus stimulation (reversibility). Radiosurgery is relevant only if lesioning is the choice. It is not an “easy option.” The complication rate is highly dependent on the experience of the operator.
8.4.6.1 Indications

Indications include Parkinson’s disease and essential tremor. Less favourable indications include post-stroke and post-encephalitic movement disorders. Advantages of radiosurgery include the fact that it is not an invasive surgery, which benefits patients with coagulopathies and the elderly, in addition to increased precision in hitting the target. Disadvantages include a lack of electrophysiological evaluation (no reassurance of correct targeting). In addition, lesion making cannot be stopped during procedure, and the latency of onset is 3–9 months.

8.4.6.2 Targets

Targets for movement disorders include:

- **Thalamotomy targets:** nucleus ventralis intermedius or post, portion of ventralis oralis posterior, ventrolateral nucleus
- **Pallidotomy target:** globus pallidus, just above optic tract, just inferomedial to internal capsule

8.4.6.3 Technique

The technique includes:

- Distortion-free MRI
- Atlas-based coordinate selection or image fusion with digital atlas (morphing)
- Almost invariably unilateral lesions
- 120–160 Gy to target, single field, 4-mm coll.
- Day-case procedure; serial MRI follow-up

8.4.6.4 Outcome

The outcome of radiosurgery for movement disorders includes:

- 88–90% successful improvement after 6–12 months in Parkinson’s and essential tremor. Less than 50% improve in post-encephalitic or post-stroke cases. Faster response results from a fast dose rate at treatment. Dyskinesias improve more than rigidity or bradykinesia.
- Complications are rare (local swelling; hemiparesis, visual field deficit).

8.4.7 Epilepsy

8.4.7.1 Rationale

The rationale for radiosurgery for epilepsy includes:

- Epilepsy associated with cerebral AVMs improves after radiosurgery even if the lesion remains.
- Focal epilepsy associated with cavernomas improves after radiosurgery (>50% seizure free).

8.4.7.2 Mesial Temporal Sclerosis

- **Technique:** anterior 2 cm of the hippocampus and the adjacent parahippocampal gyrus and temporal amygdala, about 6–7 cc volume, targeted. Radiation dose: 24 Gy minimum dose, 5.5–7.5 cc volume treated. Brainstem dose < 10 Gy, optic nerve/tract < 8 Gy
- **Outcome:** seizure control ranges between 0 and 80%. Typical pattern of response: initial increase in auras around 1 year, followed by gradual reduction of complex partial seizures. Complications: frequent headaches, dramatic (usually asymptomatic) MRI changes

8.4.7.3 Hypothalamic Hamartoma

These lesions present with precocious puberty, progressive cognitive regression and medically intractable epilepsy. Seizures can be of different types, including gelastic seizures, pathognomonic for this pathology. Open surgery carries a high risk of hypothalamic damage or neuropsychiatric sequel of the approach to the region.

Small, pedunculated lesions are the best for Gamma Knife radiosurgery. Targeting concentrates on keeping the dose to the optic system minimal. A typical dose is 18–20 Gy to the periphery of the lesion. The outcome is 40% Engel Grade 2a, 60% Engel Grade 2b. The latency is about 9 months. Improved cognition and behaviour is a major benefit in 20%. There is very low risk: no visual deficit is reported using modern image-based targeting. Poikilothermia may occur.

References

The introduction of computed tomography (CT) into clinical use renewed interest in stereotactic neurosurgery [16]. With CT, intracerebral lesions are directly visible, and the images are easy to use with a stereotactic coordinate system. After the introduction of magnetic resonance imaging MRI in the 1980s, these data sets were also incorporated into stereotactic techniques and could be used for stereotactic planning and surgery [57, 58]. Stereotactic-guided techniques were developed to target pathological lesions within the brain. Technically, a target and an entry point are selected just like in stereotactic biopsy. The entry point marks the craniotomy site. Commonly, a catheter is inserted and advanced to the target point, and preparation is performed along this predefined trajectory until the target point and therefore the tumor is reached. Kelly developed a technique of volumetric stereotactic surgery: the compass system. In contrast to the point-in-space stereotactic technique, the volumetric technique provides calculation of the tumor volume and therefore of the borders of a lesion. A computer system is required for this complex mathematical calculation [17, 18, 38, 39, 40].

Although the frame-based stereotactic technique is very exact and deep-seated lesions can be approached very successfully, the whole system is bulky and interferes with the surgical procedure.

In 1986, Roberts et al. [62] introduced a frameless neuronavigation system into clinical use. The frame was no longer necessary for calculation of the three-dimensional space of the patient’s head and brain and was replaced by fiducials glued to the patient’s head. In contrast to the frame-based, stereotactic-guided technique, an intraoperative feedback of the actual position of an instrument was provided by this frameless stereotactic navigation system. Various techniques were developed for neuronavigation and instrument tracking. The working principles are based on ultrasonic impulse detection [3, 60, 62], articulated mechanical arms [28, 49, 80] and optical detection of infrared flashes [15, 24, 63, 68].

Nowadays, neuronavigation systems have become standard in modern neurosurgery, and the systems preponderantly work using a cableless technique based on light emitting diodes (LEDs).

Representative of frameless neuronavigation systems, the BrainLAB system is described in this chapter [24]. Many navigation systems similar in design and function are offered by various other companies. This navigation system is an LED-based system with passive reflection of the infrared flashes by specially coated spherical markers. The star-shaped marker array, also called the reference star, is fixed to the patient’s head holder in a rigid position and has three reflective markers. The infrared flashes emitted by LEDs arranged around the camera system are reflected by these marker spheres. The tool for patient registration, the pointer, has two markers. The geometry of the pointer tool is known by the navigation computer. By detecting the position of the three markers of the reference star in relation to the position of the two markers of the pointer, the computer can calculate the location of the tip of the pointer tool. The patient’s head must be prepared with five skin fiducials before imaging (CT or MRI). The data are transferred to the planning station. The images are displayed on the computer screen; the region of interest (e.g., the tumor) is outlined in colors.

After finishing the surgical plan, the data are transferred from the planning station to the neuronavigation system. The images are displayed on the computer screen in a three-planar format. The patient is positioned for surgery with the head secured in the fixation device, and the reference star is attached to the head holder. The patient’s head is digitized by tipping the pointer tool onto the skin fiducials. Using the relative position of the pointer tool to the reference star, the computer can calculate the position of the patient’s head.

Alternatively to the fiducial reference system, a laser-based system using the contour of the head is available. The advantage of this contour-based registration procedure is that an additional imaging with skin markers is not necessary. After registration, the pointer tool can be used for navigation. The position of the pointer is displayed on the computer screen in real time, and surgical planning can be performed. The tip of the tool can be virtually prolonged to calculate the best trajectory to the target area. Special adapters can be mounted onto various
surgical instruments (e.g., the bipolar forceps) and they can be used for navigation too. Even the operating microscope can be equipped with a marker array, and the focus point is displayed on the computer screen. A heads up display is provided, and in this mode, the predefined contours of the tumor can be visualized in the microscope’s focus [22]. Image fusion technique allows the integration of various imaging data like PET, fMRI, and DTI into the neuronavigation system [6, 7, 25, 67]. PET fusion with the navigation data is in particular helpful for the treatment of low-grade glioma with a hot spot on PET and only vague tumor borders on MRI or CT [26, 75]. In these patients an additional fusion of fluid-attenuated inversion recovery (FLAIR) MRI sequences to the navigation can be useful to delineate the tumor margins [46].

### 8.5.3 Intraoperative Imaging

Frameless neuronavigation systems in modern neurosurgery are usually based on preoperatively performed image data. Although good results concerning complete removal of the visible tumor can be achieved if the neuronavigation is handled in its proper form, intraoperative imaging is helpful in some cases. The brain is not a firm organ, and brain shift up to 1 cm can change the anatomical situation completely [14, 32, 50, 52]. The brain shift can be induced by brain edema, especially after the opening of the dura and within tumor resection. Therefore, intraoperative imaging can be crucial for optimal tumor resection by updating the actual anatomical situation.

A long-used technology for intraoperative localization of pathologic structures is ultrasound (Fig. 8.5.1a–c). It is suitable for localization of deep-seated lesions [2, 78]. The possibility of intraoperative resection control using ultrasound is discussed controversially [2, 31, 78]. The development in this field seems to be encouraging, particularly the option of three-dimensional ultrasound images, which may lead to new dimensions in intraoperative imaging [20, 33, 76]. The real-time integration of ultrasound into a neuronavigation system as well as 3D visualization and image fusion seem to improve the surgical results [11, 34, 41, 51].

![Fig. 8.5.1](image-url) a Ultrasound machine. b and c Intraoperative ultrasound B-scan of a cystic intracerebral lesion
Lunsford and Okudera reported the intraoperative use of computed tomography in the 1980s [12, 42, 43, 54, 55, 56]. Nowadays, a mobile CT scanner with high image quality is used. Useful and flexible employment as well as successful integration in the operating room setting has already been reported [10, 21, 27, 47]. We have a lot of experience with mobile CT (Fig. 8.5.2a, b) [23]. The mobile CT can be integrated easily into the operative setting; no additional instruments are necessary. However, in tumor surgery, the use for intraoperative resection control is limited to contrast-medium-enhancing lesions. The borders of a low-grade glioma are not sufficiently visible on CT images.

Intraoperative MRI (iMRI) could be the method of choice for this purpose. In 1994, iMRI was introduced into the field of neurosurgery [35]. The field strength of the MR equipment used varies between 0.12 and 1.5 Tesla, but most centers use low-field systems. Different solutions for iMRI are employed. Applying vertical open MRI [4, 5, 66], the surgical procedure is performed with the patient positioned inside the scanner. Due to the patient’s position, the operative setting is completely different than without iMRI. The working space for the surgeon is very limited. MRI-compatible surgical instruments as well as a compatible microscope are required. This is not necessary when mobile MRI is used.

Sutherland et al. [71] described an MRI scanner mounted to the ceiling. The scanner can be moved to the patient if an iMR scan is necessary. Alternatively, the MR scanner can be located in another room beside the operating room, and the patient can be moved to the scanner [70]. The surgery is performed with a distance to the magnet, and the operative setting does not need to be changed (e.g., position of the patient or the surgeon). For both solutions, a very large operating room or two rooms are necessary. Other authors report a compact mobile MR scanner with an integrated navigation system that can be stored under the operating table (Fig. 8.5.3) [29, 37, 65]. The scanner is draped and can be brought into position if imaging is necessary. Special instruments are not required. A useful application is reported in low-grade gliomas and pituitary adenomas [44, 64, 77] as well as in stereotactic biopsy, aneurysm surgery, epilepsy surgery and spine surgery (Fig. 8.5.4a, b) [8, 9, 13, 30, 36, 45, 72, 79, 81]. However, the employment of iMRI can be expanded to all situations where intraoperative imaging seems to be necessary.

Despite the actual high costs of iMRI, this technology will probably become standard in modern neurosurgery. High-field scanners will provide enthusiastic images of anatomical and functional data using fMRI, diffusion-weighted MRI, MR angiography, diffusion tensor imaging and MRI spectroscopy [1, 53, 69, 72, 74].

Another interesting method that is used to obtain intraoperatively up-to-date information about functional areas in eloquent brain regions is the combination of navigation with electrophysiological methods [48]. The relationship of the tumor to eloquent brain areas, especially during surgery in the central region can be visualized after transferring the functional data, for example, from direct electrical cortical mapping to the navigation system [59, 61].

Furthermore, future prospects include image-guided robotic surgery [73].
Fig. 8.5.2  (continued)  b Pre-(left) and intraoperative (right) CT imaging

Fig. 8.5.3  Polestar MRI scanner for intraoperative use (with friendly permission of the neurosurgical clinic, Johann Wolfgang Goethe University, Frankfurt/Main, Germany)
Fig. 8.5.4  a Pre- (left) and intraoperative (right) MR image of a malignant glioma. b Pre- (left) and intraoperative (right) MR image of a pituitary adenoma (with friendly permission of the neurosurgical clinic, Johann Wolfgang Goethe University, Frankfurt/Main, Germany)
8.5.4 Guidance for Neuronavigation with the BrainLAB VectorVision System

8.5.4.1 Hardware and Software

The following hardware is required:
1. Planning station
2. Neuronavigation system (Fig. 8.5.5)
   a) High-end computer systems
   b) Infrared light emitting and detecting camera system
   c) Reflective marker system
   d) Touch screen monitor
3. Marker-based registration with skin fiducials or
4. Laser-based registration without fiducial markers

The following software is required:
1. VectorVision (actual version)
2. Image fusion software for multimodal neuronavigation

The following items are useful:
1. Microscope integration (semi-robotic functions)
   a) Tool tracking (the microscope follows the instrument)
   b) Go to target (the microscope finds the position of a predefined target)
   c) Target return (the microscope moves the focus point to the target from every new position)
2. Heads-up display (HUD) (the contour of the tumor is displayed in the microscope’s field of vision) (Fig. 8.5.6)
3. Video integration (Fig. 8.5.7)

8.5.4.2 Navigation Planning

Before starting the procedure, the following questions should be answered:
1. What kind of patient positioning is used (prone, supine, head rotation)?
2. Which surgical approach will be carried out?
3. What is the position of the head-holder pins?
4. What type of imaging will be used?
   a) MRI 3D data sets or 2- to 3-mm CT slices are necessary
   b) Various image data sets like fMRI, DTI or PET can be fused to the navigation data set

8.5.4.3 Marker-Based Registration

The marker-based registration includes the following steps:
1. Depending on the surgical head position planned five markers have to be glued on to the patient’s head, surrounding the target area.
2. Imaging
3. Data transfer to the planning station
4. Defining the target area (tumor)
5. Image fusion
6. Planning of the surgical approach
7. Marker registration

![Image of BrainLAB neuronavigation system](Fig. 8.5.5)
![Heads-up display](Fig. 8.5.6)
8.5.4.4 Patient Registration

The following steps are included in the patient registration:
1. Data transfer to the neuronavigation system
2. Display of three planes and the 3D reconstruction
3. Patient positioning and head fixation in the head holder (e.g., Mayfield clamp) according to the preplanned approach
4. Fixation of the reference star adapter and the reference star itself
5. Patient registration with the pointer tool by tipping onto the fiducials (take care not to move the fiducials during the head fixation maneuver and pointer tipping; this can lead to decreased accuracy)
6. Definition of the tumor borders and planning of the craniotomy

8.5.5 Indication for Neuronavigation

The accuracy in neuronavigation depends on:
1. Imaging slice thickness
2. Patient's position
3. Skin displacement during head fixation and/or patient registration
4. Brain shifting due to
   a) Cerebrospinal fluid loss
   b) Application of mannitol
   c) Tumor reduction

The mean accuracy of the patient registration is 0.7 mm. The intraoperative brain shift varies between 1.5 and 6.0 mm with an average of 3.9 mm.

Surgical planning using neuronavigation cannot replace anatomical knowledge. The localization of the lesion within the three-dimensional space of the brain and the best approach must be known before the employment of computer techniques. Then, neuronavigation can be used as a helpful tool to improve the surgical procedure.

In general, neuronavigation can be used for all neurosurgical procedures. The additional time that is necessary for the navigation set-up range is between 15 and 30 min in our department and is justifiable. Sometimes, the navigation is used only at the beginning of surgery to perform a perfectly located small craniotomy and sometimes it is used throughout the entire procedure. Even during endoscopic procedures, for example, in transsphenoidal pituitary surgery, the navigational aid can be useful, especially in complex cases or reoperations [19].

Standard indications are:
1. Deep-seated tumors (Fig. 8.5.8)
2. Small tumors (Fig. 8.5.9)
3. Endoscopic surgery guidance (Fig. 8.5.10)
4. Tumors of eloquent areas
5. Skull base tumors
6. Frameless biopsy (Fig. 8.5.11)
Fig. 8.5.8 Deep-seated lesion

Fig. 8.5.9 Small lesion
### Suggested Reading


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**Fig. 8.5.10** Endoscope guidance

**Fig. 8.5.11** Frameless stereotactic biopsy using the neuronavigation system. The *red line* demonstrates the virtual prolongation of the biopsy needle (*yellow*)


Medical doctors treating patients with spasticity are today confronted with an increasing number of potential therapeutic treatment options. In order to be able to select among these treatment interventions, it is important to understand and differentiate between the elements of spasticity.

The spinal reflex loop generates the stretch reflex. This reflex starts with the alpha motor neurons situated in the anterior horn of the spinal cord. The alpha motor neurons send axons through a peripheral nerve to make contact with the endplate zone in the muscle cells via the neuromuscular junction. Feedback regarding the activation of the muscle is generated in muscle spindles and Golgi tendon organs. Information is fed back to the motor neurons via sensory neurons. The sensory neurons complete the reflex loop within the spinal cord by projecting monosynaptically or polysynaptically to motor neurons through spinal interneurons. For a review on impaired reflex function and altered muscle mechanics in spasticity, see [10, 29].

**8.6.2 Muscle Stiffness in Sitting Spastic Patients**

In the daily clinical situation, diagnoses and validation of spasticity are determined by resistance to passive movement and exaggeration of the tendon reflex. This is in full accordance with a widely accepted definition of spasticity: “...a motor disorder characterized by velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflexes, as one component of the upper motor neuron syndrome” [17].

It is important to understand how the results of the clinical examination relate to the results from more objective evaluation techniques. Therefore, we need to investigate the different components that add to an increase in the clinically observed resistance, when a spastic muscle is stretched.

The resistance can be divided into an increase in the:

1. Passive stiffness of tendons, joints, or muscles
2. Intrinsic stiffness of the contracting muscle fibers
3. Stiffness mediated by the stretch reflex

For an in-depth review of reflex and non-reflex elements of hypertonia in the human plantar flexor muscles, see [32, 31].

To isolate the importance of the different components, a brief passive stretch can be applied to the isometric muscle of interest during different voluntary activities. In healthy and spastic persons, such studies can be performed by imposing well-defined angular displacements around a joint and then measuring changes in force and/or changes in the electrical activity of the muscle [1, 20, 34]. Figure 8.6.1 shows a schematic outline of such a setup for the ankle joint.

![Fig. 8.6.1 A schematic presentation of the setup for studying the stretch reflex during sitting, standing, and walking in the plantar and dorsiflexors. The foot is mounted on a platform. Torque and position are measured from the platform. To elicit a stretch reflex, a motor connected to the platform (not shown) rotates the ankle joint. The mechanical importance of the stretch reflex is measured through changes in the joint torque. The stretch reflex can also be recorded electrically as the compound muscle action potential through bipolar surface EMG electrodes placed above the muscles of interest. To measure the non-reflex stiffness component in the plantar flexors, the stretch reflex should be inhibited at the time of the stretch. This can be done by stimulating the tibial nerve at the popliteal fossa (for details on this technique, see [34]). Taken from [32]](image-url)
Spasticity and Muscles: Basics for Understanding the Different Treatment Modalities

Figure 8.6.2 demonstrates the increase in ankle joint torque in the spastic and contralateral plantar flexors of a hemiplegic patient after imposing a well-defined passive dorsiflexion. The total torque increment is the sum of the reflex-mediated torque and the non-reflex-mediated torque (see Fig. 8.6.2). The non-reflex torque increment is measured during a continuously electrical stimulation of the tibial nerve innervating the ankle plantar flexors. The electrical stimulation abolishes the stretch reflex [34]. The reflex torque (total torque minus non-reflex torque increment) exceeds the non-reflex torque with nearly a factor of two in the contralateral and spastic leg. The reflex torque and the non-reflex torque in the spastic leg both exceed the ones in the contralateral leg.

8.6.3 The Non-Reflex/Muscle Component

Part of the torque opposing the stretch stems from the properties of the collagen tissue (passive properties) and the contractile apparatus in the stretched muscles (intrinsic properties). The sum of these passive and intrinsic properties is termed the non-reflex properties (Fig. 8.6.2).

The passive stiffness at a joint is reported to increase up to several hundred percent in spastic patients depending on the investigated joint, joint position, patient group, and applied method [33, 18, 20]. In hemiplegics, a 50% increase in passive stiffness of the spastic ankle during slow passive dorsiflexion is found [33]. When the passive stiffness is measured in a more acute stage, an increase in passive stiffness of 39% in the affected leg is found 3 months after stroke [18]. A low correlation exists between the increased passive stiffness and factors such as the range of motion (ROM), the Ashworth score, and the Fugl-Meyer lower extremity motor score. This indicates that the early changes in the mechanical response to stretch in plantar flexors occur without regard to the level of disability. The changes in passive stiffness may be due to changes in collagen tissue, tendons, joint capsules, and the muscles, possibly leading to clinically observable contractures. Changes in the Achilles tendon most likely lead to the observed increase in stiffness, but one cannot exclude the fact that changes in other collagen tissues or muscle fibers themselves add to the increased passive stiffness.

Changes in the muscle fibers should be reflected in the intrinsic stiffness. Sinkjær [33] found a significant increase in the intrinsic stiffness of the ankle dorsiflexors in spastic MS patients and observed similarly an insignificant increase of 20% of the hemiplegic patients' ankle plantar flexors. These findings are consistent with physiological, morphometrical, and histochemical investigations demonstrating changes of the muscle fibers, which are specific to the spastic muscle. If the muscles were relatively immobilized, the patients would probably be particularly susceptible to this type of potentiation. The changes in triceps surae muscles resulting from disuse or from immobilization in the shortened position, which has been demonstrated in animal experiments, can be considered a useful model for the changes in paretic "overactive" muscles [31].

Although the reason for the pathological changes in the mechanical properties of the contractile elements of the spastic muscles as well as alternations of the connective tissue (e.g., in the tendon) is still speculative, the
marked increase in passive and intrinsic stiffness reported by several authors suggests that a peripheral non-reflex-mediated input can importantly contribute to spastic muscle tone.

### 8.6.4 Reflex-Mediated Mechanical Muscle Responses

In the active muscle, the stretch reflex makes a large contribution to the total mechanical stretch response in healthy subjects [1, 22]. In both healthy and spastic subjects at low and intermediate contraction levels, the reflex-mediated mechanical response is approximately 50% of the total response in the ankle plantar flexors. In moderately spastic MS patients, the reflex-mediated stiffness in the ankle plantar flexors was unchanged compared with healthy control subjects. In spinal cord injured (SCI) subjects, a system identification method that separated non-reflex and reflex contributions showed increased non-reflex stiffness as well as increased reflex stiffness in the passive and weakly contracted ankle extensors [20]. All of the patient groups had clinical signs of spasticity when measured by the Ashworth scale [2].

Increased muscle tone is not caused only by an increase in non-reflex properties (passive and intrinsic muscle components). The hypothesis is that the spastic patients are unable to inhibit the mechanically strong stretch reflex due to an impaired spinal and descending control in the relaxed “clinical” situation.

The increased stretch reflex in the relaxed spastic muscle and at weak precontractions can be caused by reduced postsynaptic and presynaptic inhibitions and/or changes in postactivation depression [27]. These are all inhibitory mechanisms, which are believed to be important to make the muscle relax in healthy subjects. As the muscle in healthy subjects is made increasingly active, these inhibitions are removed, and the reflex stiffness expresses itself fully as it has already done in the spastic subject’s relaxed “uninhibited” muscle.

### 8.6.5 Neuropathology of the Increased Muscle Tone and Exaggerated Stretch Reflex at Rest in Spastic Patients

In the resting healthy subject, the spinal motor neurons (“alpha motor neurons”) are silent and far from their firing threshold. This is because there is limited activity in the major excitatory pathways to the motor neurons (corticospinal cells and Ia afferents with monosynaptic projections to the motor neurons discharge at a low rate), and more importantly, tonic activity from descending and peripheral inhibitory input may also contribute. In addition to this, the activity of gamma motor neurons and hence the sensitivity of the muscle spindles to stretch are also low. Only a limited muscle spindle discharge is, therefore, evoked by a stretch. The central effect of the Ia afferents on the alpha motor neurons is diminished through presynaptic inhibition, which has been shown to be prominent in the resting subject. In spastic patients at rest, there now seems to be agreement with the fact that the sensitivity of muscle spindles to stretch is not increased. There is, therefore, no reason to maintain the view that increased gamma motor activity should play a role in spasticity (the so-called gamma spasticity).

In several studies, the transmission in different inhibitory pathways has been reported to be deficient in at least some populations of spastic patients. This includes reciprocal Ia inhibition [6], Ib inhibition [8], and recurrent inhibition [19]. This decreased transmission presumably leads to increased excitability of the alpha motor neurons, and this may be a factor contributing to spasticity at least in some spastic patients.

Presynaptic inhibition only seems to be decreased in some spastic subjects. For the lower limb, it is decreased in MS patients and paraplegic patients, but not in hemiplegic patients [13, 25].

The current understanding of the spinal pathophysiology of spasticity is that it is a multifactor syndrome that can be caused by almost any combination of deficient transmission in a number of spinal control mechanisms, including Ia reciprocal inhibition, presynaptic inhibition, recurrent inhibition, Ib inhibition, post-activation depression, and probably several other mechanisms.

Generalizations regarding the mechanisms of increased stretch reflex activity in spastic patients are clearly problematic on this complex background. Therefore, it should be kept in mind that the following paragraph is a simplification and does not necessarily apply to all spastic patients.

### 8.6.6 The Threshold and Gain of the Pathologic Stretch Reflex

In principle, two distinct parameters may be altered in the pathologic stretch reflex:

1. Initially, the threshold of the stretch reflex (which is equivalent to the threshold of the motor neuron recruitment) could be reduced with the effect that a smaller or slower motion is sufficient to reach the reflex threshold.
2. Secondly, the stretch reflex gain could be changed. This expresses an abnormal increase in the stretch reflex amplitude with increasing motion or motion velocity without substantial change in the reflex threshold (see also [16]).
The threshold and gain can be found from the “input–output” relation by plotting the stretch reflex (output) for different stretch velocities (input). In the relaxed ankle plantar flexors, the threshold of the soleus muscle stretch reflex is decreased [23], however unpublished data have challenged this view. Spasticity has been linked to an increase in motor neural excitability in the relaxed “bedside” situation. The stretch reflex threshold seems to reflect this increased motor neuronal excitability in the relaxed or nearly relaxed muscle.

Several possible pathways might be involved in explaining the threshold change of the stretch reflex, such as absent reciprocal inhibition [6], a changed, intrinsic regulation of transmitter release from the Ia afferents in spastic patients [27], changes in gamma motor neuron activity, and changes in activity in descending motor pathways of the brainstem that affect the postsynaptic inhibition. Since the stretch reflex is much less sensitive to presynaptic inhibition than the H-reflex [21], it is less clear if a decreased presynaptic inhibition [13, 36] can explain a shift in threshold.

8.6.7 Muscle Stiffness During Walking in Spastic Patients

Muscle and cutaneous reflexes are highly modulated during locomotion in an adaptive manner within each phase of the step cycle [5, 12]. This modulation is often lost or severely reduced in patients with spasticity. Increased muscle tone relates to more functional motor tasks; it becomes, therefore, important also to investigate the “non-reflex/muscle component” together with the spinal/central integration of afferent input during more functional motor tasks such as walking.

8.6.7.1 The Non-Reflex/Muscle Component

The increased passive stiffness and intrinsic muscle stiffness found in sitting spastic subjects are also present during walking. Based on indirect force measurements of Achilles tendon in hemiparetic patients, Berger et al. [3] demonstrated that the non-reflex stiffness was increased during walking. They suggested that spastic hemiparetic patients could develop a larger muscle tension during walking at a lower level of neural drive (EMG activity) than healthy control subjects. This was seen as a benefit since it facilitates the patient to support body weight during the stance phase of walking in spite of the inability to activate the soleus muscle. This might be correct, but it should be remembered that a major part of the increase in non-reflex stiffness is caused by an increased passive stiffness, which will impair dorsiflexion in swing [35]. This becomes even more prominent in spastic patients because they have a decreased voluntary drive to the ankle dorsiflexors. In addition, spastic patients often co-contract their muscles during walking, which further increases the non-reflex stiffness.

8.6.7.2 Muscle Reflexes During Spastic Walking

On top of an increased non-reflex stiffness, the reflex modulation that takes place during walking in healthy subjects [38] is often lacking in spastic patients [14, 35]. The impaired reflex modulation has been interpreted to increase the muscle stiffness because of disrupted, super spinal control of the stretch reflex [14, 39].

Nielsen et al. [28] investigated the properties of the stretch reflex during walking and standing to allow for a more general understanding of how the input–output properties of the neural circuits involved in the stretch reflex control are affected in spastic patients. This was accomplished by comparing the input–output relation obtained in the early stance and early swing phase of walking with the input–output properties of the stretch reflex in sitting stroke patients. In healthy controls, a large difference was found in the threshold of the stretch reflex in the early swing phase of walking (309 deg/s) compared with sitting (71 deg/s) at a matched tibialis anterior muscle EMG activity. In stroke patients, this difference in threshold was considerably reduced to a minor difference in threshold of 108 deg/s in the early swing phase compared with 74 deg/s in sitting. No change was found in the slope of the input–output relations (Fig. 8.6.3). This suggests that the change in motor task seems to change the threshold but not the gain (slope) of the input–output properties of the stretch reflex. Furthermore, this task-specific change in threshold was small in spastic patients.

The difference between the stretch reflex threshold during sitting and walking can be considered as a “safety range” in which the ankle joint velocity can be varied without eliciting a stretch reflex. The “safety range” is higher by a factor of three or more in control subjects. Consequently, the range in which the velocity of the dorsiflexion can be varied in the swing phase without eliciting the stretch reflex is smaller in patients. Dorsiflexion is expected to be associated with stretch reflex bursts in the ankle plantar flexor muscles if the ankle joint velocity exceeds the stretch reflex threshold, causing the foot to do a rapid dorsiflexion. Because of this, the person would be prone to stumble or fall. Therefore, the patient has to adapt the walking speed to his/her ability to suppress the stretch reflex of the plantar flexors in the transition from stance to swing.

The peripheral changes, which take place during walking in spastic patients, are summed up in Fig. 8.6.4.
figure shows a sketch of the ankle joint stiffness during a full step cycle in healthy persons. The total stiffness is composed of passive, intrinsic, and reflex-mediated components. In healthy subjects, the total stiffness in the stance phase will increase as the intrinsic stiffness increases throughout the stance (due to increased central input to the muscle) and as the reflex stiffness and passive stiffness increase when the plantar flexors are stretched. In swing, the plantar flexor stiffness will depend on the passive component only when the central input to these muscles is zero, and the reflex threshold is switched from “low” in stance to “high” in swing. In spastic patients, the intrinsic stiffness and reflex stiffness are likely to be nearly normal and the passive stiffness increased in stance. In the swing phase, the passive stiffness is increased, and the intrinsic stiffness is zero (except if a co-contraction takes place). Because of the reduced stretch reflex threshold, the reflex stiffness will express itself if the dorsiflexion becomes too fast (Fig. 8.6.3).

Clinicians are faced with several situations where spasticity is responsible for major patient disability. Before treatment is started, the goals of therapy should be clearly identified:

1. In spastic patients who are not able to walk, but who suffer from contractures or painful spasms, antispastic treatment is meant to decrease the muscle tone to make the muscles become “flaccid.” This will improve the quality of life for these patients, and today, powerful treatments are available.

2. In spastic patients who have maintained the ability to walk, the goal of antispastic treatment is very different, at least during the active part of the day. Here, the aim is to inhibit unwanted muscle activity and to reinforce wanted activity in a coordinated pattern that would improve walking. More knowledge of the regulation and importance of spinal and descending control mechanisms during movement in healthy persons and spastic patients is necessary to improve such antispastic treatments. For example, clonidine, cyproheptadine, and baclofen, which are all able to modulate reflexes, have different modulatory effects on locomotion.

Walking in spastic patients may benefit from treatments that prevent the increased motor-neuronal excitability in order to lower the stretch reflex threshold. Nielsen & Sinkjaer [24] showed that baclofen increased the velocity threshold of the soleus stretch reflex during sitting in MS patients, but at the same time, it weakened the muscle contraction. An alternative method for reducing the stretch reflex during walking is an electrical stimulation of peripheral nerves that activates inhibitory pathways [14, 37]. By applying stimulation above motor threshold to the deep peroneal nerve in spastic stroke patients at the transition from stance to swing, it was shown that the
threshold of the soleus stretch reflex can be extensively increased and a near normal phasic modulation of the stretch reflex restored during walking. Interestingly, stimulation above motor threshold will cause a direct stimulation of the dorsiflexors and thereby assist in improving the dorsiflexion. This will further prevent the subject from stumbling.

The relationship between modulation of reflexes and locomotion will need further exploration to determine which treatments are optimal.

After a central motor lesion (cerebral or spinal), a profound disinhibition of short-latency stretch reflexes and the loss of voluntarily mediated motor functions take place. These changes are associated with two forms of adaptation: the development of spastic muscle tone and plasticity of spinal and central sensory-motor centers, which can be specifically trained. There is increasing evidence in the literature that the focus in neurorehabilitation of patients following stroke should be on retraining function and strengths. The rationale behind this approach is that as function is relearned, likely through plastic changes of the remaining central sensory-motor centers, spasticity will decrease. Controlled clinical studies of new neurostimulation–triggered, task-specific rehabilitation methods indeed show that patients benefit in function and quality of life [30].

**Suggested Reading**

Critical Neurosurgical Care

Edited by Christianto B. Lumenta
Consciousness Impairment
LUDWIG SCHÜRER, STEFAN WOLF, AND CHRISTIANTO B. LUMENTA

9.1 Basics

In neurosurgical intensive care, one principal goal of therapy is to preserve or improve the level of consciousness. Verifying the level of consciousness is an important element for therapeutic decisions and therapy control in some patients. In other patient groups, consciousness is deliberately eliminated to take advantage of the cerebro-protective effects of certain sedatives. Therefore, neurosurgical intensive care differs from other forms of intensive care, as sedation alters the function of the target of neurointensive care.

If there is an impairment of the level of consciousness, there are three key questions arising:
• What is the reason for this disturbance?
• Is there a therapeutic option to revert this disturbance?
• What is the prognostic value of the disturbance of awareness?

A definition of the consciousness is a prerequisite to be able to assess it.

9.1.2 Definition of Consciousness

Perhaps no concept is as difficult to define and understand as consciousness. The following definition is offered:

Consciousness accompanies and controls the interaction of an organism with its environment by interacting between an external stimulus to the organism and the reaction of the organism to this stimulus. The ability of an organism to be conscious depends, among other things, on its physiological integrity.

A complex definition of consciousness includes:
• Attention and the ability to direct and change this attention voluntarily
• Creation and processing of abstract ideas and communication of those by words or other symbols
• The ability to assess the significance of an action in advance, i.e. to have expectations and plans
• Knowledge of oneself and of other individuals

9.1.3 Morphologic Correlate of Consciousness

According to our experience, an individual is not bound by the completeness of the above definition. Loss of function of several brain areas is not necessarily followed by a loss of consciousness. On the other hand, it is known that the damage of specific brain areas (e.g. mesencephalon) is followed by a loss of consciousness.

The morphological correlate of consciousness is found in a system of brain areas extending from the reticular formation up to the cortex. It can be divided into three parts:
1. The activating reticular ascending system (ARAS)
2. The system of the general generation of consciousness in the thalamus and basal ganglia
3. A system of self-consciousness which is supposed to be located in the parietal cortex

9.1.3.1 The Activating Reticular Ascending System

The ARAS extends from the brain stem up to the hypothalamus. It receives afferent input from the spine, from the nuclei of the brain nerves, from the cerebellum and from the cerebral hemispheres and sends impulses to those structures as well (Fig. 9.1.1).

The ARAS has an important function for wakefulness/alertness. Depression of neuronal activity or its destruction results in reduced/abolished wakefulness, whereas its stimulation is followed by an arousal reaction.

It is important to note that sleep is an active process of the brain. During sleep, activation of the middle raphe results in decreased neuronal activity of the ARAS. Coma, therefore, is not a “form of very deep sleep” but the symptom of a loss of function.

Lesions in the locus coeruleus result in the inability to be aware of external stimuli. Lesions in thalamic areas and basal ganglia create a stage of awareness without the ability of getting in contact with the environment.
9.1.4 Mechanisms of Alterations in the State of Consciousness

There is a variety of reasons that lead to alterations or loss of consciousness:

- Morphologic brain damage (trauma, subarachnoid hemorrhage (SAH), stroke):
  - Damage to the reticular formation and ARAS
  - Bilateral lesions of the intralaminar thalamic nuclei
  - Bilateral damage of the hemispheres
  - Major damage to the dominant hemisphere
- Disturbances of the supply of the brain with nutrients:
  - Oxygen
  - Glucose
- Metabolic disturbances
- Intoxications

9.1.5 Grading of Disturbances of Consciousness

Unfortunately, the terminology of disturbances of consciousness is not uniform. In neurointensive care, derangements of consciousness occur in different grades:

- Clouding of consciousness
- Lethargy
- Obtundation

- Stupor
- Coma

Other forms of disturbed consciousness include the persistent vegetative state, the minimally conscious state, akinetic mutism and the locked-in syndrome.

9.1.5.1 Clouding of Consciousness

A mildly depressed level of awareness and slowing of abstract thinking is defined as clouding of consciousness.

9.1.5.2 Lethargy

Undisturbed lethargic patients lie quietly or sleep. On stimulation, they can react, but only in a rudimentary way. Verbal communication and intellectual functions are moderately impaired.

9.1.5.3 Obtundation

Obtundation is a more severe form of lethargy, as stronger external stimuli are necessary to get into contact with the patient. Verbal and intellectual capacities are severely impaired. The patient can answer simple questions. Once external stimulation subsides, lethargic patients fall back to sleep immediately.
Stuporous patients require a high degree of stimulation to provoke arousal. They are incapable of speaking but may grunt some inappropriate words, which are hardly understandable. Simple commands may be followed inconsistently. Upon cessation of external stimuli, patients in a stupor return to their previous state.

Coma

In the clinical routine, coma is defined as a state in which the patient is incapable of following commands, does not open his eyes and does not speak in response to painful stimuli.

Grading of Coma

For brief and reliable communication between health care professionals, several scaling systems have been developed to reproducibly describe a given deficit.

Since its publication in 1974 by Teasdale and Jennett, the Glasgow Coma Scale (GCS) has become increasingly popular (Table 9.1.1). Other grading systems should no longer be used.

The GCS is a semi-quantitative scale which originally was developed for medical assistance personal. The evaluation can be performed within one minute. The sum of three independent scales for eye-opening, verbal and motor response is documented as a basic function of arousal and consciousness. It has been shown that the initial score of patients with subarachnoid hemorrhage and traumatic brain injuries correlates with the outcome of those patient groups. Of special importance is the GCS level of 8 or less, i.e. patients who do not talk and do not obey commands, as this threshold is used for invasive intracranial pressure (ICP) measurement, intubation and mechanical ventilation (see Sect. 9.2).

Frequent Neurosurgical Causes of Altered Consciousness

Many intracranial disturbances go along with increased intracranial pressure. When intracranial pressure rises quickly, the level of consciousness is depressed. Frequent neurological diagnoses include:

- Hypertensive encephalopathy
- Ischemic stroke
- Intracranial hemorrhage
- Subarachnoid hemorrhage
- Meningitis
- Brain trauma

Approach to the Comatose Patient

Although innumerable insults can result in deterioration of consciousness, the initial approach to stabilization remains the same as for any acute cardiorespiratory emergency:

- Cardiovascular stabilization (airway, breathing, circulation)
- Emergency neurologic exam
- Blood samples for analysis (sodium, glucose including quick test, urea, blood gas sample, toxicity screen)
- Emergency supportive medications if necessary (glucose, naloxone, thiamine)
- Cranial computed tomogram if necessary
- Mannitol if intracranial pressure is suspected or herniation signs are present
- Correction of Metabolic abnormalities

<table>
<thead>
<tr>
<th>Points</th>
<th>Best eye</th>
<th>Best verbal</th>
<th>Best motor</th>
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<tr>
<td>6</td>
<td>–</td>
<td>–</td>
<td>Obey</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>Oriented</td>
<td>Localizes pain</td>
</tr>
<tr>
<td>4</td>
<td>Spontaneous</td>
<td>Confused</td>
<td>Withdraws to pain</td>
</tr>
<tr>
<td>3</td>
<td>To speech</td>
<td>Inappropriate</td>
<td>Flexor (decorticate)</td>
</tr>
<tr>
<td>2</td>
<td>To pain</td>
<td>Incomprehensible</td>
<td>Extensor (decerebrate)</td>
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<tr>
<td>1</td>
<td>None</td>
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Table 9.1.1 Glasgow Coma Scale
9.2 Intracranial Hypertension

LUDWIG SCHÜRER, STEFAN WOLF, AND CHRISTIANTO B. LUMEN'TA

9.2.1 Basics

Therapy of increased ICP is the focus when treating patients with severe neurosurgical pathology. An increase of ICP is compromising brain perfusion with ensuing cerebral ischemia and brain swelling. This can result in brain herniation with a fatal clinical course. Therefore, a critical increase of ICP is a central factor in the genesis of secondary brain damage. In contrast to the primary lesional damage, this secondary brain damage is preventable and amenable to treatment.

A possible relation of increased intracranial pressure and neurological outcome has been the focus of neurotraumatologic research for decades. In the patients of the North American traumatic coma data bank, duration and extent of intracranial hypertension over a critical threshold of 20 mmHg was an independent predictor of poor neurological outcome after severe head injury. New clinical studies show a relation between aggressive treatment of elevated ICP and an improved neurological outcome. The analysis of patients who develop secondary neurological deterioration shows that cerebral perfusion pressure – as long as it is higher than 50–60 mmHg – does not have an influence on outcome, while in this patient collective, an increased ICP above 20 mmHg was associated with an unfavorable result.

9.2.2 Pathophysiology

The ICP is the pressure exerted by the contents of the skull on the dura mater. Normal ICP varies between 5 and 15 mmHg and includes the (compressible) brain tissue (80–83%) and the incompressible fluids blood (3–11%) and cerebrospinal fluid (CSF) (5–15%). Physiologically, the increase in volume of one component is compensated by a decrease in volume of the others, usually by shift of CSF into the spinal canal. If this is not possible, intracranial pressure rises.

The brain is a Starling resistor, which in combination with the mean arterial pressure (MAP) defines the cerebral perfusion pressure (CPP). In other words:

\[ \text{CPP} = \text{MAP} - \text{ICP} \]

An intracranial space-occupying lesion (i.e., tumor, bleed, edema) in the initial phase can be compensated by shift of CSF into the spinal canal as well as by increased CSF resorption. After the reserve capacities are exhausted, a further increase of intracranial volume leads to an exponential rise of ICP.

The measure for the stiffness of the brain is defined as elastance \( \Delta P / \Delta V \). The reciprocal of this term is called compliance. The value of elastance increases with reduced reserve capacity; the value of compliance decreases. This coherence can be described by the classical exponential volume–pressure curve (Fig. 9.2.1).

A slow elevation of ICP (within weeks) may be caused by a growing tumor or a chronic subdural hematoma; a more rapid ICP rise (within hours) can be the result of obstruction of the CSF pathways. Fast ICP increases (few minutes) usually are the consequences of hemorrhage or changes in blood volume.

Fig. 9.2.1 Pressure–volume curve. [Courtesy of Marmarou, Saunders, Philadelphia (2004)]
A rapid increase of ICP results in hemodynamic changes to ascertain a sufficient brain perfusion. The initial rise of ICP results in a reduction of CPP; this is followed by a decrease of cerebrovascular resistance (CVR).

\[
\text{CVR} = \frac{\text{CPP}}{\text{CBF}}
\]

The ensuing vasodilation leads to an increase of cerebral blood volume (CBV). The consequence is a further rise of ICP. A vicious circle can start to turn, which is termed vasodilatory cascade. One central goal of the specific therapy of elevated ICP is to interrupt and reverse this circle (vasoconstrictory cascade). In this context, it is important to understand the autoregulation of brain blood flow.

In the physiological range (MAP between 50 and 125 mmHg) blood flow is kept constant by changes of arteriolar diameters. Below and above an MAP of 50 mmHg and 125 mmHg the arterioles react in a pressure passive way. In the range of autoregulation a decrease of CBF can be achieved via reduction of arteriolar diameters, finally resulting in a decrease of ICP (Fig. 9.2.2).

In conditions of disturbed autoregulation, cerebral blood flow depends on the value of MAP. ICP is positively correlated to MAP, i.e. the higher the MAP, the higher the intracranial blood volume and ultimately the ICP (Fig. 9.2.3).

### 9.2.3 Measurement Devices for Intracranial Pressure

An invasive ICP measurement device is necessary to exactly determine the pressure in the cranial vault. All efforts to measure ICP non-invasively have failed in the clinical routine so far.

**Fig. 9.2.2** Intact autoregulation and ICP. [Modified after Lang, JNNP 74:1053 (2003)]

**Fig. 9.2.3** Disturbed autoregulation and ICP. [Modified after Lang, JNNP 74:1053 (2003)]
9.2.3.1 Ventricular ICP Devices
An intraventricular drainage catheter connected to an external pressure transducer is still the “golden standard” of intracranial pressure monitoring. With the help of this technique, it is possible to measure ICP and drain CSF for ICP reduction as well. A key advantage of this technical setup is the possibility of recalibrating the system in vivo. Simultaneous CSF drainage and correct measurement of ICP is not possible. The risk of infection with careful handling is approximately 5% per application.

9.2.3.2 Parenchymal ICP Devices
The insertion of a ventricular catheter into a swollen brain with midline shift can be difficult or impossible. For these cases, parenchymal devices are available. They produce stable measurements with acceptable drift, independent of the position of the head. The risk of significant bleeding during insertion as well as the risk of infection is less than with a ventricular device (below 1%).

Disadvantages of the parenchymal probes are the impossibility of draining CSF and the lack of in vivo recalibration.

9.2.3.3 Devices for Concurrent ICP Measurement and CSF Drainage
The technological solution of the Spiegelberg III probe offers both the possibility of CSF drainage and accurate ICP measurement at the same time. A pneumatic balloon incorporated around the catheter serves for ICP measurement. This pneumatic system is recalibrated in vivo every hour. Other systems manufacturers combine a standard ventricular catheter with a piezoelectric pressure manometer.

9.2.3.4 European Standard
The European standard is as follows:
- The first-line device for ICP monitoring is an external ventricular drain.
- If a patient shows critical elevated ICP that is only manageable by continuous CSF drainage, either a parenchymal device for monitoring ICP additionally to the ventricular drain or a device designed for combined monitoring and CSF drainage is to be used.
- A routine change of ventricular catheters is not recommended. The catheter should be left in place only as long as it is needed.
- Prophylactic application of antibiotics for ventricular drains is not recommended.
- Epidural, subdural or subarachnoidal ICP measurement techniques are imprecise and should not be applied.

9.2.4 Selection of Patients for ICP Measurement
The necessity for ICP measurement is either deducted by a pathological CCT scan or a consciousness impairment score of 8 or less on the GCS (i.e. patients who do not talk and do not obey commands). The following principles hold true for head trauma patients as well as patients with intracranial bleeding, subarachnoid hemorrhage or postoperative neurosurgical complications.

9.2.4.1 European Standard
The European standard for selecting patients for ICP measurement is as follows:
- An intracranial pressure monitor is necessary in patients with consciousness impairment and a pathological cranial computed tomogram (CCT) with hematoma, contusions, brain edema or compressed basal cisterns.
- In patients with a head injury, a GCS score of 8 or less and inconspicuous CCT, ICP measurement is recommended if at least two of the following criteria are fulfilled: age greater than 40 years, systolic arterial pressure less than 90 mmHg and decerebrate or decorticate posturing on motor exam (unilateral or bilateral).
- ICP measurement in awake patients with head trauma can be considered if they show contusions in the CT scan.
- ICP measurement should be considered for patients with head injury and normal CCT who need sedation for extracranial reasons (i.e. thoracic trauma requiring mechanical ventilation) and where secondary cerebral deterioration cannot be discerned.

9.2.5 Treatment of Increased Intracranial Pressure
After removal of a surgically accessible mass, treatment of elevated intracranial pressure follows an escalating staircase protocol:
- First-line therapies:
  - Body elevation (30 degrees)
  - Sufficient sedation
  - Cerebral perfusion pressure (CPP) between 50 and 60 mmHg
Fentanyl/Sufentanil. Analgesia is required in almost all neurointensive care patients, and morphine derivatives like fentanyl appear to be an appropriate choice. Sufentanil has a short duration of action and is used especially for patients in the recovery phase. The recommended dosages are:

- Fentanyl induction dose: 0.1–0.2 µg/kg
- Fentanyl maintenance dose: 0.25–10 µg/kg/h via infusion pump
- Sufentanil maintenance dose: 0.5–2 µg/kg/h via infusion pump

**Recommendation.** Propofol, midazolam and fentanyl/sufentanil are used alone or in combination. All continuous doses should be individually titrated to avoid overdosing of sedation. Additionally, if ICP is uncritical and otherwise feasible, a daily interruption in continuous analgesia and sedation is recommended to re-evaluate the doses needed.

9.2.5.3 Drainage of Cerebrospinal Fluid

In situations of elevated intracranial pressure, drainage of the CSF compartment is the most efficient and fastest method to reduce ICP. It is possible to drain CSF continuously or discontinuously. In severe cases, continuous CSF drainage is more efficient to control ICP. It is noteworthy that correct measurement of ICP via the fluid column is not possible during CSF drainage.

**Recommendation.** An additional parenchymal probe is necessary to be able to monitor ICP correctly during CSF drainage in severely ill patients. Unnecessary and too-generous drainage of CSF may cause exacerbation of brain edema via increased filtration pressure into the tissue.

9.2.5.4 Cerebral Perfusion Pressure

Maintenance of an adequate perfusion pressure to the brain reduces the risk of ischemic episodes to the brain parenchyma. Different treatment strategies exist. At the beginning of the 1990s, it was advocated to elevate perfusion pressures of 80–90 mmHg to disrupt the vasodilatory cascade (according to M. Rosner). Contrary, there is the “Lund Concept,” which tolerates a CPP as low as 50 mmHg to minimize the formation of vasogenic brain edema. Contemporary research advocates a CPP between 50 and 60 mmHg to minimize the side effects of either extreme treatment.

**Recommendation.** CPP should be kept between 50 and 60 mmHg. Measures to decrease ICP have priority over the elevation of the perfusion pressure with volume and catecholamines.
9.2.5.5  Moderate Hyperventilation

Hyperventilation-induced hypocapnia leads to vasocostriction, increase of cerebrovascular resistance and decrease of cerebral blood flow and volume, leading to a reduction of ICP.

*Recommendation.* $P_{CO_2}$ should be kept above 35 mmHg, since further reduction can reduce cerebral blood flow significantly, thus leading to secondary cerebral ischemia. During acute neurological deterioration, if deep sedation, CSF drainage or application of mannitol cannot influence episodes of increased intracranial pressure, short periods of forced hyperventilation (down to a $P_{CO_2}$ of 30 mmHg) may be considered. Forced hyperventilation should only be performed with indwelling catheters for measurement of oxygen saturation in the jugular bulb ($S_jO_2$) or for measurement of the local cerebral oxygen tension ($P_{aO_2}$). With the help of these techniques, episodes of ischemia ($S_jO_2 < 55\%$ or $P_{aO_2} < 10\,\text{mmHg}$) occurring during forced hyperventilation can be detected.

9.2.5.6  Osmotherapeutics: Mannitol and Hypertonic Saline (NaCl 7.5%)

*Mechanism of Action.* Mannitol, an alcohol derivative of mannose, is the most popular osmotic agent to control increased ICP. Mannitol dehydrates the swollen brain by osmotic fluid shifts. Mechanistic studies have revealed that mannitol reduces blood viscosity and diameter of pial vessels. Apart from fluid shifts to the intravascular space, mannitol leads to an increased deformability of red blood cells. Brain blood flow is increased because of the better fluidity of the blood and the improved vascular filling. The fast increase of CBF is followed by a vasoconstriction (autoregulatory response) with a consecutive decrease of the cerebral blood volume, going along with a decrease of ICP.

Apart from osmotic effects, NaCl has positive vasoregulatory, hemodynamic, neurochemical and immunologic properties. New data indicates that osmotherapeutic hypertonic saline solution (NaCl 7.5%) has fewer side effects and is at least as effective as mannitol in decreasing elevated ICP.

NaCl has a higher reflection coefficient ($\sigma = 1.0$) than mannitol ($\sigma = 0.9$), signifying that the substance is not passing the blood–brain barrier. While for mannitol a “rebound phenomenon” is discussed, this probability is reduced for hypertonic NaCl.

*Recommendation.* Application of mannitol in a dose of 0.25 g/kg b.w. and 1 g/kg b.w. effectively reduces increased ICP. Volume deficits need to be corrected. Mannitol infusion is disadvised above a serum osmolarity of 320 mOsm because of the risk of renal failure. A bolus administration of mannitol has a more pronounced effect on the ICP than continuous infusion.

NaCl 7.5% may be applied in a dose of 1.0–2.0 g/kg b.w. to treat elevations of ICP in situations where mannitol is no longer effective or in exchange with mannitol to reduce the side effects. The application of NaCl 7.5% should be discontinued if the serum sodium concentration is above 155 mEq/L.

9.2.5.7  Barbiturates

Barbiturates decrease ICP via changes of the vascular tone, reduction of brain metabolism and inhibition of free radical mechanisms and lipid peroxidation. The most important mechanism seems to affect coupling of brain perfusion and metabolism ($CMRO_2$). A decrease of $CMRO_2$ is followed by a reduction of brain blood flow and cerebral blood volume, ensuing in an ICP reduction. Severe side effects of this substance class are hypotension, pneumonia and suppression of the immune system.

Three different patterns of ICP changes after barbiturate boluses are observed: good, moderate and lacking decrease of ICP. The outcome of patients with good ICP response is significantly better than of those patients who did not react with an ICP reduction after barbiturate.

*Recommendation.* Barbiturates should be considered individually for patients with severe injury with otherwise intractable elevations of ICP. Prophylactic barbiturate treatment is not advisable because of the side effects of the substance. When barbiturates are used, dosage should be controlled by burst-suppression EEG. In addition, careful hemodynamic monitoring and generous fluid replacement reduces hypotensive episodes during barbiturate usage.

9.2.5.8  Moderate Hypothermia

Hypothermia leads to a temperature-dependent reduction of metabolism and – like barbiturates – via a reduction of cerebral blood volume to a fall in ICP. Decrease in body temperature results in membrane stabilization and can limit the spread of brain edema. Reduction of body temperature reduces excessive $Ca^{++}$ and glutamate fluxes into the cells, thus limiting delayed neuronal death after cell injury. Hypothermia reduces inflammatory reaction and liberation of cytokines. The role of hypothermia in neurosurgical patients is uncertain, as only one of two randomized, controlled trials could prove its effectiveness.

*Recommendation.* We use moderate hypothermia of around 35°C in selected patients with otherwise intractably elevated ICP, especially after traumatic brain injury (TBI) and subarachnoid hemorrhage.
9.2 Intracranial Hypertension

It has to be noted in this context that hyperthermia (fever) is deleterious for patients with intracranial hypertension. Aggressive cooling is performed if body temperature rises above 38°C.

9.2.5.9 Decompressive Craniectomy

Decompressive craniectomy with generous removal of the skull bone and dura extension plasty has been performed in selected patients for treatment of otherwise untreatable intracranial hypertension for more than 50 years. This operation leads to an effective control of intracranial hypertension. Despite that, it is unknown whether this invasive measure leads to an improvement of outcome.

Currently, it is unclear whether this operation should be performed at the end of the scale of the second-tier therapies or whether it should be performed relatively early in a selected patient group.

Recommendation. Decompressive craniectomy is recommended in patients with:

- Unilateral lesions [i.e. epidural hematoma (EDH), subdural hematoma (SDH), contusions > 25 mL]
- Midline shift between 1 and 2.5 cm
- Significant brain swelling

In addition, the following criteria have to be fulfilled:

- Patient should be younger than 65 years
- GCS motor score > 1
- At least one pupil reacting to light

Lesions on the dominant hemisphere are not a contraindication for decompressive craniectomy.
9.3 Water and Electrolyte Regulation

LUDWIG SCHÜRER, STEFAN WOLF, AND CHRISTIANTO B. LUMENTA

9.3.1 Introduction

Fluid and electrolyte disturbances are common in critically ill neurosurgical patients, as central nervous system (CNS) damage may affect the brain’s ability to keep regulating their homeostasis.

The potential consequences of fluid and electrolyte disturbances on the predamaged brain are profound and influence the development of cytotoxic or vasogenic brain edema, loss of cerebral autoregulation, increased intracranial pressure or decreased perfusion pressure.

Early recognition and appropriate management of fluid and electrolyte disorders are important to minimize secondary brain damage.

9.3.2 Basics

9.3.2.1 Body Water

Total body water (TBW) varies considerably (45–80%, mean approx. 55%) and depends on age, sex and leanness. TBW is distributed in two compartments. Three fifths represent the intracellular fluid compartment and two fifths are found extracellularly. The extracellular fluid compartment can be divided into the intravascular (25%) and the interstitial space (75%).

9.3.2.2 Electrolytes

In the extracellular compartment, sodium and chloride are predominant, whereas in the intracellular space, potassium and phosphate are prevailing. Extracellular sodium normally ranges from 135–145 mEq/L. Only 2% of the sodium is located intracellularly.

The opposite holds for potassium. Nearly all potassium is found intracellularly; only 2% is found extracellularly. The normal extracellular potassium level is 3.5–5.0 mEq/L. The high intracellular to extracellular gradients of sodium and potassium are maintained by the sodium/potassium ATPase pump and are required to maintain a normal membrane potential.

Since the distribution of sodium essentially corresponds to the extracellular volume and water is freely permeable within the fluid spaces, two rules of thumb can be formulated:
1. Primary disturbances of the sodium concentration result in variations of the extracellular space, given that the system for osmotic regulation is intact.
2. Disturbances of the water content are followed by alterations of the intra- and extracellular volume. If the ratio of water content to normally dissolved solutes is changing, an alteration of osmolarity is the consequence.

9.3.2.3 Osmolarity, Osmolality and Tonicity

To better understand the differences between osmolarity, osmolality and tonicity, these terms are defined in Table 9.3.1.

9.3.3 Regulation of Body Water and Osmolarity

Figure 9.3.1 summarizes volume and osmoregulation. In healthy individuals, plasma sodium and osmolarity are maintained within a markedly narrow range. This stability is achieved primarily by adjusting total body water to keep it in balance with sodium. Baroreceptors in the aorta and the atrium of the heart register blood volume and -pressure and modulate fluid intake (thirst) and fluid excretion (kidney).

Antidiuretic Hormone. The most important control mechanism is the release of antidiuretic hormone (ADH). ADH is secreted in parallel with rising serum osmolarity. The osmotic threshold for ADH release is approximately 280 mOsm/L. ADH increases water reabsorption in the kidney and leads to a concentrated urine. Under maximal ADH stimulation, the kidney can concentrate primary urine to achieve a urine osmolarity of well over 1,000 mOsm/L, thus saving water.

Besides hyperosmolarity, ADH secretion can be stimulated by a number of drugs (narcotics, barbiturates, carbamazepine) and by states of increased tone of the sym-
Regulation of Sodium

The goal of sodium regulation is the maintenance of adequate blood pressure and volume. Sodium balance of the body is modulated by renal, neuronal and humoral mechanisms.

The physical forces of hydrostatic and oncotic pressure in the renal microcirculation play a key role in the regulation of extracellular sodium concentration. An increase of renal perfusion pressure and a decrease of oncotic pressure favor sodium excretion and vice versa. Dopamine-induced vasodilation leads to higher hydrostatic pressure in the capillaries and results in sodium loss, while vasoconstriction (i.e. in hypovolemic shock or heart failure) contributes to sodium retention. Adrenergic stimulation enhances renal sodium reabsorption, while denervation reduces it.
9.3.4.1 The Renin–Angiotensin–Aldosterone System

The main hormonal mechanism influencing sodium turnover is the renin–angiotensin–aldosterone system. Reductions in blood volume are sensed by the juxtaglomerular apparatus, which is followed by renin release from the kidney. Ultimately, angiotensin II and aldosterone levels are enhanced. Angiotensin II has multiple effects as a vasoconstrictor and as a stimulator of hypothalamic thirst centers. Aldosterone causes an elevated distal tubular sodium reabsorption and potassium excretion.

9.3.4.2 Atrial Natriuretic Peptide (ANP)

The atrial natriuretic peptide (ANP), which is secreted from cardiocytes in situations of increased blood pressure and stress of the right atrium, affects kidney function directly. ANP leads to increased diuresis and natriuresis, inhibits the renin–angiotensin system as well as the release of ADH, decreases the systemic resistance and arterial blood pressure and finally decreases thirst. ANP locally released in the central nervous system seems to participate in the regulation of intracellular brain volume as well as cerebral fluid and electrolyte concentrations, possibly via stabilizing effects on brain capillaries.

9.3.5 Regulation of Potassium

Potassium secretion in the kidney occurs based upon its concentration in the distal tubule. Aldosterone, acting at the distal tubule, is released if serum potassium levels are high. It promotes not only reabsorption of sodium but also excretion of potassium. Distribution of potassium between intracellular and extracellular space is also regulated by the acid–base balance. Alkalosis, seen in hyperventilation therapy, leads to movement of potassium into the cells, lowering plasma potassium levels and promoting renal excretion. Acidosis exerts the opposite effect.

9.3.6 Fluid Regulation in the Brain

In the peripheral organs, oncotic and hydrostatic pressure regulate the distribution of intra- and extravascular fluid distribution. The blood–brain barrier (BBB) is responsible for the fluid balance in the CNS. Osmotic pressure gradients along the endothelial cells of the brain capillaries primarily determine fluid distribution between intravascular and extracellular space.

9.3.6.1 The Blood–Brain Barrier

The blood–brain barrier represents a mechanical obstacle with a mean pore size as small as 7 Å. Even small molecules like sodium are unable to diffuse through these pores and represent an osmotic force. The proportion of oncotically active solutes under particular blood–brain-barrier conditions, therefore, plays only a minor role in fluid balance within the brain. Water, exclusively, can diffuse freely through the pores of the BBB and follow osmotic gradients, which are equilibrated quickly.

As expected according to the above considerations, changes of the oncotic load of the blood as seen in conditions of hemodilution or infusion of colloids only have a minor effect on extracellular brain water or brain edema in situations of an intact BBB, whereas alterations of osmotic load (mannitol, hypertonic saline) are followed by significant changes of brain water and ICP.

9.3.6.2 Fluid Regulation in the Brain with a Damaged Blood–Brain Barrier

In areas of damaged BBB, there is an increase of permeability of the vascular endothelium for larger molecules, so that oncotic and hydrostatic pressure become responsible for fluid distribution in these regions. In these cases, colloid infusion solutions should be advantageous over crystalloids to counteract brain edema.

9.3.7 Changes of Sodium and Water Balance Following Surgery

After surgery, the retention of sodium and water is regularly observed. This is attributed to increased secretion of antidiuretic hormones and adrenocorticosteroids. The hormone levels fall again gradually during the first 3 or 4 days postoperatively, and their release is unrelated to plasma osmolarity. Many factors may contribute to the perioperative release of antidiuretic hormones:

- Hemorrhage-induced changes of the circulation
- Hypotensive drugs
- Fluid losses by emesis
- Infusion of osmiodiuretics like mannitol

It is important to be aware of the increased levels of antidiuretic hormones in the early postoperative phase or in response to trauma and to correct imbalances carefully. Injudicious intravenous infusion and inappropriate ADH secretion probably account for many cases of hyponatremia in neurosurgical patients.
Water and Electrolyte Regulation

9.3.8 Hypernatremia

Definition. In neurosurgical patients, hypernatremia, defined as serum sodium greater than 150 mmol/L, is most commonly seen in cases of diabetes insipidus (see Sect. 9.3.10) or after infusion of a hypertonic salt solution.

Symptoms. Moderate elevations of sodium concentration (3–4 mmol/L) clinically become manifest by a strong feeling of thirst. Sodium levels higher than 160 mmol/L or osmolarity greater than 330 mOsm/L lead to confusion, restlessness, lethargy, seizures, tremor and hyperreflexia.

9.3.9 Hyponatremia

Definition. Normal serum sodium is between 135 and 145 mmol/L. Severe hyponatremia is present with values below 120 mmol/L.

Aetiology and Epidemiology. In neurosurgical cases, hyponatremia is mainly seen in the syndrome of inadequate ADH secretion (SIADH) or in the so-called cerebral salt-wasting syndrome (CSWS). SIADH is thought to represent a dilution hyponatremia with normal or increased intravascular volume, whereas CSWS is defined as combined loss of sodium and free fluid. Consequently, the therapy of both syndromes is completely different.

9.3.10 Diabetes Insipidus

Definition. Diabetes insipidus is a disorder of excessive renal loss of water due to a deficient secretion of ADH, unresponsive to changes in serum osmolarity or hypertension.

Symptoms. Clinically, diabetes insipidus is characterized by polyuria and by polydipsia (craving for water) in awake patients, leading to hypernatremia. Polyuria and hyponatremia occur during the first phase usually 6–8 h after trauma or surgery, as endogenous ADH is still circulating. This first phase may last for 2–5 days and is frequently seen after manipulation of the pituitary stalk. A second phase of antidiuresis with decreased urinary output and lower serum sodium may last for 5–14 days and may be followed by permanent diabetes insipidus (lesions of the hypothalamus, tuber cinereum).

Aetiology and Epidemiology. In neurosurgical patients, diabetes insipidus results most commonly from injury to the anterior hypothalamus (anterior communicating aneurysm surgery) or the pituitary stalk (transsphenoidal operation). The incidence of diabetes insipidus following severe head injury is about 2% and appears to be more likely if there are fractures in or around the sella turcica.

In 7% of all transsphenoidal operations or craniopharyngioma surgeries, diabetes insipidus occurs but usually normalizes after 12–36 hours. Diabetes insipidus can be expected with high frequency in patients who develop brain death while receiving somatic life support.

Making the Diagnosis. The following are used to diagnose diabetes insipidus:
- High urine output > 200–250 mL/h
- Low specific gravity of urine 1.001–1.005
- Low urine osmolarity 50–150 mOsm/L
- Normal or above normal serum sodium
- Normal adrenal function

Differential Diagnoses. The following include differential diagnoses for diabetes insipidus:
- Psychogenic polydipsia
- Nephrogenous diabetes insipidus (renal insensitivity to ADH)
- Osmotic diuresis (mannitol)

Therapy for Diabetes Insipidus. Therapy for diabetes insipidus with polyuria consists of the administration of desmopressin acetate (ADH). Application is parenteral in patients with deranged consciousness and intranasal in the cooperative patient. It is advisable to postpone the first desmopressin application (wait for a negative fluid balance of 2,500 mL), because over-substitution may cause iatrogenic hyponatremia. In the awake and cooperative patient with an intact thirst center, substitution may be necessary only with urine amounts above 4,000 mL/day. Patients with lower urine output are able to substitute the water loss by drinking. The amount of water needed is regulated by thirst.

Desmopressin acetate dosing is adjusted according to the urine output. The therapeutic goal is a neutral fluid balance with a daily urine output of 2,500 mL. An existing free water deficit is corrected with hypotonic NaCl solution. The formerly given glucose 5% is an inferior alternative, because it often introduces significant glycemic disturbances.

9.3.11 Syndrome of Inadequate ADH Secretion

Definition. SIADH (Schwartz–Bartter syndrome) is defined as a continuous secretion of ADH despite hyponatremia and low serum osmolarity and normal or expanded extracellular volume.

Symptoms. Clinically, a deterioration of the level of consciousness, new focal deficits, myoclonus, seizures or increasing ICP should raise the suspicion of hyponatremia and hypo-osmolarity. Awake patients often experience paradoxical (inappropriate) thirst.
Epidemiology. About 5% of ICU patients with subarachnoid hemorrhage and traumatic brain injury are likely to develop SIADH. It can also be found in tumors, after craniotomy and in cases of meningitis.

Making the Diagnosis: The following allow for a diagnosis of SIADH:
- Normal renal and adrenal function
- Serum osmolarity < 280 mOsm/L
- Serum sodium < 134 mEq/L
- High urinary sodium (>25–30 mEq/L), often 50–150 mEq/L

The diagnosis of SIADH in the critically ill neurosurgical patient is difficult, because the volume status is difficult to assess. The diagnosis can be confirmed in the ICU when simple restriction of fluids results in reduction of urinary sodium losses and correction of hyponatremia. Measurements of uric acid may also be helpful since uric acid levels are low in SIADH and increased in hypovolemia.

Treatment of SIADH. Before restricting fluids, one must be certain that the hyponatremia is not due to CSW (see Sect. 9.3.12). For milder cases of SIADH, fluid restriction less than 1 L/day is the treatment of choice. Treatment of chronic SIADH consists in long-term fluid restriction (1,200–1,800 mL/day) and additional furosemide application (40 mg/day). The application of the tetracycline antibiotic demeclocycline (150–300 mg PO q 6 h), which partially antagonizes the ADH effect on the renal tubule, may be considered.

Treatment of CSWS and SIADH

A key feature in differentiating CSW patients from patients with SIADH is their volume status, which may be difficult to assess. Central venous pressure is not an adequate tool to establish the diagnosis of either disease. The course of fluid balance over days is more important in distinguishing between CSW and SIADH. Both patient groups have elevated ADH levels; the elevation in SIADH is inappropriate, whereas the elevation in CSWS is considered appropriate. There is no single laboratory parameter that is pathognomonic for either disease. In cases where the differential diagnosis between SIADH and CSW remains unclear despite clinical and laboratory assessment, a treatment course of substitution of sodium to a serum level of 130 mmol/L and probatory therapy with mineralocorticoid fludrocortisone (0.2 mg i. v. q 8 h) while maintaining an isovolemic state is appropriate.
9.4 Temperature Regulation

LUDWIG SCHÜRER, STEFAN WOLF, AND CHRISTIANTO B. LUMENTA

9.4.1 Introduction

Mammals and birds are homoiotherms and are able to keep their body temperature constant within a very small range despite changing ambient temperatures. In the history of evolution, thermoregulation developed gradually and became more and more efficient. This is reflected by the existence of multiple parallel hierarchical structured thermoregulatory systems in the brain. Disturbances of these complex regulatory systems by anesthesia, brain tumors or other neurologic diseases can lead to considerable alterations of body temperature with potentially life-threatening consequences.

9.4.2 Normal Control of Thermoregulation

Temperature control is achieved by three sub-systems:

- The thermoafferent system
- The integrating systems
- The effector (output) system

9.4.2.1 The Thermoafferent System

Changes in temperature of thermoreceptors, which are predominantly found in the skin but also in the thalamus, lower brain stem and spinal cord, elicit electrical impulses to free nerve endings located in the dermal and epidermal skin layers. Primary thermal afferents project to the rostral brain stem, thalamic nuclei and to the somatosensory cortex. Temperature signals from the face are conducted via projections of the trigeminal nucleus. The distribution of thermoreceptors in the skin is not uniform. The face, neck and thorax carry about five times more thermal receptors than rest of the human body. There are more cold receptors than warm receptors in the skin. Warm receptors start to discharge at temperatures over 30°C. Discharge activity increases as temperature rises.

9.4.2.2 The Integrating System

Thermal signals from peripheral receptors are integrated at several levels of the CNS (mesencephalon, medulla oblongata). If the thalamic (preoptic area) thermoregulation center is knocked out, phylogenetically older regulators are able to control temperature in a more rudimentary way.

In the preoptic area of the thalamus, incoming information on the ambient temperature is compared with an intrinsic reference signal. Change of ambient temperature above a certain threshold triggers mechanisms that regulate the disturbed temperature equilibrium by vasomotion, sweating and shivering or behavioral changes.

The temperature range that does not provoke strong thermoregulatory responses like sweating or shivering is called the neutral zone. Core temperature changes within this range are regulated by adaptation of cutaneous blood flow. In humans, this neutral zone has a value of 0.2°C but can be increased by different forms of anesthesia.

9.4.2.3 The Effector System

Autonomic responses to excessive heat are skin vasodilation, increased respiratory rate and sweating. The thermoregulatory steering is carried out by noradrenergic nerves. An increase of sympathetic activity results in vasoconstriction, a decrease in vasodilatation. Vasoconstriction results in heat preservation; vasodilatation leads to heat loss.

From the dorsal hypothalamus, the central shivering tract emerges and connects to the extrapyramidal motor tract, producing cold shivering. The core-temperature threshold for cold shivering is approx 1°C below the threshold for peripheral vasoconstriction. Metabolism can be doubled with muscle shivering, and thus heat preservation can be achieved.

9.4.3 Disturbances of Thermoregulation

9.4.3.1 Central Disturbances of Temperature Regulation

These disturbances are mostly found in patients with hypothalamic tumors or infarcts. They occur occasionally after traumatic brain injury or subarachnoid hemorrhage as well. Congenital thermoregulation defects are rare (i.e. dysautonomic syndrome). Patients with these defects are
9.4.3.2 Effects of Anesthetics on Temperature Regulation

Anesthetics inhibit thermoregulatory control and enlarge the neutral zone in a dose-dependent fashion. The trigger for sweating and active vasodilation is increased by several degrees Celsius, as is the temperature threshold for cold reaction (shivering).

Propofol. Propofol linearly increases the sweating threshold and linearly decreases the vasoconstriction and shivering threshold.

Volatile Anesthetics. Volatile anesthetics produce a non-linear reduction in the major cold-response thresholds, reducing the vasoconstriction and shivering thresholds disproportionately at higher anesthetic concentrations.

Midazolam. The short-acting benzodiazepine midazolam has only limited effects on the central temperature regulation system even in high doses.

9.4.4 Perioperative Hypothermia

It is important for the neurointensivist to be aware of thermal changes during anesthesia, since neurosurgical operations are sometimes of long duration, implying profound temperature alterations.

9.4.4.1 Early Changes of Body Temperature During Anesthesia

Hypothermia during anesthesia develops according to a typical pattern. First, there is a drop of core temperature due to redistribution of body heat from the core to the periphery shortly after induction of anesthesia. In the first hour of narcosis, typically, there is a drop of core temperature of about 1–1.5°C.

9.4.4.2 Late Changes of Body Temperature During Anesthesia

In the later course, there is a linear decrease of core temperature over time, since the heat loss is higher than endogenous heat production. The core temperature decreases at a rate of 0.5°C per hour. During this phase of anesthesia, measures to prevent heat loss are very effective. In the further course of anesthesia, the body temperature stabilizes because of reoccurrence of protective vasoconstriction at a core temperature of 34–35°C. This entity is termed perioperative hypothermia syndrome. Further heat loss is prevented by the redistribution of blood to concentrate the metabolic heat to the core. Vasoconstriction induces a thermal separation of the core and the periphery. The metabolic heat keeps the core temperature constant, while the periphery is progressively getting colder.

9.4.4.3 Pathophysiological Effects of Hypothermia

Many of the most serious side effects of intraoperative hypothermia occur during the postoperative period. They include myocardial ischemia, shivering, thermal discomfort, coagulation disorders and increased risk of surgical wound infections. Postoperative shivering is observed in up to 40% of all postoperative patients and may represent a serious problem, since it can increase oxygen consumption by 200%.

9.4.4.4 Therapy and Prevention of the Perioperative Hypothermia Syndrome

Prevention of heat loss through covering the patient with blankets or gold foil or active rewarming with warmed air mats are presently the most effective measures for minimizing perioperative hypothermia syndrome. The same systems are applied postoperatively in the ICU. Opioids (pethidine 25 mg i.v.) reduce the shivering threshold and are effective for treatment of postoperative shivering.

9.4.5 Drug-Induced Thermoregulation Imbalances

Massive doses of ethanol trigger down the neutral zone of the thalamic thermoregulatory system; moderate doses lead to vasodilation. Hypothermia is mostly the consequence, since ambient cold is much more common than excessive heat.

9.4.6 Hyperthermia

Cocaine, amphetamines and ecstasy can provoke centrally mediated hyperthermia, which is often combined with fluid imbalances.

9.4.6.1 Malignant Hyperthermia

Malignant hyperthermia is a hypermetabolic state of skeletal muscle contraction leading to more than doubled oxygen consumption. It is frequently associated with admin-
istration of halogenated inhalation anesthetics and the use of succinylcholine. The heat production results from the massive contraction of the skeletal muscles, which central temperature regulation is unable to counteract.

**Symptoms of Malignant Hyperthermia.** Symptoms of malignant hyperthermia include:

- Tachycardia or arrhythmias
- Coagulation disorder
- Progressive metabolic acidosis
- Pulmonary edema
- Rise of body temperature up to 44°C
- Muscle rigidity

**Therapy for Malignant Hyperthermia.** Therapy for malignant hyperthermia involves many steps:

- The operation is stopped immediately, and anesthesia is terminated.
- Dantrolene sodium 2.5 mg/kg i.v. is usually effective in counteracting the muscle symptoms.
- Hyperventilation with 100% oxygen is initiated.
- The patient is treated with cold infusions and surface cooling.
- Symptomatic treatment of acidosis, arrhythmias and volume disbalances is performed.

**9.4.7 Fever**

The acute phase response to inflammation is characterized by symptoms of fever, lethargy, loss of appetite and decrease in food intake. These symptoms are widely recognized in many species of animals and are thought to be regulated responses that facilitate survival. Circulating endogenous pyrogens like interleukins, tumor necrosis factor, interferon alpha and prostaglandins increase the thermoregulatory set-point in the hypothalamus. An adaptation of thermoregulatory effectors like vasoconstriction and thermogenesis by shivering leads to temperature elevation.

Blood in the subarachnoid space, brain tumors, head trauma, allergic reactions, rheumatoid diseases and tissue necrosis can cause fever as well. A state of elevated body temperature increases the inflammatory response, thus facilitating the elimination of bacteria. The ability of an organism to "produce" fever is an evolutionary advantage. On the other hand, fever above 38°C represents an enormous circulatory stress for an organism and leads to an increase of ICP in critical neurosurgical patients and should be treated.
9.5 Respiration

LUDWIG SCHÜRER, STEFAN WOLF, AND CHRISTIANTO B. LUMENTA

9.5.1 Basics

The principal function of the lung is gas exchange. The undisturbed function of the lung to accomplish this is essentially dependent on the following parameters:

- The anatomical intactness of the respiratory organs
- An undisturbed relation of ventilation and perfusion of the lung
- An intact innervation by the central nervous structures

9.5.2 Central Disturbances of Breathing

Alterations of the breathing cycle can be caused by lesions of all structures participating in the complex coordination of breathing. Possible causes of central ventilation disorders are:

- Lesions of the brain stem caused by:
  - Trauma
  - Tumor
  - Bleeding
  - Infarction
  - Infection
- Drugs and pharmaceuticals
- Hypothyroidism
- Malnutrition
- Metabolic disturbances
- Sleep apnea

9.5.3 Central Breathing Patterns

Since most comatose neurosurgical patients are ventilated to ensure adequate oxygenation of the brain, classical ventilatory patterns are rarely observed. These breathing patterns have gained much attention in trying to identify the level of damage to the brain stem; however, they are of inconsistent localizing value. Nevertheless, some the most striking are briefly described below.

9.5.3.1 Cheyne–Stokes Respiration

A disturbed CO₂ reagibility is reflected in the Cheyne–Stokes respiration. In its classical crescendo–decrescendo form, ending with a brief apneic period, it is seen after mild bihemispherical damage or metabolic suppression and commonly accompanies stupor. During the apneic phase, CO₂ in the arterial blood rises, which elicits a respiratory stimulus. CO₂ concentration falls again during ventilation and leads to a short cessation of breathing, which is again followed by a rise of carbon dioxide. This type of breathing pattern may be an early sign of transtorial herniation.

9.5.3.2 Apneustic Cluster and Ataxic Breathing

These are patterns associated with lesions of the mid-lower pons, upper medulla and caudal medulla. The function of the breathing centers is altered; irregular, brief respirations of small, random, tidal volume (ataxic or Biot’s breathing) or shallow, rapid breaths followed by pauses (cluster) are the result. The reaction of the breathing center to chemical stimuli is blunted. Patients with this disorder often react very sensitively to opioids and stop breathing after small doses of morphine.

9.5.3.3 Central Hyperventilation

This form of central ventilation disorder is found predominantly after lesions of the central brain stem and is characterized by a normal or increased PAO₂ with concomitant hypocapnia and respiratory alkalosis due to tachypnea.

9.5.3.4 Agonal Gasping

Prefinal agonal gasping reflects lower brain stem damage and is the terminal respiratory pattern of severe brain damage.
9.5.4 Gas Exchange

Moving oxygen into and carbon dioxide out of the blood occurs by simple passive diffusion. This works because of the thinness of the blood–gas barrier (0.3 μm) and its large surface area (up to 100 m²).

Gas exchange can be impaired, alone or in combination, by four major causes:

- **Hypoventilation**, which leads to an increase of blood carbon dioxide and a decrease of blood oxygen tension
- **Diffusion limitation**, as seen in pulmonary edema. This is caused by an increased thickness of the blood–gas barrier. Carbon dioxide diffuses through tissues about 20 times faster than oxygen.
- **Shunt perfusion**, in which gas exchange is impeded. Shunt refers to a condition in which blood passes through unventilated areas of the lung and therefore does not participate in the gas exchange.
- **Ventilation–perfusion mismatch**, which reflects differences in pressure within the small pulmonary vessels between the upper and lower parts of the lung. Blood goes predominantly to the lower part of the lung, as alveolar pressure is higher than pulmonary arterial pressure in the upper part of the lung.

In the supine position, pressure gradients are less pronounced. In conditions of pulmonary edema, the distribution of lung blood flow may be inverted, because there is more fluid around the pulmonary vessels at the base of the lung. This results in an increased vascular resistance in the basal lung areas, thus shifting blood flow to the more apical lung areas.

9.5.5 Indications for Intubation and Mechanical Ventilation

9.5.5.1 Intubation

As a rule of thumb, “the indication for intubation is thinking of it” (Paul Marino).

Key factors for the decision to intubate are the underlying mechanism of respiratory disturbance as well as the expected progression of the respiratory insufficiency. The criteria for intubation and mechanical ventilation summarized below can help in making the decision:

- Breathing frequency > 35/min or <10/min
- \( P_{\text{a}}O_2 \) (at \( \text{FiO}_2 = 0.21 \)) < 60 mmHg (i.e. 7.3 kPa)
- \( P_{\text{a}}O_2 \) (at \( \text{FiO}_2 = 1.0 \)) < 250 mmHg (i.e. 33 kPa)
- \( P_{\text{a}}CO_2 > 55 \text{mmHg} \) (i.e. 7.3 kPa) or <25 mmHg (i.e. 3.3 kPa)
- pH < 7.25
- Loss of protective airway reflexes
- Secretion that cannot be coughed up
- Head cannot be held upright for 5 s
- Airway obstruction (stridor, “fighting” for air)
- Progressive pulmonary infection
- Fever > 38.5°C or hypothermia < 35.0°C
- Deterioration of the clinical state, despite intensive chest physiotherapy
- Bulbar paralysis (mostly in neuromuscular diseases)
- Paralysis of respiratory muscles (high spinal cord lesions, neuromuscular diseases)

Usually, more than one of these criteria are given when the decision is in consideration.

9.5.5.2 Ventilation

Mechanical ventilation is applied when the patient cannot breathe sufficiently to sustain life, as with respiratory failure, respiratory muscle fatigue or massively increased work in breathing. Trauma patients should be intubated and ventilated if they have a GCS less than or equal to 8 (i.e. they do not talk and do not obey commands and therefore cannot protect their airway) and in cases of severe maxillofacial trauma where bleeding and swelling can obstruct the airway.

While most patients in need of mechanical ventilation are already intubated, in cooperative patients with intact respiratory stimulus and airway protection reflexes, a trial of non-invasive ventilation without intubation is warranted.

In patients with pulmonary obstructive disease and neuromuscular diseases, the progress of blood–gas values and lung-function parameters are considered. Respiratory fatigue and agitation are important criteria, because in these states, respiratory decompensation with threatening hypoxia can develop quickly.

9.5.5.3 Tracheostomy

There is strong evidence that early tracheostomy improves survival in intensive care patients. Additionally, the rate of nosocomial pneumonia is reduced and airway care for the patient is facilitated.

**Recommendation.** If a prolonged period of mechanical ventilation (more than ten days) is anticipated, the decision for a bedside dilative tracheotomy is strongly recommended. With contemporary techniques under bronchoscopic guidance, the procedural risk is minimal. In patients with severe head injury or poor-grade SAH, the procedure should be performed even on day one after admission to the neurosurgical ICU, since brain edema and ICP may be poor for the following few days.
9.5.5.4 When Not to Intubate

If there is no chance of meaningful survival of the patient, intubation is not to be considered. This may be fulfilled in patients with terminal cancer or with severe subarachnoid hemorrhage or traumatic brain injury. If ever possible, this is best to be considered with the patient and his or her relatives in advance of pulmonary decompensation.

9.5.6 Principal Modes of Mechanical Ventilation

In the past decades, a myriad of different labels for modes of mechanical ventilation have been invented. A basic distinction of mechanical ventilation modes can be made by the mode of volume and pressure control and by the possibility and mode of triggering additional spontaneous breaths. While some of these modes are attractive from theoretical and physiological considerations, none of them was shown to be superior in prospective, randomized trials. Therefore, the clinician at the bedside should use the kind of mechanical ventilation he or she is familiar with. Contemporary ventilation modes include the possibility and regulation of the amount of support for spontaneous breathing. If this is not wanted, deepening of sedation and/or paralysis is necessary and not mechanical prevention from the ventilation machine.

9.5.6.1 Volume-Controlled Ventilation

With volume-controlled ventilation (VCV), a preset tidal volume (VT) irrespective of the pressure needed to apply this volume is delivered. Respiration frequency, peak gas flow and inspiration–expiration ratio are separately adjustable. Increasing the inspiratory time span decreases the peak airway pressure in this setting. If the compliance of the chest, lung and abdomen is extremely low (stiff thorax), elevated peak inflation pressure (PIP), gas trapping and barotrauma, and possibly cardio-circulatory compromise, may ensue. With air leaks (e.g. due to a leaking cuff or a bronchopleural fistula), the tidal volume delivered will decrease.

9.5.6.2 Pressure-Controlled Ventilation

Pressure-controlled ventilation (PCV) limits the pressure, and the delivered breathing volume is dependent on the stiffness (compliance) of the thorax–lung system. Using this mode, the target pressure and the inspiratory time are predetermined to achieve a desired tidal volume. The lower the compliance of the thorax and lung, the less volume is delivered in PCV. Changes in inspiratory and expiratory resistance, secretions, bronchospasm or pneumothorax impair the delivered tidal volume in this respiratory setting.

9.5.6.3 Combined Ventilation Modes

For combination modes, synchronized intermittent mandatory ventilation with pressure support is possible. The latest generation of ventilation machines has the option of ventilating with pressure-regulated volume control, volume-assured pressure support and volume support. Volume-controlled modes are associated with an increased risk of high alveolar pressures, while in pressure-controlled modes with varying tidal volumes, P_{a}CO_{2} is less well controlled.

9.5.6.4 Biphasic Positive Airway Pressure Ventilation

Biphasic positive airway pressure ventilation (BIPAP) is a special kind of a PCV mode that has recently gained popularity. With BIPAP, the patient has the possibility of breathing anytime spontaneously on two different continuous positive pressure levels or, if spontaneous respiration is absent, the patient is ventilated by the machine in a controlled fashion. The changes of the pressure levels are time triggered. This form of ventilation allows the independent adjustment of expiration pressure and expiration time as well as the setting of the inspiration pressure and inspiration time. Setting the pressure levels and time intervals allows for controlled ventilation.

9.5.7 Positive End-Expiratory Pressure

The application of a positive airway pressure during expiration is called positive end-expiratory pressure (PEEP). PEEP is combined with all modes of artificial respiration. The principal rationale for applying PEEP is to prevent alveolar units from end-expiratory collapse, thus increasing functional residual capacity. A basal or physiologic PEEP of 5 cm H_{2}O should be applied in every patient under mechanical ventilation. PEEP is called continuous positive airway pressure (CPAP) if the patient is breathing completely spontaneously.
9.5.8  Recommended Ventilator Settings for the Neurosurgical Patient

Albeit never proven, there is common agreement that the \( P_aO_2 \) should be kept around or slightly above 100 mmHg for neurosurgical patients. This is in contrast to general ICU patients, where a \( P_aO_2 \) above 60 mmHg is accepted. The rationale behind this concept is to provide adequate oxygenation even in areas of the brain with disturbed perfusion, as the \( P_aO_2 \) is the driving pressure for tissue oxygenation. \( F_iO_2 \) is therefore corrected to the lowest value providing a \( P_aO_2 \) of 100 mmHg. PEEP is adjusted to gain an \( F_iO_2 \) of lower than 0.5.

Whether a volume-controlled mode or a pressure-controlled mode of ventilation is applied is at the discretion of the treating physician. Both modes are adjusted such that tidal volume is kept at 6–8 mL/kg b.w. to avoid overdistention and ventilator-associated lung injury. Formerly applied higher inspiratory volumes of 10–15 mL/kg b.w. volumes are considered deleterious even in patients without lung injury. Target plateau pressures are below 35 mmHg, and peak inspiration pressure (PIP) is adjusted to less than 50 cm H_2O. In the initial phase after an intracranial pathology, controlled moderate hyperventilation to a \( P_eCO_2 \) of 35 mmHg is part of the treatment concept to reduce ICP. With low tidal volumes of 6–8 mL/kg b.w., increased respiratory rates up to 30/min are sometimes necessary.

9.5.8.1  Acute Lung Injury in Neurosurgical Patients

In patients with brain pathology and acute lung injury, a collision between brain and lung protective ventilation seems sometimes unavoidable. From a pulmonary perspective, strict control of tidal volume is warranted, concomitantly with an early rise of PEEP levels to maximize functional residual capacity and to keep \( F_iO_2 \) as low as possible. Most neurosurgical patients tolerate higher PEEP values up to 20 mmHg without significant increase of ICP. In this setting, ICP measurement is mandatory, and even permissive hypercapnia is possible. Extended cerebral monitoring, including measurement of local cerebral oxygen tension (\( P_lO_2 \)) and cerebral blood flow, may be helpful. In lung-injured patients, one should first attempt to decrease \( F_iO_2 \) below 0.5 and then reduce the PEEP level.

9.5.9  Side Effects of Mechanical Ventilation

9.5.9.1  Effects on the Cardiovascular System

Positive pressure ventilation (PPV) increases thoracic pressure during inspiration and decreases venous return to the heart. PEEP may reduce cardiac output by a diminished venous return as a consequence of elevation of intrathoracic pressure. This can lead to a decreased arterial pressure along with a decreased cerebral perfusion pressure. Volume substitution and application of vasopressors can effectively correct this hemodynamic problem. Therefore, adequate volume resuscitation is mandatory in neurosurgical patients. The former recommendation of “keeping the patient dry” is no longer valid.

9.5.9.2  Effects of Mechanical Ventilation on the Kidneys

Mechanical ventilation is often associated with a decreased diuresis and sodium excretion. These effects are caused by the increased intrathoracic pressure, which influences kidney function by decreased perfusion pressure and cardiac output. Sympathetic tone is increased, as well as circulating plasma levels of renin, aldosterone and antidiuretic hormone. The secretion of atrial natriuretic peptide is reduced.

9.5.9.3  Effects of Mechanical Ventilation on the Digestive Organs

Icterus and liver function disturbances can be induced by a decrease of liver perfusion caused by mechanical ventilation. Ventilation increases hydrostatic pressure in the liver veins and biliary ducts.

9.5.9.4  Effects of Mechanical Ventilation on the Brain

The pathophysiology of the regulation of brain hemodynamics is described in Sect. 9.2.2. Briefly, elevation of arterial \( CO_2 \) leads to dilation of brain arteriolar resistance vessels. This is followed by an increase of cerebral blood volume (and ICP) and cerebral blood flow (CBF). A decrease of arterial \( CO_2 \) results in vasoconstriction, a decrease of intracerebral blood volume and ICP and a reduction of CBF. This can lead to cerebral ischemia.

Hypoxia is followed by an elevated cerebral blood flow; hyperoxia has only limited effects on brain perfusion.
In mechanical ventilation with PEEP, the elevation of intrathoracic pressure may lead to an increase of central venous pressure, which theoretically can impede venous outflow from the brain and increase ICP. However, in praxis, even reductions in ICP after elevation of PEEP have been observed; the exact reasoning remains speculative.

### 9.5.10 Weaning from the Respirator

Weaning from mechanical ventilation involves gradual withdrawal of mechanical ventilation support and the transfer of the mechanical work of breathing (WOB) from the machine to the patient. Patients with only short-term ventilation pose little difficulty in removal of the ventilatory support. The discontinuation of ventilatory support in patients recovering from severe illness, including long periods of mechanical ventilatory support, may be extremely challenging.

The final consideration as to whether a patient is still dependent on ventilatory support is with a spontaneous breathing trial (SBT). The tolerance of the SBT is assessed according to the respiratory pattern, gas exchange, hemodynamics and subjective well-being of the patient. The time for the duration of an SBT may range from a few minutes in a postoperative patient to repeated trials for some hours in patients after long periods of mechanical ventilation. Implementation of a systematic SBT in the form of a weaning protocol in fixed schedules may facilitate earlier recognition of a successful weaning time point in an individual patient.

#### 9.5.10.1 Prerequisites for Weaning in Neurosurgical Patients

A patient considered for weaning from mechanical ventilation should have controlled ICP for more than 24 hours. If measured, brain tissue oxygenation should be in an uncritical range above 15 mmHg. Common criteria for the start of weaning are:

- $P_aO_2$ above 60 mmHg
- $F_iO_2$ lower than 0.5
- PEEP/CPAP below 8 cm H$_2$O
- $P_aCO_2$ should be 45 mmHg
- No new or acute organ failure
- No new changes on chest X-ray

#### 9.5.10.2 Methods of Weaning from the Respirator

Weaning by use of a T-piece is the classical weaning technique. The ventilator is removed from the patient and humidified supplemental oxygen is given during the SBT. A more sophisticated approach for patients difficult to wean is an SBT performed while the patient is still on the ventilator. CPAP mode offers continuous positive airway pressure (e.g. 5 cm H$_2$O) and a low level of pressure support (e.g. 5–10 cm H$_2$O). With pressure support weaning, all breaths are patient triggered and pressure limited. When the level of pressure support is high, nearly complete ventilatory support is provided.

If this fails, too, the mandatory breath rate set on the ventilator may be decreased progressively, requiring a more spontaneous breathing effort to maintain ventilation. In patients ventilated for longer than 1 week, the mandatory rate is decreased to one or two breaths per minute. If the patient is tolerating this setting, an SBT can be considered.

### 9.5.11 Extubation Criteria

A patient successfully weaned from the ventilator is considered ready for extubation when he is sufficiently alert, has control over his saliva and has adequate airway protection reflexes. Most often, successful weaning and extubation time points are identical. However, patients with brain stem lesions or impaired consciousness may well be able to breathe without ventilatory support but still need transitory or permanent airway protection via tracheostomy.
9.6 Nutrition

LUDWIG SCHÜRER, STEFAN WOLF, AND CHRISTIANTO B. LUMENTA

9.6.1 Basics

Nutrition is a key issue of neurointensive care treatment because of its effects on the immune system, wound healing and outcome. In several studies, a relation of the nutritional status of the patient and the ensuing outcome could be established. Prolonged underfeeding leads to a breakdown of muscle and visceral protein to meet metabolic requirements, leading to weight loss and organ dysfunction.

9.6.2 Effect of Nutrition on the Immune System and Outcome

Malnutrition causes thymic atrophy, reduces T-cell proliferation and alters cellular immunity, complement activity, cytokine production and antibody affinity. The link between malnutrition, risk of infection and mortality is established. General surgery patients with low serum protein levels do have higher infection rates. Patients with traumatic brain injury who were fed early had a reduced infection rate and length of stay (LOS) in the ICU. Head-injured patients receiving a sufficient amount of calories do have a significantly better survival rate. It appears that malnutrition reduces the immune response. Special diets also may have distinct effects on the immunologic capacity.

9.6.3 Effects of Stress and Malnutrition

Trauma or other sorts of stress have distinct influences on the ability of an individual to cope with fasting. The hormonal status following injury is characterized by increases of catabolic substances. After head injury, there is hypermetabolism; the levels of catecholamine, glucocorticoid, glucagon and growth hormone are high. Insulin concentrations are inadequately low in view of the hyperglycemic state in stressful situations. Concomitantly, insulin resistance at a cellular level often develops. Persistence of stress combined with fasting rapidly depletes muscle protein, impairs the immune response and leads to organ dysfunction.

9.6.4 Assessment of the Nutritional Need

Energy requirements are dependent on body weight and the amount of stress. In principle, assessment of the daily caloric needs can be determined individually and precisely by measurement of oxygen consumption and carbon dioxide production using indirect calorimetry (e.g. Deltratrac®). However, in a routine setting besides university research, this adds tremendous efforts and cost without proven benefit.

If indirect calorimetry is not available, the Harris–Benedict equations from 1919 provide an estimate for caloric needs using age, sex, weight and height of the individual patient. These formulas have never been evaluated for neurosurgical intensive care patients or patients with severe metabolic disorders like sepsis, and the estimations provided are regarded as far too low.

The simplest and – for clinical routine – surprisingly practical method for rough assessment of energetic requirements is based on the weight of the patient. Typically, 20–25 kilocalories per kg of ideal body weight are sufficient to satisfy the average caloric need.

9.6.5 When to Start Nutrition and How?

Patients who are expected to stay in the ICU for more than 1 day are supplemented with nutrition. There is general agreement that nutrition should be given via gastric or jejunal tube in patients with an intact gastrointestinal tract. Integrity of the gut may be better preserved using the enteral route. Besides that, enteral nutrition is cheaper than parenteral solutions. Feeding via gastric tube is started immediately after the patient is admitted to the ICU. Reflux is checked frequently and is tolerated if below 200 mL/h. If enteral feeding fails due to disturbances in gastric emptying, parenteral nutrition is administered additionally and enteral feeding recommenced the following day.
9.6.6 What to Feed?

A recommended nutritional formula gives equal weight to the three basic components of nutrition:
- 1 g glucose contains 16.7 J or 4 kcal
- 1 g amino acids contains 4 kcal
- 1 g fat contains 9 kcal

All components, not only carbohydrates, are provided continuously without prolonged periods of interruption to exclude unphysiologic variations in blood glucose levels.

9.6.6.1 Carbohydrates

The majority of non-protein calories are typically provided using disaccharides and polysaccharides. The preferred carbohydrate is glucose. It is administered to reduce gluconeogenesis from amino acids, to supply the brain and blood cells with substrate and to deliver the necessary energy for protein synthesis.

9.6.6.2 Protein

Protein is administered as a mixture of amino acids. Administration of pure albumin is useless, since degradation of albumin is slow. Amino acid solutions should contain all eight essential amino acids and a balanced mixture of non-essential ones, including glutamine. Amino-acid supplementation has to be combined with administration of calories (glucose), unless the energy for protein synthesis is not available.

9.6.6.3 Lipids

Fat emulsions serve as high-caloric nutrients. Suitable substrates include 10–20% long chain triglyceride (LCT) emulsions. They are manufactured from soybean or sunflower oil. For long-term nutrition, the maximal dose should be less than 2 g/kg b.w. per day. Regular determinations of blood triglyceride values are necessary if fat is administered over prolonged periods of time. With values above 300 mg%, fat administration has to be reduced to avoid the so-called fat overload syndrome.

9.6.6.4 Immunonutrition

The type of lipid administered may have important implications in the critically ill. Omega-6 fatty acids are precursors of arachidonic acid metabolites, which are potent inflammatory mediators, whereas omega-3 fatty acids are potentially able to control the inflammatory response. Immunonutrition is studied well in patients with severe neurologic diseases; clinical evidence is insufficient to recommend routine use of these products.

9.6.6.5 Vitamins and Trace Elements

In long-time nutrition, trace elements (i.e. zinc, selenium) should be supplemented as well as water and fat-soluble vitamins.

9.6.6.6 Glucose Control

Strict control of blood glucose levels (80–110 mg/dL) by generous insulin administration and frequent control of blood glucose concentration has been shown to reduce mortality, infection rate and multisystem organ failure in critically ill ICU patients. In head-injured patients, it has been known for more than a decade that high glucose levels are associated with a poor outcome.

For glucose control, virtually every patient admitted to the neurosurgical ICU needs insulin provided via syringe pump with 501 U./50 mL. If the necessary daily dose of insulin exceeds 2401 U. per day, the amount of glucose administered is decreased instead of a further insulin rise. In cases of severe insulin resistance, xylitol as an insulin independent carbohydrate, often mixed with glucose, may be considered as an energy source. Table 9.6.1 provides a protocol for insulin adjustment according to measured blood glucose levels. This protocol provides the nurse at the bedside a useful tool to guide insulin without contact with the ICU physician.
### Table 9.6.1 Glucose control

<table>
<thead>
<tr>
<th>Start</th>
<th>Blood sugar between 80 and 110 mg/dL</th>
<th>No action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood sugar above 110 mg/dL</td>
<td>Start insulin with 2 I.U./h</td>
</tr>
<tr>
<td></td>
<td>Blood sugar above 200 mg/dL</td>
<td>Start insulin with 4 I.U./h</td>
</tr>
<tr>
<td></td>
<td>Control of blood sugar after newly added insulin after 1 h: proceed to stabilization phase.</td>
<td></td>
</tr>
<tr>
<td>Stabilization phase</td>
<td>Blood sugar between 80 and 110 mg/dL</td>
<td>Unchanged insulin dose. If trend recognizable, adjust by (0.1–)0.5–1 I.E./h</td>
</tr>
<tr>
<td></td>
<td>Blood sugar between 110 and 140 mg/dL</td>
<td>Increase insulin dose by 0.5–1 I.U./h</td>
</tr>
<tr>
<td></td>
<td>Blood sugar above 140 mg/dL</td>
<td>Increase insulin by 1–2(-3) I.U./h</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia, more than 10 I. U. insulin per hour</td>
<td>Decrease nutrition by 25% until normoglycemia</td>
</tr>
<tr>
<td></td>
<td>Control of blood sugar after 1 h until two consecutive values are normoglycemic: Proceed to normoglycemia phase.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood sugar between 60 and 80 mg/dL</td>
<td>Reduce insulin dose</td>
</tr>
<tr>
<td></td>
<td>Blood sugar between 40 and 60 mg/dL</td>
<td>Discontinue insulin</td>
</tr>
<tr>
<td></td>
<td>Blood sugar below 40 mg/dL</td>
<td>Discontinue insulin and give 10–20 g Glucose i.v.</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>In the case of hypoglycemia: tight control of blood sugar every 30–60 minutes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control blood sugar every 4 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Proportional adaptation of insulin dose according to blood sugar change. For example, if blood sugar falls by 20%, reduce insulin dose by 20%. Rough estimate is sufficient.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood sugar out of normal range</td>
<td>Return to stabilization phase</td>
</tr>
<tr>
<td></td>
<td>Every time: check dose of nutrition and insulin according to documentation. Any undocumented changes?</td>
<td></td>
</tr>
</tbody>
</table>
9.7 Multiresistant Infections in Neurointensive Care Patients

LUDWIG SCHÜRER, STEFAN WOLF, AND CHRISTIANTO B. LUMENTA

9.7.1 Basics

More than 70% of the bacteria that causes hospital-acquired infections are resistant to at least one antibiotic. Multiresistant pathogens constitute an increasing problem in ICUs worldwide. This chapter briefly reviews transmission and treatment modalities of antibiotic-resistant pathogens, i.e. methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE) and extended spectrum beta-lactamase-producing gram-negative germs (ESBL).

9.7.1.1 Common Measures

The predominant spread of MRSA, VRE and ESBL infection is by the hands of health care workers. As eradication with antibiotics is often not possible, isolation of the patient is the most important and effective measure in counteracting the spread of the multiresistant germ.

The following measures have to be undertaken immediately after the diagnosis of multiresistant bacteria is established:
- Isolation of the patient in a single room.
- Inform the patient (if possible) about the nature of the measure.
- Place notice on the door of the room about the isolation.
- The room should be frequented as little as possible; rounds are made in front of the (open) door.
- All material not needed for patient care is removed.
- The room is entered only if there is work to do.
- The room is entered only with gown, mask and gloves.
- Hand disinfection is required before entering the room and before leaving it.
- After leaving the room, all garments are thrown into respective containers.
- Daily disinfection of all surfaces in the room.
- Waste is put in plastic bags and removed as B-waste.

The isolation is maintained until at least three consecutive microbiological cultures are negative.

9.7.2 Methicillin-Resistant Staphylococcus aureus

9.7.2.1 Epidemiology

Methicillin-resistant Staphylococcus aureus is a common bacterial pathogen, responsible for a variety of infections. Virtually all MRSA infections or colonizations have been acquired from an external source. A de novo development of methicillin resistance via genetic transfer of the SCCmec gene has occurred only a few times worldwide. Treatment of infection is difficult due to its resistance to most antibiotics.

It is evident that the problem of antibiotic resistance has been amplified in healthcare settings, where antibiotics are frequently used and strains with resistance factors enjoy a selective advantage. The most important measure is control of transmission apart from control of antimicrobial use.

9.7.2.2 Clinical Significance

Worldwide, 15–20% of the healthy population carry S. aureus, which has a natural occurrence in the mucous membranes of the nose. The prevalence of MRSA colonization varies widely and ranges from 0.2 to 2.2%. MRSA acquisition is frequently associated with long-term stay in health care settings, past antimicrobial use, indwelling catheters, decubitus ulcers and postoperative wounds. The risk of infection increases with the duration of nasal colonization. A patient with nasal colonization admitted to an ICU has 60 times the risk of a fatal MRSA infection compared to a patient who was MRSA-negative at admission.
9.7.2.3 Diagnosis and Screening for MRSA

If routine bacteriological cultures (tracheal secretion, urine, blood, CSF) reveal the diagnosis of MRSA, additional smears from the nose, the axilla and the perineum are obtained. Active surveillance smears are used in risk groups of patients without proven infection entering the ICU to prevent endemic MRSA spread. Risk groups are: patients transferred from hospitals in Arabic countries and the USA, nursing home patients, and patients hospitalized elsewhere for a long time. These patients are isolated until the microbiological testing is obtained.

9.7.2.4 Treatment

9.7.2.4.1 Colonization with MRSA
Skin colonization with MRSA is not treated systemically. Nasal colonization is cured with mupirocin ointment (three times a day for three days). Body washing is performed with octenisan for three consecutive days. Afterwards, surveillance cultures are taken at days 4, 5 and 6 after diagnosis. Isolation is withdrawn after three negative culture results are obtained. If there are still positive cultures, this sequence is repeated.

9.7.2.4.2 Infection with MRSA
Skin treatment is performed as described above, regardless of the skin colonization status. Additionally, MRSA infections are treated with a triplicate combination therapy:

- **Vancomycin**: starting dose $3 \times 1$ g/day, afterwards adapted to plasma levels
- **Fosfomycin** $3 \times 5$ g/day
- **Rifampicin** $1 \times 600$ mg/day

Alternatively to this combination, the oxazolidinone Linezolid, $2 \times 600$ mg/day, is possible.

Fosfomycin and Linezolid penetrate the blood–brain barrier (BBB) well. Vancomycin – a big molecule – enters the brain in situations of meningitis with open BBB in sufficient amounts. In MRSA meningitis with an indwelling external ventricular drain, 10–20 mg vancomycin can be given intracisternally. After drug application, the ventricular drain is closed for 15 min, if possible.

MRSA infections are treated until three negative culture results on three consecutive days are obtained. In patients with MRSA meningitis, the application of antibiotics is recommended for at least 14 days.

9.7.3 Vancomycin-Resistant Enterococcus

9.7.3.1 Epidemiology

Spontaneous vancomycin resistance mutations have not been observed. In the USA, VRE is exclusively found in patients who were treated in health care settings. In healthy individuals, VRE has not been isolated. In Europe, the glycopeptide avoparcin has been used for years as a growth promoter in animals, and VRE has been isolated in the intestines of healthy individuals and on processed meat products.

9.7.3.2 Clinical Significance

Usually, the pathogenicity of VRE is low. In the intensive care setting, they are feared in severely ill patients, causing wound infections, infections of the urinary tract, endocarditis and sepsis. Due to their treatment problems, VRE add significantly to morbidity and costs.

9.7.3.3 Diagnosis

Cultures of wounds, urine and blood with antimicrobial testing help to make the diagnosis. Skin testing, as performed in MRSA infection, is not necessary.

9.7.3.4 Treatment

9.7.3.4.1 Colonization with VRE
Cure with mupirocin ointment (three times a day for three days). Body washing is performed with octenisan for three consecutive days. Isolation is withdrawn after three negative culture results are obtained. If there are still positive cultures, this sequence is repeated.

9.7.3.4.2 Infection with VRE
Skin treatment is performed as described above, regardless of the skin colonization status. Additionally, VRE infections are treated with a triplicate combination therapy:

- **Vancomycin**: starting dose $3 \times 1$ g/day, afterwards adapted to plasma levels
- **Fosfomycin** $3 \times 5$ g/day
- **Rifampicin** $1 \times 600$ mg/day

Alternatively to this combination, the oxazolidinone Linezolid, $2 \times 600$ mg/day, is possible.

Fosfomycin and Linezolid penetrate the blood–brain barrier (BBB) well. Vancomycin – a big molecule – enters the brain in situations of meningitis with open BBB in sufficient amounts. In VRE meningitis with an indwelling external ventricular drain, 10–20 mg vancomycin can be given intracisternally. After drug application, the ventricular drain is closed for 15 min, if possible.

VRE infections are treated until three negative culture results on three consecutive days are obtained. In patients with VRE meningitis, the application of antibiotics is recommended for at least 14 days.

9.7.4 Extended Spectrum Beta-Lactamase-Induced Resistance

9.7.4.1 Epidemiology

Beta-lactamases are enzymes produced by gram-negative bacteria that can inactivate beta-lactam antibiotics (penicillins, cephalosporins). Extended spectrum beta-lactamases can also inactivate the so-called broad-spectrum cephalosporins (ceftaxime, cefotaxime, ceftazidime) and hydrolyze monobactams (aztreonam). They are mostly found in *Escherichia coli* and *Klebsiella pneumoniae* but increasingly also in other families of the Enterobacteriaceae (Proteus, Enterobacter, Salmonella) and in *Pseudomonas*
aeruginosa. The resistance is plasmid mediated, signifying that it can be transferred horizontally not only within, but also between different species.

9.7.4.2 Clinical Significance

Most of ESBL-induced infections concern the urinary tract. However, the occurrence of multiresistant strains in catheterized ICU patients can be the source of infection to other organs. ESBL leads to a prolonged hospital stay and an increased mortality.

9.7.4.3 Diagnosis

Routine microbiological testing does not detect ESBL. Since there are more than 150 ESBL types existing, an in vitro microbiological diagnosis is often not possible. Frequently, ESBL is only detected in vivo due to failure of antibiotic treatment. According to the data of the Surveillance System of Antibiotic Use and Bacterial Resistance in German Intensive Care Units, ESBL-producing bacterial strains are only isolated in 40% of the microbiology labs.

9.7.4.4 Treatment

Recommended substances to treat ESBL infections are carbapenems. In severe infections, they are combined with aminoglycosides. Dosages include:

- Imipenem: $4 \times 500 \text{ mg/day}$
- Gentamicin: starting with 320 mg/day, and adapted to plasma level
The perception of acute and post-operative pain is a complex interaction that involves sensory, emotional, psychological and behavioural factors. Trauma to any part of the body, and nerve damage in particular, can lead to changes within other regions of the nervous system, which influence subsequent responses to sensory input. Surgical trauma is associated with an injury response or "inflammatory response", depending on the release of intracellular contents from damaged cells and inflammatory cells such as macrophages, lymphocytes and mast cells. Nociceptive stimulation also induces a neurogenic inflammatory response with the release of substance P, neurokinin A and calcitonin gene-related peptide (CGRP) from the peripheral terminals of nociceptive afferent fibres. Release of these peptides results in an increased excitability of sensory and sympathetic nerve fibres, vasodilatation and extravasation of plasma proteins.

When the trauma is severe, several inflammatory mediators such as potassium, serotonin, bradykinin, substance P, histamine, cytokines, nitric oxide and products from the cyclooxygenase and lipoxygenase pathways of arachidonic acid contribute to sensitize high-threshold nociceptors, producing the phenomenon of peripheral sensitisation [1]. The zone of "primary hyperalgesia" surrounding the site of injury is generated by peripheral nervous changes following surgical and other forms of trauma. The primary hyperalgesia is associated with an increased response to normally innocuous mechanical stimuli (alldynia) in a zone of "secondary hyperalgesia". These changes, responsible for central sensitisation, depend on the processes that occur in the dorsal horn of the spinal cord following injury [1].

Transmission of nociceptive information is indeed subject to modulation at several levels of the neuraxis, including the dorsal horn. Afferent impulses arriving in the dorsal horn initiate inhibitory mechanisms, which limit the effect of subsequent impulses by the effect of stimulation of the local inhibitory interneurons and the action of descending pathways from the brain. In the dorsal horn, incoming nociceptive messages are modulated by endogenous and exogenous agents that act on opioid, alpha-adreno-, GABA and glycine receptors located at pre- and post-synaptic sites. Both GABA and glycine are involved in inhibition of nociceptive input, and loss of their inhibitory action can result in features of neuropathic pain [2, 3].

Unlike pain in adults, it is more difficult to assess and efficaciously treat paediatric pain. Recent evidences have shown the deleterious physiologic effects of pain and the beneficial results of efficacious post-operative analgesia. In 2001, the American Academy of Paediatrics and the American Pain Society issued a statement to ensure humane and competent treatment of pain and suffering in all children and adolescents in order to focus the attention on an interdisciplinary therapeutic approach, including pharmacologic, cognitive–behavioural, psychological and physical treatments [4]. The following provides guidelines and major goals for dealing with acute pain in clinical practice:

**Guidelines**
- A collaborative, interdisciplinary approach to pain control, including all members of the health care team
- Assessment and frequent reassessment of the patient's pain
- Use of both drug and non-drug therapies to control and/or prevent pain

**Major goals**
- Reduce the incidence and severity of patient's post-operative pain
- Educate patients about the need to communicate regarding unrelieved pain so they can receive prompt evaluation and effective treatment
- Enhance patient comfort and satisfaction
- Contribute to fewer post-operative complications and shorter stays after surgical procedures

Some principles can be extended to all forms of acute pain, but some of them are particularly decisive in post-operative pain management [5]. The following principles
describe safe and effective acute post-operative pain management:
- Adverse physiological and psychological effects result from unrelieved severe pain.
- Proper assessment and pain control require patient involvement.
- Pain is best treated early, because established, severe pain is more difficult to treat.
- While it is not possible to completely alleviate all pain in the post-operative period, it should be possible to reduce pain to a tolerable or comfortable level.
- Post-operative analgesia should be planned preoperatively, with consideration given to the type of surgery, perioperative use of analgesics and regional anaesthetic techniques.
- One should provide frequent assessment of pain intensity and charting of analgesia.
- Adequate education of all involved in pain management, including the patient, is important.
- Formal programmes, protocols and guidelines covering acute pain management are advised.

The need for a multidisciplinary team and a pre- and post-operative pain management program represents an important goal in order to obtain effective pain relief and optimize medical care and rapid recovery after post-operative procedures.

There are some commonly used methods of measurement of pain that have proven to be reliable. Observational and behavioural measures consider the child's reaction to pain. Self-report measures rely on the child's description of his experience of pain. Biological measures consider some physiologic parameters that may be modified by the presence of pain, such as heart and respiratory rates, blood pressure, etc. [1]. In infants and non-verbal children, self-report measures are unavailable, but behavioural indices (motor responses, vocalization, facial expressions, crying and complex behavioural responses such as the sleep–wake patterns) can be easily evaluated to assess pain.

Different behavioural scales have been validated by several studies that enrolled infants and neonates [6, 7]. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) is one of the most common scales used for post-operative pain management [8]. Composite measures of pain have been developed combining behavioural and biological items, such as the Objective Pain Scale and the Comfort Scale [9, 10]. Self-report measures of pain represent the gold standard in older children who can describe the subjective pain experience [11]. These methods include different strategies such as routine and direct questioning, verbal and non-verbal methods (i.e. pictorial scales) and self-rating scales. The Visual Analogue Scale (VAS) and Facial Pain Scale are two of the most common self-rating scales for assessing pain intensity in children [12]. The Oucher Scale is a variant of the faces scale and is designed to measure pain intensity in children aged 3–12 years [13].

### 9.8.3 Post-operative Pain Management

There is evidence that patients benefit from the use of multimodal, or balanced, analgesia after surgery. Non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, local anaesthetics, adjuvant drugs and opioids are employed in combination to improve pain relief (Table 9.8.1). Multimodal analgesia employs a variety of drugs, given by different routes, to achieve analgesia, with a reduction in the incidence and severity of side effects. The best approach to post-operative pain therapy is based on pharmacologic protocols, using all drugs involved in post-operative pain relief (Table 9.8.1). In fact, a correct use of drugs for pain should control symptoms and achieve a good outcome. As the World Health Organization (WHO) guidelines support, there are two main goals to consider [14]: pain therapy must be assessed “by the patient” and “by the ladder”.

#### 9.8.3.1 By the Patient

Different factors may alter the amount of pain suffered by the individual patient. The general conditions, the patient himself, his disease and psychological factors are important to consider in order to start an adequate pain management regimen. It is now generally agreed that unrelieved severe acute pain exacerbates premorbid tendencies for anxiety, hostility, depression or preoccupation with health. In a few cases, the inability to cope with pain may create an acute psychotic reaction. For all these reasons, psychological approaches are an integral part of the medical care of children with pain.

#### 9.8.3.2 By the Ladder

Analgesic pharmacotherapy is the mainstay of postoperative pain management. The guiding principle of analgesic management is the individualization of therapy. Through a process of repeated evaluations, drug selection and administration is individualized so that a favourable balance between pain relief and adverse pharmacological effects is achieved and maintained (Table 9.8.1). An expert committee convened by the WHO has proposed a useful approach to drug selection for acute and chronic pain states, which has become known as the “analgesic ladder”. When combined with appropriate dosing guidelines, this approach is capable of providing adequate pain
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9.8.3 Post-operative Pain Management

relief to patients. Emphasizing that pain intensity should be the prime consideration in analgesic selection, the approach advocates three basic steps:

Step 1. Patients with mild to moderate post-operative-related pain should be treated with a non-opioid analgesic, which should be combined with an adjuvant drug if a specific indication exists. For example, a patient with mild to moderate arm pain caused by fracture may benefit when a tricyclic antidepressant is added to acetaminophen.

Step 2. Patients who are relatively opioid naive and present with moderate to severe pain, or who fail to achieve adequate relief after a trial of a non-opioid analgesic, should be treated with an opioid conventionally used to treat pain of this intensity. This treatment is typically accomplished by using a combination product containing a non-opioid (e.g., aspirin or acetaminophen) and an opioid (such as codeine, buprenorphine or propoxyphene). This drug can also be co-administered with an adjuvant analgesic.

Step 3. Patients who present with severe pain or fail to achieve adequate relief following appropriate administration of drugs on the second rung of the analgesic ladder should receive an opioid agonist conventionally used for

### Table 9.8.1 Scientific evidence for pharmacological interventions to manage postoperative pain in children

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral (alone)</td>
<td>I</td>
<td>Effective for mild to moderate pain. Relatively contraindicated in patients with renal disease and risk of or actual coagulopathy. Risk of coagulopathy, gastrointestinal bleeding and other factors should be carefully examined.</td>
</tr>
<tr>
<td>Oral (adjunct to opioid)</td>
<td>I</td>
<td>Potentiating effect resulting in opioid sparing. Caution as above.</td>
</tr>
<tr>
<td>Parenteral (ketorolac)</td>
<td>I</td>
<td>Effective for moderate to severe pain. Useful where opioids are contraindicated or to produce “opioid sparing”, especially to minimize respiratory depression, sedation and gastrointestinal stasis. Best used as part of a multimodal analgesia regimen.</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral (systemic)</td>
<td>IV</td>
<td>As effective as parenteral in appropriate doses. Use as soon as oral medication is tolerated.</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>I</td>
<td>Has been the standard parenteral route, but injections painful and absorption unreliable. Hence, avoid this route when possible.</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>I</td>
<td>Preferable to intramuscular because of patient comfort and a reduced risk of needle-stick injury.</td>
</tr>
<tr>
<td>Intravenous</td>
<td>I</td>
<td>Parenteral route of choice after major surgery. Suitable for titrated bolus or continuous administration. Significant risk of respiratory depression with inappropriate dosing.</td>
</tr>
<tr>
<td>PCA (systemic)</td>
<td>I</td>
<td>Intravenous or subcutaneous routes recommended. Good steady level of analgesia. Popular with patients but requires special infusion pumps and staff education.</td>
</tr>
<tr>
<td>Epidural and intrathecal</td>
<td>I</td>
<td>When suitable, provides good analgesia. Risk of respiratory depression (as with opioids by other routes), but sometimes delayed in onset. Requires careful monitoring. Use of infusion pumps requires additional equipment and staff education. Expensive if infusion pumps are employed.</td>
</tr>
<tr>
<td><strong>Local anaesthetics</strong></td>
<td>epidemic and intrathecal</td>
<td>I</td>
</tr>
</tbody>
</table>
pain of this intensity, such as morphine or fentanyl. This drug may also be combined with a non-opioid analgesic or an adjuvant drug.

9.8.4 Pharmacological Classification of Analgesic Drugs

Analgesic drugs can be divided into four groups:
- Non-opioid analgesics
- Opioid analgesics
- Adjuvant analgesics (drugs with other primary indications that can be effective analgesics in specific circumstances)
- Topical analgesics

9.8.4.1 Non-opioid Analgesics

The non-opioid analgesics (acetylsalicylic acid, acetaminophen and the NSAIDs) constitute a heterogeneous group of compounds that differ in chemical structure but share many pharmacological actions. These drugs are useful alone for mild to moderate pain (step 1 of the analgesic ladder) and provide additive analgesia when combined with opioid drugs in the treatment of more severe pain [15, 16].

Acetylsalicylic acid is a potent inhibitor of cyclooxygenases which is used frequently in medical care. Acetaminophen (or paracetamol) is a specific drug with characteristics similar to NSAIDs. Paracetamol has analgesic and antipyretic properties and is devoid of the side effects typical of the NSAIDs [15, 16]. The administration of paracetamol in children and infants for postoperative pain after minor surgery is a well-established and safe treatment option, if appropriately used. However, if paracetamol is dosed according to traditional recommendations (about 2 mg/kg body weight), frequently a sufficient analgesic effect cannot be achieved immediately after painful interventions [17]. Recently, a higher initial dose (40 mg/kg body weight) was suggested for effective postoperative pain control [18]. The risk for liver toxicity appears to be very low if the daily paracetamol dose does not exceed 90 mg/kg body weight in healthy children and if specific risk factors of the individual patient are always considered [18].

The NSAIDs can be categorized into four different groups:
1. **NSAIDs with low potency and short elimination half-life.** The prototype of this group is ibuprofen. The bioavailability of ibuprofen is complete; the elimination is always fast even in patients with severe impairment of the liver or kidney function. Ibuprofen is used in single doses between 200 mg and 0.8 g. Ibuprofen (at low doses) appears particularly useful for treatment of acute and post-operative pain.
2. **NSAIDs with high potency and short elimination half-life.** The drugs of this group are standard in the therapy of rheumatic pain. The most widely used compound is diclofenac, which is less active on COX1 than on COX2. This is taken as a reason for the low incidence of gastrointestinal side effects. This group contains important drugs such as indometacin and ketoprofen. All of them show high oral bioavailability and good effectiveness in post-operative pain relief.
3. **NSAIDs with intermediate potency and elimination half-life.** This group of drugs is intermediate in potency and speed of elimination. Some forms of migraine and post-operative pain appear as adequate indications for diflunisal and naproxen.
4. **NSAIDs with high potency and long elimination half-life.** The fourth group consists of the oxicam drugs (meloxicam, piroxicam and tenoxicam). The long half-life (days) does not make these oxicam drugs a first choice for acute and post-operative pain. Their main indication is inflammatory pain likely to persist for days (i. e. bone metastases). The high potency and long persistence in the body may be the reason for the higher incidence of serious adverse effects in the gastrointestinal tract and the kidney.

Table 9.8.2 shows the NSAIDs most commonly used in adults and in children for post-operative pain relief.

9.8.4.2 Opioid Analgesics

Postoperative pain of moderate or greater intensity should generally be treated with a systemically administered opioid analgesic [1, 4]. The need for analgesia largely depends on the magnitude of the surgical trauma. Generally, the greater the magnitude of surgery, the greater the post-operative discomfort. Major surgery usually requires postoperative pain therapy with opioids associated with other drugs, such as oral or parenteral NSAIDs and local anaesthetics, administered in different ways (wound infiltration, peripheral nerve block, epidural or i. v.). Opioids should be used in a multimodal balanced analgesia approach that minimizes opioid requirement and the degree of their side effects, such as respiratory depression, nausea, vomiting, constipation and urinary retention [19].

The mechanism of action of opioid analgesics depends on the interaction of these molecules with specific receptors to which they bind and their intrinsic activity at that receptor [1]. The receptors have a pharmacologic nomenclature: mu (µ) [1 and 2], delta (δ) and kappa (κ). All opioids exert their effects by activating one or more of these receptors. Analgesia involves activation of mu receptors in the brain and kappa receptors in the spinal cord. mu receptors are involved in respiratory depression and intestinal constipation. The contribution of delta receptors...
### Table 9.8.2 NSAIDs commonly used for post-operative pain relief in adult and paediatric patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Paediatric dosage</th>
<th>Adult dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>10–15 mg/kg every 4–5 h 20–40 mg/kg every 6 h rectally or Bolus 20 mg/kg + 15 mg/kg every 4 h Bolus 40 mg/kg + 20 mg/kg every 6 h</td>
<td>325–650 mg every 4–6 h (max 4 g/day)</td>
<td>No gastroenteric or hematologic side effects; no antiflogistic effect</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>5–10 mg/kg every 6–8 h</td>
<td>200 mg every 3–4 h</td>
<td>Gastroenteric or haematologic side effects, antiflogistic effect</td>
</tr>
<tr>
<td>Naproxen</td>
<td>5 mg/kg every 8–12 h</td>
<td>0.5–1 g/day</td>
<td>Gastroenteric or haematologic side effects, antiflogistic effect</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Bolus: 1–3 mg/kg every 8 h Drip: 0.20 mg/kg/h</td>
<td>10 mg every 4–6 h (max 40 mg/day) 10–30 mg every 4–6 h i. m. or i. v. (max 90 mg/day)</td>
<td>Renal and hepatic toxicity</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>10–15 mg/kg every 6–8 h</td>
<td>0.5–1 g every 4–6 h</td>
<td>Reye's syndrome (children), gastroenteric or haematologic side effects</td>
</tr>
</tbody>
</table>

### Table 9.8.3 Opioid agonist drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg) equianalgesic to 10 mg morphine IM</th>
<th>P.O.</th>
<th>Half-life (h)</th>
<th>Duration of action (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>130</td>
<td>200</td>
<td>2–3</td>
<td>2–4</td>
<td>Usually combined with a non-opioid</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15</td>
<td>30</td>
<td>2–3</td>
<td>2–4</td>
<td>Usually combined with a non-opioid</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>100</td>
<td>50</td>
<td>2–3</td>
<td>2–4</td>
<td>Usually combined with a non-opioid. Norpropoxyphene toxicity may cause seizures.</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>2–3</td>
<td>3–4</td>
<td>Multiple routes of administration available. Controlled release available. M6G accumulation in renal failure.</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2–3</td>
<td>7.5</td>
<td>2–3</td>
<td>2–4</td>
<td>No known active metabolites. Multiple routes available.</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>3–5</td>
<td>15–190</td>
<td>4–8</td>
<td>Plasma accumulation may lead to delayed toxicity. Dosing should be initiated on a p.r.n. basis. When switching to methadone from another opioid, potency may be much greater than expected; the dose of methadone should be lowered by 75–90% to account for this.</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10 (p.r.)</td>
<td>2–3</td>
<td>3–4</td>
<td>No oral formulation available. Less histamine release.</td>
</tr>
<tr>
<td>Heroin</td>
<td>5</td>
<td>60</td>
<td>0.5</td>
<td>3–4</td>
<td>High-solubility morphine prodrug.</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2</td>
<td>4</td>
<td>12–15</td>
<td>4–8</td>
<td>Plasma accumulation may lead to delayed toxicity</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>Empirically, transdermal fentanyl 100 µg/h = 2–4 mg/h intravenous morphine</td>
<td>48–72</td>
<td></td>
<td>Patches available to deliver 25, 50, 75 and 100 µg/h</td>
<td></td>
</tr>
</tbody>
</table>
Specific Aspects of Critical Care for Children

The potential utility of an adjuvant analgesic is usually suggested by the characteristics of the pain or by the existence of another symptom that may be amenable to a non-analgesic effect of the drug. The adjuvant drugs more frequently used in post-operative pain are corticosteroids, neuroleptics and benzodiazepines.

9.8.4.4 Topical Analgesics

Topical formulations are useful for needle procedures, including EMLA, a cream containing a eutectic mixture of two local anaesthetics (lidocaine 2.5% and prilocaine 2.5%). This is very effective in numbing the skin and the tissues just underneath the skin. Topical local anaesthetics can be used in the management of painful cutaneous and mucosal lesions and as a medication prior to skin puncture. However, the depth of the skin which becomes numb is dependent upon how long the cream is left on. The maximum depth is about 6–7 mm after the cream has been left on the skin for 2 h.

This medication has been successfully used for a number of painful procedures, including bone marrow aspiration and lumbar puncture; the cream should be applied from 30 min to 1 h before the shot or needle procedure [20]. EMLA has proven to be safe, with low plasma local anaesthetic concentration. Mild side effects generally disappear spontaneously within 1 or 2 h (skin paleness, redness, a changed ability to feel hot or cold, swelling, itching and rash). It should not be used in children affected by a rare condition of congenital or idiopathic methaemoglobinemia or in infants under the age of 12 months who are receiving treatment with methaemoglobin-inducing agents [20].

Table 9.8.4 Opioids commonly used for postoperative pain relief in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Iv/sc starting dose</th>
<th>Oral starting dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>–</td>
<td>0.5–1 mg/kg every 3–4 h</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Bolus: 0.015 mg/kg every 2–4 h</td>
<td>0.06 mg/kg every 3–4 h</td>
<td>Nausea, vomiting, urinary retention</td>
</tr>
<tr>
<td></td>
<td>Drip: 0.006 mg/kg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Bolus: 0.05–0.1 mg/kg every 2–4 h</td>
<td>0.15–0.3 mg/kg every 4 h</td>
<td>Nausea, vomiting, urinary retention, pruritus</td>
</tr>
<tr>
<td></td>
<td>Drip: 0.03 mg/kg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Bolus: 0.5–1 γ/kg every 1–2 h</td>
<td>–</td>
<td>Nausea, vomiting, urinary retention, pruritus, respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Drip: 0.5–3.0 γ/kg/h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Bolus: 0.1–0.5 γ/kg every 1 h</td>
<td>–</td>
<td>Nausea, vomiting, urinary retention, respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Drip: 0.1–0.25 γ/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>Bolus: 0.2 γ/kg every 1 h</td>
<td>–</td>
<td>Respiratory depression, haemodynamic alterations</td>
</tr>
<tr>
<td></td>
<td>Drip: 0.1–0.5 γ/kg/min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

receptors to analgesia is unclear and may be more closely related to euphoria.

Opioid Classification. Based on their interactions with the various receptor subtypes, opioid compounds can be divided into agonist, partial agonist, and mixed agonist–antagonist drugs. The pure agonist drugs are most commonly used in clinical pain management, both in adult patients and in children (Tables 9.8.3 and 9.8.4). The mixed agonist–antagonist opioids (pentazocine, nalbuphine, butorphanol and dezocine) and the partial agonist opioids (buprenorphine) play a minor role in the management of post-operative pain because of the existence of a ceiling effect for analgesia. The pure agonist opioid drugs appear to have no ceiling effect for analgesia. As the dose is raised, analgesic effects increase until either analgesia is achieved or the patient loses consciousness. This increase in effect occurs as a log-linear function: dose increments on a logarithmic scale yield linear increases in analgesia. In practice, it is the appearance of adverse effects, including confusion, sedation, nausea, vomiting or respiratory depression that imposes a limit on the useful dose.

9.8.4.3 Adjuvant Analgesics

The term “adjuvant analgesic” describes a drug that has a primary indication other than pain but is analgesic in some conditions. A large group of such drugs, which are derived from diverse pharmacological classes, is now used to manage non-malignant pain. In the post-operative patients, these drugs may be combined with primary analgesics in any of the three steps of the analgesic ladder to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side effects. The potential utility of an adjuvant analgesic is usually suggested by the characteristics of the pain or by the existence of another symptom that may be amenable to a non-analgesic effect of the drug. The adjuvant drugs more frequently used in post-operative pain are corticosteroids, neuroleptics and benzodiazepines.
**9.8.5 Patient-Controlled Analgesia**

Patient-controlled analgesia (PCA) generally refers to a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug “on demand” according to parameters set by the physician. Use of a PCA device allows the patient to overcome variations in both pharmacokinetic and pharmacodynamic factors by carefully titrating the rate of opioid administration to meet individual analgesic needs. At the paediatric age, PCA is recommended for children of 8 years or more without disabilities, in whom moderate to severe pain is anticipated for 24 h or more. Most children over the age of 7 years understand the PCA concept, and sometimes even younger children can learn to use PCA, but some may not have the cognitive or emotional resources to use it. In these patients, Nurse- or Parent-Controlled Analgesia (NCA/PCA) represents a more suitable modality of drug administration.

As a continuous infusion, PCA allows a steady analgesic serum concentration with safety and efficacy in pain control [21]. Morphine is the most common drug used in PCA, followed by fentanyl and hydromorphone [21]. The selection of opioid used in PCA is perhaps less critical than the appropriate selection of parameters such as bolus dose, lockout and background infusion rate [22]. PCA dosage regimens must be individualized on the basis of pain intensity, and monitoring pain parameters must be age appropriate. Monitoring involves measurements of respiratory rate, level of sedation and oxygen saturation. Efficacy of PCA therapy is assessed by self-reporting, visual analogue scales, faces pain scales and usage pattern. The effectiveness of analgesic techniques may be limited by the incidence and severity of adverse effects; potential adverse effects of PCA therapy, including respiratory depression, nausea, vomiting and pruritus, can be prevented or controlled by the use of adjuvant drugs and by careful titration. To date, safety and efficacy of PCA has been established, and a role of this procedure has been proposed in postoperative pain management as well as burns, oncology and palliative care.

**9.8.6 Conclusions and Perspectives**

Acute and post-operative pain has emerged as an important issue due to ethics aspects and associated morbidity and mortality. Substantial progress in understanding peripheral, spinal cord and brain mechanisms involved in acute post-operative pain continues to be made with important consequences for treatment. The diagnosis and treatment of the cause of acute pain must always have high priority, and post-operative pain management is an important goal in order to optimise medical care.

Improved understanding of the pharmacology of the analgesics and of the development of new techniques for analgesic administration have greatly enhanced the ability of medical doctors to successfully manage patients in pain. For some post-operative conditions, the success of pharmacological strategies is remarkable, but more action is necessary. Firstly, more paediatric centres are needed to develop specific post-operative pain programmes. Secondly, collaboration between centres will be necessary to provide large enough samples of patients with the various pain conditions, considering the lack of data on this field. Finally, we must consider that the incidence of post-operative pain in children is similar to that of adults but that our knowledge of how to help children cope with acute pain is underdeveloped. The psychological and physiological uniqueness of children must not be forgotten.

Cooperation and communication between the anaesthesiologist, surgeon and paediatrician are essential for successful anaesthesia and pain management in paediatric patients. The introduction of acute pain services has been shown to improve post-operative pain relief, but it is foreseeable that their role should expand and integrate into general perioperative care. For all these reasons, the alleviation of pain and anxiety in post-operative children is actually a high priority of all post-operative services, and all persons involved in perioperative management of these patients are very much a part of “continuity of care” concept to obtain effective pain relief.

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