Craniofacial and Intracranial Manifestations of Langerhans Cell Histiocytosis: Report of Findings in 100 Patients

OBJECTIVE. The purpose of this study was to review the craniofacial and intracranial clinical and radiologic manifestations of patients diagnosed with Langerhans cell histiocytosis (LCH). This report will compare the frequency of the various manifestations found in our series with those reported in the medical literature.

CONCLUSION. In LCH, involvement of the calvaria, skull base, maxillofacial bones, and hypothalamic–pituitary axis is fairly common. The precise location of these lesions contributes to the variety of clinical manifestations of LCH, which includes scalp and/or facial swelling, seizures, hearing loss, recurrent otitis media, gingival bleeding, proptosis, diabetes insipidus, and cranial nerve palsies.

Langerhans cell histiocytosis (LCH) is a rare disease of unknown cause. LCH, formerly known as histiocytosis X, is a disease entity composed of three rare proliferative disorders of bone marrow–derived antigen-presenting cells of the dendritic cell line, also known as Langerhans cells [1]. LCH is composed of three distinct clinical syndromes that show indistinguishable histology. Characteristically, these lesions stain positively with histochemical stains, S-100 and CD1a. Eosinophilic granuloma is limited to bone in patients usually 5–15 years old. Hand-Schüller-Christian disease is characterized by multifocal bone lesions and extraskeletal involvement of the reticuloendothelial system (RES) and pituitary gland, usually seen in children 1–5 years old. In Letterer-Siwe disease, there is disseminated involvement of the RES with a fulminant clinical course in children less than 2 years old [2, 3].

LCH is a rare disease, with a reported incidence of 0.2–2.0 cases per 100,000 children under 15 years old [4]. LCH is usually a self-limited disease, with a varied clinical and radiologic presentation. The prognosis is generally poor in children with organ dysfunction. In the absence of organ dysfunction, children with either localized or multifocal LCH have an excellent prognosis [5]. The clinical and radiologic presentations of LCH are variable and range from a lytic skeletal lesion incidentally seen at radiography to widespread disease with severe organ dysfunction [5].

Materials and Methods

Between 1997 and 2007, 100 patients with biopsy-proven LCH were treated in the oncology unit at Schneider Children’s Hospital at Long Island Jewish Medical Center. A retrospective review of radiographic images and reports was performed. There were 48 male patients and 52 female patients ranging in age from 4 months to 24 years. The average age at presentation was 4 years. All patients underwent imaging studies, mostly skeletal surveys and CT. Thirty-seven of 100 patients underwent MRI of the brain during their course of treatment.

Results

Calvaria

Ninety-six percent of the patients in this series had bone involvement. Those patients without bone involvement had varying clinical manifestations, such as pulmonary disease, lymphadenopathy, and visceral organ and skin lesions. Fifty-eight of 96 patients (60%) had a solitary bone abnormality, and 38 patients (40%) had multiple lesions. By far, the most common bone involved in the series was the skull, affecting 52 of 96 patients (54%). In particular, the calvarium was affected in 45% of patients. Of the patients with calvarial involvement, the parietal bone was most commonly affected, in approximately half of the patients. Patients...
with skull involvement may be asymptomatic or have a palpable soft-tissue mass. The lesions are round or oval lytic lesions, involve the full thickness of the calvarium, have circumscribed margins, and have characteristic beveled edges [6]. The beveled edge represents the unequal destruction of the outer and inner tables of the skull (Fig. 1). A bone sequestrum is highly characteristic. The classic button sequestrum is a radiolucent lesion surrounding a central bone opacity and may be found in other disease processes, such as osteomyelitis [7]. On MRI, the calvarial lesions are isointense to gray matter on T1, isointense or hyperintense on T2, and show variable enhancement after gadolinium administration (Fig. 2).

**Skull Base**

Of the 52 LCH patients with skull involvement in our series, the skull base, in particular, was affected in 27 patients (52%). The temporal bone was most commonly involved, affecting 13 patients, accounting for 48% of patients with skull base involvement and 13% of the entire series of 100 patients diagnosed with LCH. Two patients had bilateral mastoid involvement.

Eosinophilic granuloma of the temporal bone has been described, beginning with the earliest reports of the disease [8]. The radiologic findings of temporal bone involvement typically show destructive, lytic “punched out” bone lesions involving the mastoids, with the squamous portion and middle ear less affected [9] (Fig. 3). CT is the preferred imaging technique for describing the extent of temporal bone involvement and has a role in monitoring disease activity and response to treatment.

Some patients have an associated soft-tissue mass, which enhances homogeneously on CT and MRI after contrast administration. On MRI, the soft-tissue mass is hyperintense on T2, with variable signal intensity on T1 (hypointense to isointense) [10] (Fig. 4).

One of the patients in our series presented with an isolated abducens sixth-nerve palsy. CT showed extension of disease from the mastoids to the petrous apex, Dorello’s canal, and cavernous sinus, which has rarely been reported in the literature (Fig. 5). Those few reported cases with involvement of the cavernous sinus and petrous apex also involved the clivus, which was not involved in this particular case [11]. However, two patients in the series of 100 patients had lesions involving the clivus.

Finally, the jugular foramen was involved in 2% of our series of patients. LCH involvement of the jugular foramen is very rare. One of the two patients was a 2-year-old boy who presented clinically with hoarseness and difficulty swallowing (Fig. 6). CT of the head and neck revealed a large, lytic lesion...
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Facial swelling is a common clinical problem in the pediatric population. Khanna et al. [12] classified pediatric facial swelling into the following four groups: acute swelling with inflammation, nonprogressive swelling, slowly progressive swelling, and rapidly progressive swelling. LCH typically presents as rapidly progressive facial swelling.

Distinguishing an aggressive process such as LCH from a more benign process such as osteomyelitis can sometimes be difficult. Both may present with rapidly progressive facial swelling. For example, an 8-year-old boy in our series presented with rapidly progressing frontal swelling, with associated skin induration. Without any history of trauma, the presumptive clinical diagnosis was frontal sinusitis with an associated subgaleal abscess, or Pott’s puffy tumor. However, CT was performed, which showed an aggressive, lytic punched out lesion arising from the frontal sinus, with an associated large soft-tissue mass. Subsequent MRI revealed extension of this process into the epidural space. Biopsy revealed LCH (Fig. 7).

The most common location of maxillofacial involvement of LCH in our series and reported in the literature is the mandible. The mandible is the second most common location of LCH involvement overall, the skull being the most common. Of the 100 patients in this series, 15 had mandible lesions and one of those was bilateral involvement. Mandible lesions tend to destroy alveolar bone, which produces the radiologic appearance of “floating teeth” [3] (Fig. 8). The maxilla and/or maxillary sinus was affected in 8% of patients in the series. In particular, the hard palate was involved in 3% of the patients in our series (Fig. 9). Gingival bleeding or swelling may also be a presenting manifestation of LCH involvement of the hard palate.

Once thought of as a rare occurrence, orbital involvement in LCH has increased in frequency in the literature over the past 10 years [13]. Patients typically present with proptosis and periorbital edema. The reported incidence of orbital involvement is 12–20% [14, 15]. In our series, 11% of patients had orbital involvement. Characteristically found on CT, a destructive lesion usually involves the lateral wall of the orbit. A large soft-tissue component extends into the extraconal space, ocular adnexa, and infratemporal fossa. The greater wing of the sphenoid bone is typically eroded, with epidural extension into the middle cranial fossa [14] (Fig. 10). The lateral rectus muscle is often inseparable from the mass. Previous reports have described intraocular involvement and brain parenchyma, but these are rare findings. Orbital masses are usually extraconal and are thought to be of bone origin [14–17]. The boundaries of the lesion are best delineated on MRI, specifically T1-weighted sequences with gadolinium. The orbital lesions are typically isointense on T1, T2, and proton density sequences and enhance avidly after contrast administration [18–20].

CNS Manifestations

LCH commonly affects the CNS; however, rarely is this the only site. The most common CNS locations involved are the hypothalamic–pituitary axis and cerebellum [18, 21, 22]. Diabetes insipidus is the most common endocrine manifestation of LCH. Eleven patients in our series (11%) had diabetes insipidus. Nine of the 11 patients also had skeletal involvement. Diabetes insipidus is more commonly observed in association with multisystem disease, especially in those patients with skull and orbital involvement [18, 23].

MRI findings in central diabetes insipidus are characterized by lack of high signal intensity on T1-weighted sequences and gadolinium enhancement.
intensity of the posterior pituitary on T1-weighted images, which is often associated with enhancement and thickening of the pituitary stalk of greater than 3 mm [4, 24] (Fig. 11). However, the posterior pituitary bright spot frequently persists in patients with diabetes insipidus; therefore it is not a very reliable characteristic [25].

Neurodegenerative changes are the second most frequent pattern, although still considered rare, affecting about 1–3% of LCH patients [4, 26, 27]. The findings compose mostly bilateral symmetric lesions in the cerebellum and basal ganglia of variable signal quality on MRI, depending on site and stage of the lesion. Less frequently, lesions in the extraaxial spaces—the meninges, pineal gland, and choroid plexus—are observed [4, 28]. Of 100 patients reviewed in this series, only 37 patients underwent MRI of the brain. Two (2%) of the patients had intraparenchymal lesions, both of which were located in temporal lobes. Two (2%) of the patients showed evidence of cerebral atrophy (Fig. 2).

One patient had mesial temporal sclerosis, which may have been incidental, and 3% of the patients had extraaxial lesions. No patients in this series, who underwent MRI of the brain, showed any evidence of disease in the cerebellum, basal ganglia, choroid plexus, or pineal gland.

**Discussion**

In this retrospective review of 100 patients, we described the wide spectrum of craniofacial and intracranial manifestations of LCH (Table 1). In our study population, females and males were equally affected, with approximately a 1:1 ratio. Many studies have stated a male preponderance, citing ratios of between 1.6 to 2.0 to 1 [29–34]. The average age of patients in this series was 4 years and ranged between 4 months and 24 years.

Craniofacial involvement with osseous lesions in the bones of the orbits and the calvaria has long been recognized as a classic presentation of LCH [4, 35–37]. Head and neck manifestations of LCH are frequent.

**TABLE 1: Craniofacial Involvement in 100 Patients with Langerhans Cell Histiocytosis**

<table>
<thead>
<tr>
<th>Area Involved</th>
<th>No. of Patients (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>96</td>
</tr>
<tr>
<td>Solitary</td>
<td>58</td>
</tr>
<tr>
<td>Multifocal</td>
<td>38</td>
</tr>
<tr>
<td>Calvarium</td>
<td>52</td>
</tr>
<tr>
<td>Parietal</td>
<td>46</td>
</tr>
<tr>
<td>Skull base</td>
<td>27</td>
</tr>
<tr>
<td>Temporal</td>
<td>13</td>
</tr>
<tr>
<td>Clivus</td>
<td>2</td>
</tr>
<tr>
<td>Jugular foramen</td>
<td>2</td>
</tr>
<tr>
<td>Mandible</td>
<td>15</td>
</tr>
<tr>
<td>Orbits</td>
<td>11</td>
</tr>
<tr>
<td>Hard palate</td>
<td>3</td>
</tr>
<tr>
<td>Maxilla or maxillary sinus</td>
<td>8</td>
</tr>
<tr>
<td>Pituitary stalk or diabetes insipid</td>
<td>11</td>
</tr>
</tbody>
</table>
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with reported frequencies varying from 50–80% [4, 38, 39]. In our series, 54% of patients had craniofacial osseous involvement, which included the calvaria, skull base, temporal, and maxillofacial bones. Calvarial lesions, which are common, were seen in 45% of patients in this series. These lesions typically have sharp borders with unequal involvement of the inner and outer tables, resulting in a characteristic beveled-edge appearance seen on radiographs and CT scans. These calvarial lesions may or may not have an associated soft-tissue mass or dural invasion, both of which are better evaluated on MRI. Classically, these patients present with a tender, palpable scalp soft-tissue mass.

The clinical manifestations of LCH are widely varied and are entirely dependent on the particular location of the craniofacial bones involved. For example, LCH of the temporal bone may manifest as mastoid...
swelling, deafness, vertigo, middle ear polyps, otorrhea resistant to medical treatment, and erosion of the posterior bony external auditory canal [40]. Delayed diagnoses are frequent because otological findings are similar to other conditions such as acute mastoiditis, recurrent chronic otitis media, cholesteatoma, or external otitis [10, 41].

The characteristic radiologic finding of temporal bone involvement includes destructive, lytic (punched out) bone lesions involving the mastoids. The radiologic differential diagnosis includes mastoiditis, rhabdomyosarcoma, and metastasis [39]. The temporal or mastoid bone was involved in 13% of patients in our series and in 48% of those patients with skull base involvement. Reported frequencies of temporal bone involvement vary from 15% to 60% [29, 34, 41, 42–45].

Other less commonly affected areas in the skull base described in this review are the clivus and jugular foramen. LCH involvement of the clivus has rarely been reported in the literature and was seen in two patients in this series [11, 46, 47]. Apart from LCH, the differential diagnosis of a clival mass in children includes metastatic disease from neuroblastoma, leukemic deposits, lymphoma, osteomyelitis, tuberculosis or fungal granuloma, chordoma and chondrosarcoma, local extension from nasopharyngeal carcinoma, or pituitary tumor [47]. The jugular foramen is another location rarely involved by LCH. The more common lesions found in the jugular foramen include paraganglioma, schwannoma, meningioma, and metastasis [48]. However, in a child with a skull base lesion, LCH must be included in the differential diagnosis.

Facial swelling is a common clinical problem in the pediatric population. The origins of a facial mass or swelling can vary from congenital causes to acquired conditions such as infection and benign or malignant conditions in soft-tissue or bone. LCH must be considered in the differential diagnosis for rapidly progressive facial swelling, especially when associated with cranial nerve deficits [12].

Patients with LCH and bone involvement often have adjacent soft-tissue involvement. The overall reported incidence of orbital involvement of LCH is between 12% and 20% [14, 15]. Eleven (11%) patients in our series had orbital findings. Patients typically present with proptosis, facial swelling, or periorbital edema. In patients with primary orbital involvement, other lesions such as metastatic neuroblastoma, osteomyelitis, Ewing’s sarcoma, choroma, lymphoma, and rhabdomyosarcoma must be excluded [14]. Both LCH and metastatic neuroblastoma characteristically involve the posterolateral part of the orbit, where the frontal bone and greater wing of the sphenoid meet [12].
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Fig. 8—23-year-old man with gingival bleeding. 
A, Lateral oblique radiograph of left mandible shows expansile, lytic lesion in superior alveolar ridge (arrows), resulting in “floating teeth.” 
B, Axial CT image shows expansile, lytic lesion, with associated periosteal reaction (arrow).

Fig. 9—3-year-old girl with gingival swelling and bleeding. Coronal reformatted CT image shows soft-tissue mass arising from hard palate (arrow).

Fig. 10—3-year-old boy who presented with periorbital swelling and proptosis. 
A and B, Axial CT soft-tissue (A) and bone (B) images show large mass eroding lateral wall of left orbit and greater wing of sphenoid bone (arrows). 
C and D, Coronal T1-weighted MR images, without and with gadolinium enhancement better delineate borders of this lesion (arrows), located in lateral orbital wall.
The appearance of floating teeth in the mandible or maxilla should also suggest the diagnosis of LCH, especially when seen in conjunction with multiple skull lesions in a pediatric patient. The floating-teeth appearance can also occur in patients with metastatic neuroblastoma, malignant lymphoma, and familial dysgammaglobulinemia [3, 49]. Usually affecting 10% of LCH patients, the mandible is the second most common bone involved in LCH, with the skull being the most common [29, 32]. These patients usually present with gingival bleeding/swelling or facial swelling. Typically associated with mandible or maxilla lesions, the gingival tissues are affected frequently in patients with LCH, with reported frequencies up to 20% [2, 35].

CNS involvement in LCH is common, and has been reported in 16% of patients [13, 50]. The most common intracranial site of involvement is the hypothalamic-pituitary axis [13, 51]. Diabetes insipidus is the most common endocrine manifestation of LCH and is attributable to decreased secretion of antiuretic hormone [18]. Growth hormone deficiency (GHD) is the most frequent anterior pituitary hormone deficiency among patients with LCH and pituitary dysfunction. GHD is usually diagnosed years after posterior pituitary deficiency and is responsible for growth retardation. Described initially as a rare complication, GHD is now estimated to affect up to 42% of LCH patients with diabetes insipidus [52–56]. Eleven patients in our series (11%) had diabetes insipidus, which is consistent with recent literature, which varies from 10% to 20% [5, 29, 33, 34].

Other intracranial CNS changes have been reported recently in the literature with increasing frequency. According to Prayer et al. [4], in a series of 163 patients, neurodegenerative gray-matter changes in the cerebellum occurred in 40% of patients and basal ganglia in 26% of patients. Intraxial, white-matter parenchymal changes resulted in a leukencephalopathy-like pattern in 36%. Meningeal lesions were found in 29%, and choroid plexus involvement was seen in 6%. These intracranial CNS changes were rarely seen in our series of 100 patients, although only 37 patients underwent MRI of the brain during their clinical course.

In conclusion, LCH can be a diagnostic dilemma for pediatricians and radiologists. Although most commonly presenting as eosinophilic granuloma or solitary bone lesion, the clinical presentation varies greatly depending on the precise location of involvement. Common clinical presentations include scalp or facial swelling, seizures, hearing loss, recurrent otitis media, gingival bleeding, proptosis, diabetes insipidus, and cranial nerve palsies. Typically found on imaging as an aggressive intracranial or craniofacial lesion, LCH must be included in the differential diagnosis of malignant processes such as metastatic neuroblastoma or rhabdomyosarcoma and benign processes such as osteomyelitis.

References
