MR Imaging Presentation of Intracranial Disease Associated with Langerhans Cell Histiocytosis

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BACKGROUND AND PURPOSE: Intracranial manifestations of Langerhans cell histiocytosis (LCH) are underestimated in frequency and diversity. We categorized the spectrum of MR imaging changes in LCH.

METHODS: We retrospectively reviewed 474 MR images in 163 patients with LCH and 55 control subjects. Lesions were characterized by anatomic region and signal intensity. Brain atrophy was assessed.

RESULTS: We noted osseous lesions in the craniofacial or skull bones in 56% of patients, meningeal lesions in 29%, and choroid-plexus involvement in 6%. In the hypothalamic-pituitary region, infundibular thickening occurred in 50%; pronounced hypothalamic mass lesions in 10%; and infundibular atrophy in 29%. The pineal gland had a cystic appearance in 28%, and pineal-gland enlargement (>10 mm) was noted in 14%. Nonspecific paranasal-sinus or mastoid opacifications were seen in 55% of patients versus 20% of controls, and accentuated Virchow-Robin spaces occurred in 70% of patients versus 27% of controls (P < .001). Intra-axial, white-matter parenchymal changes resulted in a leukencephalopathy-like pattern in 36%. Enhancing lesions in a vascular distribution were noted in 5%. Gray-matter changes suggestive of neurodegeneration were identified in the cerebellar dentate nucleus in 40% and in the supratentorial basal ganglia in 26%. All patients with neurodegenerative lesions had lesions in the extra-axial spaces. Cerebral atrophy was found in 8%.

CONCLUSION: In LCH, cranial and intracranial changes at MR imaging include 1) lesions of the craniofacial bone and skull base with or without soft-tissue extension; 2) intracranial, extra-axial changes (hypothalamic-pituitary region, meninges, circumventricular organs); 3) intracranial, intra-axial changes (white matter and gray matter); and 4) cerebral atrophy.
with LCH to provide a working scheme for the evaluation of suspected CNS LCH (14). In the framework of the large, multicentric LCH trials, a registry of LCH patients with CNS changes was established. Over the past years, information about 163 patients with 474 MR imaging studies was collected. On the basis of this uniquely large series, we could assess the broad spectrum of intracranial findings in LCH and describe the characteristic morphologic patterns. The distinctness of these morphologic features leads to a hypothesis about the possible pathophysiologic background of CNS LCH. Our new classification of cranial and intracranial LCH, should 1) provide a guideline for the evaluation of cranial MR images in patients with known or suspected CNS LCH to aid prompt diagnosis and 2) contribute to a better understanding of the underlying disease mechanisms with a potential impact on new therapeutic approaches.

**Methods**

**Patients**

Since 1993, 474 brain MR images of 163 patients with LCH have been sent to the study center for central review. This group included 65 female patients and 98 male patients for a female-to-male ratio of 1:1.5. At the time of the first image, patients’ ages ranged 0.4–47 years (median, 8.2 years). At the time of diagnosis, patients ranged from neonates to adults aged 40.4 years (median, 2.8 years). The interval between the diagnosis of LCH and the first brain MR study was 1.2 years (in cases with primary CNS manifestations) to 20.6 years (median, 1.8 years).

To prove the importance of our findings, we compared the MR findings of the patients with LCH with those of a control group of 55 age-matched patients without LCH.

**MR Imaging**

MR images were obtained at 63 institutions in 20 countries by using various techniques. We considered only those MR studies that included 1) images in at least two section planes, 2) T2-weighted images (T2WI) and T1-weighted images (T1WI), and 3) images with and those without contrast enhancement that allowed proper assessment of intracerebral changes. Inappropriate section thickness or image quality in the hypothalamic pituitary region, pineal gland, and skull base was not an exclusion criterion as long as the gray matter and white matter could be sufficiently assessed. As a consequence, the frequency of findings in the respective regions was related to the number of available imaging studies on which the structures of interest could be evaluated adequately. The image evaluation was done according to the scheme shown in Table 1. Follow-up studies performed at variable intervals were available in 99 patients.

**Control Study**

To assess the importance of opacifications in the paranasal sinuses and/or mastoids and the visibility of the Virchow-Robin spaces (VRS), we compared the MR images from 65 patients with those of 55 age-matched control subjects without LCH (Table 2). The control subjects underwent MR examinations at the Department for Neuroradiology, University Clinic of Vienna, for diverse indications. Twenty-seven control subjects had malignant brain tumors and had received chemotherapy or irradiation before the MR study. In the other 28 subjects, MR was performed for the evaluation of epilepsy (n = 9), cerebral malformations (n = 3), inflammatory disease (n = 3), metabolic disorders (n =

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**TABLE 1: Scheme for the evaluation of cranial MR images in patients with LCH**

<table>
<thead>
<tr>
<th>Anatomic Structure</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial bones and skull base</td>
<td>Bone destruction, tumorous infiltration, intracranial extension</td>
</tr>
<tr>
<td>Paranasal sinuses</td>
<td></td>
</tr>
<tr>
<td>Ethmoidal</td>
<td>Bone destruction</td>
</tr>
<tr>
<td>Maxillar</td>
<td>Opacification (fluid intense, tissue intense)</td>
</tr>
<tr>
<td>Sphenoidal</td>
<td>Enhancement</td>
</tr>
<tr>
<td>Intracranial and extra-axial</td>
<td>With or without bone destruction</td>
</tr>
<tr>
<td>Meninges</td>
<td>Infiltration, enhancement, symmetry</td>
</tr>
<tr>
<td>Epidural</td>
<td></td>
</tr>
<tr>
<td>Subdural</td>
<td></td>
</tr>
<tr>
<td>Circumventricular organs*</td>
<td></td>
</tr>
<tr>
<td>Hypothalamic-pituitary region</td>
<td></td>
</tr>
<tr>
<td>Anterior pituitary</td>
<td>Size (empty sella, atrophy, normal, enlarged), symmetry, enhancement</td>
</tr>
<tr>
<td>Posterior pituitary</td>
<td>Size, T1WI hyperintensity present or absent</td>
</tr>
<tr>
<td>Infundibulum</td>
<td>Size (measured in at least 2 planes) normal, thickened &gt;2.6 mm, cranial-caudal different, threadlike &lt;1 mm</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Mass lesions, enhancement</td>
</tr>
<tr>
<td>Intracranial and intra-axial parenchymal</td>
<td></td>
</tr>
</tbody>
</table>
We included only MR imaging examinations performed between May and September to consider the possible influence of season and associated common cold infections on MR findings in the sinuses. Only studies that sufficiently assessed the paranasal sinuses and mastoid air cells were considered.

The 55 control subjects and 65 patients with LCH were aged 3 months to 47 years; this range corresponded to the age range of the 163 patients in the overall study group. To consider the possible influence of chemotherapy and/or cranial irradiation before the MR examination, both patients and control subjects were assigned to untreated and treated groups.

Statistical Analysis

To compare the frequency of VRS and sinus changes in LCH patients with and those without CNS disease and those with and those without treatment and also in control subjects with and those without treatment, we used the Fisher exact test and the \( \chi^2 \) test, when appropriate. Because we found an overall significant difference in sinus changes between these groups, we additionally compared the frequency of sinus changes in untreated LCH patients with those of untreated nontumor control subjects and compared treated LCH patients with the tumor control subjects. In addition, we found an overall significant difference was for VRS; therefore, we also compared the patients with CNS LCH with the overall control group (Table 2).

Results

Changes in the Craniofacial Bone, Skull Base, and Sinus

In 125 studies (56%) of 91 patients, osseous lesions were observed in the craniofacial bones or skull base on at least one MR imaging study (Table 3). In 33 studies, only a single osseous lesion was seen, and in 92, as many as seven simultaneous lesions were observed in the craniofacial bones or skull base. Contrast enhancement was seen in patients with additional epidural involvement. The most frequently involved bones were the temporal bone (54%), the orbit (37%), the vault (47%), and the extraorbital facial bones (30%).

The paranasal sinuses or mastoids were opacified in 36 (55%) of 65 patients (Fig 1), as opposed to 11 (20%) 55 control subjects (Table 2). These changes were both of solid or fluid signal intensity. The ethmoid sinuses were involved in 49% of the patients with LCH; the mastoids in 43%; the maxillary sinuses in 26%; and the sphenoid sinus in 8%. No biopsy of the sinus changes were done. Bone destruction of the paranasal sinus was seen in six LCH cases with mass lesions involving the sphenoid, and in three LCH cases with ethmoid involvement.

Intracranial/Extra-Axial Changes

Dura-Based Masses.—Dura-based masses were seen 48 patients (29%) and involved the subdural spaces in 21 and the epidural spaces in 27. These masses were isointense to hypointense to brain on T1WI with inconstant contrast enhancement; they appeared hypointense on T2WI (Fig 2A). In four patients, histopathologic examination of surgical specimens from such lesions revealed active LCH or

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**TABLE 2: Results of the control study**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Patients with CNS LCH</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Treatment</td>
<td>With Treatment</td>
</tr>
<tr>
<td>Sinus/mastoid opacification</td>
<td>11/19 (58%)</td>
<td>25/46 (54%)</td>
</tr>
<tr>
<td>Dilated VRS</td>
<td>9/11 (81%)</td>
<td>21/32 (66%)</td>
</tr>
</tbody>
</table>

**TABLE 3: Morphology of intracranial lesions in 163 patients with 474 MR imaging studies**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>MR Imaging Studies</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial bones and/or skull base</td>
<td>125</td>
<td>91</td>
</tr>
<tr>
<td>Paranasal sinuses</td>
<td>196</td>
<td>88</td>
</tr>
<tr>
<td>Ethmoid</td>
<td>90</td>
<td>64</td>
</tr>
<tr>
<td>Maxillary</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>Sphenoidal</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Intracranial and extra-axial changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>Subdural</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>Choroid plexus</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Pineal gland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged &gt;10 mm</td>
<td>48</td>
<td>23</td>
</tr>
<tr>
<td>Cystic</td>
<td>102</td>
<td>46</td>
</tr>
<tr>
<td>Solid</td>
<td>111</td>
<td>56</td>
</tr>
<tr>
<td>Hypothalamic-pituitary region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior pituitary, assessable</td>
<td>241</td>
<td>139</td>
</tr>
<tr>
<td>Empty sella</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Small</td>
<td>75</td>
<td>39</td>
</tr>
<tr>
<td>Normal</td>
<td>134</td>
<td>73</td>
</tr>
<tr>
<td>Enlarged</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Posterior pituitary, assessable</td>
<td>248</td>
<td>124</td>
</tr>
<tr>
<td>Bright spot present</td>
<td>46</td>
<td>26</td>
</tr>
<tr>
<td>Bright spot absent</td>
<td>239</td>
<td>98</td>
</tr>
<tr>
<td>Pituitary stalk, assessable</td>
<td>393</td>
<td>137</td>
</tr>
<tr>
<td>Normal</td>
<td>188</td>
<td>87</td>
</tr>
<tr>
<td>Thickened &gt;3 mm</td>
<td>140</td>
<td>68</td>
</tr>
<tr>
<td>Cranial-caudal difference</td>
<td>59</td>
<td>32</td>
</tr>
<tr>
<td>Threadlike &lt;1 mm</td>
<td>65</td>
<td>40</td>
</tr>
<tr>
<td>Hypothalamic mass lesions</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>Intracranial and intra-axial changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WM changes, vascular pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visible VRSs</td>
<td>112*</td>
<td>54†</td>
</tr>
<tr>
<td>Space-occupying lesions</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Leukoencephalopathy-like pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periventricular</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>Brain stem, pons</td>
<td>74</td>
<td>44</td>
</tr>
<tr>
<td>Cerebellar WN</td>
<td>76</td>
<td>39</td>
</tr>
<tr>
<td>GM changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>74</td>
<td>42</td>
</tr>
<tr>
<td>Cerebellar dentate nuclei</td>
<td>139</td>
<td>65</td>
</tr>
</tbody>
</table>

* 196 analyzed.
† 88 analyzed.
fibroxanthomatous changes, consistent with "old burned out" LCH lesions. Two of 27 patients (four studies) had combined epidural and subdural involvement. Epidural involvement was combined with osseous lesions in all but one case. A lesion was assumed to lie in the epidural space when it could not or could hardly be delineated from the underlying bone (Fig 2A and B), or when the dura was displaced inward as a sign of a pathologic process between the skull and the dura as opposed to the normal position of the dura (adjacent to the skull) in cases of subdural lesions.

Choroid-Plexus Lesions.— Bilateral choroid-plexus lesions were found in 10 patients. All of these lesions had intermediate signal intensity on T1WI and marked hypointensity on T2WI (Fig 2B). These findings suggested calcification, which was proved in three cases with available CT scans. The appearance of the choroid plexus was interpreted as pathologic on the basis of the following criteria: size of more than one-third the width of the trigonum and/or plane, smooth calcifications that could not be mistaken for normal plexus calcifications (rare in children), a cloverleaf-like appearance that differed from the cauliflower-like appearance of the plexus papillomas, and/or increased size on follow-up studies. Other choroid-plexus lesions were not found. Enhancing thickening of the falx cerebri and tentorium were seen in one patient each. Infiltration of the falx and tentorium was diagnosed in cases of enhancing masses that led to thickening of these structures, as compared with other regions of the dura.

Pineal Gland.— The pineal gland had cystic changes in 46 patients (28%) and increased size (>10 mm) in 23 (14%), with a maximum size of 24 mm. Biopsy in one patient showed a xanthomatous granuloma.

Hypothalamic-Pituitary Involvement.— The thickness of the infundibulum was assessable in 393 studies in 137 patients. The infundibulum was normal (<3.00 mm in thickness) (15) on 188 MR studies in 87 pa-
Patients. Thickening of the infundibulum (>3.00 mm) was seen on 140 images in 68 patients (Fig 3A). In 17 cases, the diameter of the stalk could not be delineated because it was confluent with a hypothalamic mass. Histopathologic studies of biopsy samples from tumorous hypothalamic-pituitary lesions in six patients revealed active LCH. On 59 images (32 cases), the width of the infundibulum was different in its cranial and caudal portions (Fig 3B). Threadlike thinning of the stalk (<1 mm) was noted in 65 MR images (40 cases). Lack of infundibular contrast enhancement was seen on 36 images (24 cases), 12 of which depicted a threadlike infundibulum. Nineteen images revealed a normal-sized, nonenhancing infundibulum. In three cases (five images) the lack of contrast enhancement was seen with a thickened infundibulum; in two of these, the infundibulum was threadlike on the follow-up study. In six patients, histopathologic studies of tumorous hypothalamic-pituitary lesions revealed active LCH.

Intracranial/Intra-Axial Changes

Supratentorial White Matter.— Two major patterns of supratentorial white matter lesions were distinguished. The most frequent signal-intensity changes were prominent, dilated VRS, which was noted in 61% of patients with LCH (Fig 4A). In eight patients, images showed symmetrical lesions with prolonged T1 and T2 relaxation times following a vascular pattern, with strong contrast enhancement and mass effect (Fig 4B). Eight other patients had supratentorial white matter lesions with a leukoencephalopathy-like but no vascular pattern; that is, poorly defined patchy areas of low signal intensity on T1WI and high signal intensity on T2WI or proton density-weighted images without contrast enhancement (Fig 4C).

Infratentorial White Matter.— Infratentorial white matter lesions involved the pons in 44 patients (27%) (Fig 4D). These were associated with dentate nucleus changes in all but one. Pontine lesions consisted of T2WI hyperintensities, with either a microvascular pattern or patchiness. Enhancement was observed in eight cases (Fig 4E).

Deep Gray Matter.— Analysis of structures in the deep gray matter revealed a clear infratentorial predilection and symmetry of lesions in 65 patients (40%). Lesions in the dentate nucleus showed high signal intensity on T1WI; this was best depicted on T1WI with magnetization transfer contrast (Fig 5). In 44 of 65 patients, the dentate nucleus also appeared hyperintense with FLAIR and T2WI sequences (Fig 5). In this state, the formerly sharp margins of the region with abnormal signal intensity was blurred and faded into the surrounding white matter (Fig 5). As seen on follow-up images in a few patients, these changes occurred a few months to 6 years after the initial examination. The end stage of such changes consisted of sharply delineated CSF-intense holes, which included the dentate nucleus and the surrounding white matter (Fig 6) Space-occupying effect was not observed in pontine or dentate-nucleus lesions. In 35 patients, cerebellar changes occurred with or after pathologic signal-intensity changes in the basal ganglia on both sides. In 42 patients, the pallidum appeared hyperintense on T1WI and hypointense, isointense, or hyperintense on T2WIs (Fig 5); in three patients, the caudate nucleus was also involved. In four patients, the major supratentorial finding was a signal-intensity loss in the pallidum and putamen on T2WI. In these patients, this T2 signal-intensity loss was also seen in some structures of the midbrain (Fig 7).

All patients with parenchymal changes had lesions in the extra-axial spaces.

Brain Atrophy.— Signs of brain atrophy were seen in 13 patients. Five patients had localized atrophy of the cerebellum, which was combined with midbrain atrophy in four (Fig 7). One patient had localized midbrain atrophy.

Clinical Symptoms and Therapy

Patients with dilated VRS as the only parenchymal finding had no neurologic symptoms (Table 4). In 54 of 72 patients with parenchymal lesions (other than dilated VRS) at MR imaging, neurologic symptoms were reported. These ranged from subtle tremor and abnormal reflexes without disability in 13 patients to pronounced ataxia with severe impairment in 39. Eighteen patients with clear parenchymal changes in the cerebellum and/or basal ganglia were reported to be clinically asymptomatic. All 16 patients with leukoencephalopathy-like lesions or a pronounced vascular pattern had severe neurologic disabilities. All
of these patients had additional neurodegenerative lesions in the cerebellum or basal ganglia.

Of the 72 patients with parenchymal changes, 62 had been treated with chemotherapy, and 15 received additional irradiation before CNS LCH was diagnosed. In contrast, 10 patients with lesions of the same MR appearance received neither cytostatic nor irradiation before the CNS lesions were diagnosed.

Six of the patients with parenchymal disease died from progressive neurologic deterioration. Three other patients with CNS LCH died: one from a hypothalamic syndrome, one from progressive LCH, and the third from a myelodysplastic syndrome.

**Correlation with Histologic Findings**

Biopsy results from the parenchymal lesions were available in 12 patients. In two patients, active LCH infiltrates with CD1a+ cells were proved by biopsy of space-occupying and contrast-enhancing lesions in the pons or cerebellum. In one patient (with a history of biopsy-proved extracranial LCH), a mass lesion (which was isointense to hypointense on T1WI) involving the pons and cerebellum was shown to be an astrocytoma, grade III. Biopsy of cerebellar T2 prolongation in six patients revealed normal cerebellar tissue (in one patient) or loss of Purkinje cells with gliosis (in five patients). In two patients, superficial biopsy of supratentorial lesions yielded only fragments of normal gray and white matter.

**Results of the Control Study**

Paranasal Sinuses and Mastoid Opacification.—MR images in 65 LCH patients (46 treated, 19 untreated) and 55 control subjects (27 treated, 28 un-
FIG 5. Axial images in a 9-year-old asymptomatic boy with a 7-year history of LCH. Top row, T2WI show the hyperintense appearance of the dentate nucleus (white arrow) and its surrounding white matter (black arrow). Note the normal appearance of the lentiform nucleus. Bottom row, T1WI with magnetization transfer contrast show the hyperintense appearance of the dentate nucleus and the lentiform nucleus (white arrows).

FIG 6. Coronal T1WI in a 12-year-old boy with a 10-year history of LCH, severe neurologic symptoms, and intellectual impairment. Image shows CSF-intense holes in the regions of the dentate nuclei.

FIG 7. Axial T2WIs in the same patient as in Figure 4A.
A. Cerebellar atrophy with thinned cerebellar peduncles.
B. Midbrain atrophy with wide interpeduncular cistern and distant mammillary bodies, with hypointensity of the pars compacta of the substantia nigra (arrow)
treated) were compared with respect to opacification in the paranasal sinuses and mastoids (Table 2). Configuration and signal intensity of these opacifying changes corresponded to fluid levels, polyps, and/or soft tissue. Contrast enhancement was seen in the last two conditions, which occurred in 36 (55%) LCH patients (25 treated, 11 untreated) and 11 (25%) control subjects (four untreated, seven treated). The \( \chi^2 \) test showed a significant difference \( (P < .005) \). Comparison of the treated and untreated groups showed no significant difference.

**Visible VRS.**—T2WIs of 43 LCH patients (32 treated, 11 untreated) and 55 control subjects (27 treated, 28 untreated) were compared with respect to the visibility of the VRS. The VRS was visible in 30 (70%) of LCH patients (21 treated, nine untreated) and 15 (27%) control subjects (seven untreated, eight treated). The \( \chi^2 \) test showed a significant difference \( (P < .001) \). Comparison of the treated and untreated groups showed no significant difference.

**Discussion**

In this comprehensive study, we described the impressively wide scope of brain changes in LCH, as shown on instantaneous MR images obtained at various times in the course of disease. Because of the retrospective and multicentric nature of the study, we could not provide standardized chronologic information about the evolution of various lesions on follow-up images. Also, we could not address the true incidence of CNS LCH. Earlier investigators estimated that the frequency of diabetes insipidus, the hallmark of hypothalamic pituitary region (HPR) involvement, is 5–50% (16), whereas the estimated incidence of neurodegenerative LCH is 1–3% (1, 16).

Our recent observations in cases with only parenchymal abnormalities on MR images and no overt clinical signs or symptoms suggest that many cases are undiagnosed and that the actual incidence of CNS LCH might be higher than expected.

Cranial-facial involvement with osseous lesions in the bones of the orbits and the calvaria has long been recognized as a classic presentation of LCH (17–19). The observation of opacification in the paranasal sinuses or mastoids in 55% of LCH patients as opposed to 25% of controls was significant and striking. Because no histopathologic material was obtained in the patients of our series, the nature of the opacifications remains unclear. In most cases, possible LCH manifestations and other inflammatory or neoplastic processes cannot be distinguished. Opacifications of the paranasal sinuses and mastoid air cells are a common and nonspecific finding in the pediatric population and are seen with allergies and common colds (20, 21). We found that these changes were significantly less common in control subjects than in patients, taking into account the seasonal variations at the time of study. The predilection for these cavities (mastoid, ethmoidal sinus), which serve as conduits for cranial nerves, may result because the cranial nerves propagate immune processes from the cervical lymph nodes to intracerebral regions, where they primarily approach structures not protected by a blood-brain barrier (BBB) (22).

According to our series, the intracranial manifestations of LCH show a striking preference for regions without a BBB. Apart from the pituitary, extra-axial structures in the cranium include the meninges, the ependyma, the choroid plexuses, and the pineal gland. The pineal gland, together with median eminence, area postrema, organum vasculosum of the
lamina terminalis, subcommissural organ, and subfor- 
nical organ, form the circumventricular organs. None 
of these structures possess a BBB. This lack of BBB 
allows agents that normally do not have access to 
intracerebral regions to reach cerebral structures and 
trigger brain functions, and it allows other substances 
that cannot otherwise leave the brain (eg hypotha-
lamic hormones) to reach their target organs (22). 
The hypothalamus itself is protected by the BBB; 
however, it forms a functional unit with the circum-
ventricular organs. In addition, the neuroendocrine 
cell populations in the hypothalamus have been 
shown to project outside the BBB (22, 23). Therefore, 
these parts of the hypothalamic nuclei, which are 
functionally involved in the pathophysiology of CNS 
LCH, might reasonably be considered structures 
without a BBB.

The hypothalamic-pituitary axis is, by far, the most 
frequently involved intracranial region in LCH, and 
the resulting diabetes insipidus is a clinical hallmark 
of LCH. The imaging findings in central diabetes 
insipidus have been well described in the last decade. 
The most frequent morphologic change is a thickening 
greater than 3 mm [15]) with enhancement of the 
pituitary stalk, accompanied by lack of the normal 
T1WI shortening in the posterior pituitary (24, 25). 
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pituitary stalk, accompanied by lack of the normal 
T1WI shortening in the posterior pituitary (24, 25). 
This so-called bright spot is related to the presence of 
vasopressin-containing granules (25–27). In addition, 
threadlike narrowing of the infundibulum with a max-
imum width less than 1 mm can be seen. The absence 
of hyperintensity in the posterior pituitary and the 
presence of an infundibular or hypothalamic mass are 
nonspecific findings. These can be seen in a variety 
of disorders, including intracranial tumors (mostly ger-
minomas), granulomatous diseases (sarcoidosis, We-
gener granulomatosis), leukemia, posttraumatic 
changes, autoimmune polyendocrinopathy, autoimmune 
infundibuloneurohypophyisits, brain malformations, 
familial disease, and idiopathic diabetes insipidus (15, 28–34).

Meningeal lesions usually have signal intensity cor-
responding to soft tissue (intermediate intensity on 
T1WI and T2WI with moderate or marked, uniform 
contrast-enhancement). Such lesions resemble lympho-
matous, leukemic, or carcinomatous infiltrates. 
Choroid-plexus lesions, which might otherwise mimic 
plexus papillomas, are characterized by a marked 
signal intensity loss on T2WI, suggesting calcification. 
The presence of calcium was proved in two cases in 
which CT scans showed marked hyperattenuation.

The subfornical organ is adherent to the ventral 
surface of the fornix and protrudes into the third 
ventricle at the level of the interventricular foramina, 
partially covered by the choroid plexus. Involvement 
of this area might be suspected with lesions involving 
the choroid plexus and/or the ependyma of these 
regions.

The pineal gland, like the HPR, meninges, and 
choroid-plexus organs, does not possess a BBB (22). 
Therefore, it enhances after the administration of 
contrast material. The diagnosis of a pineal-gland 
lesion is not always straightforward and mainly based 
on its size and configuration (35). The high frequency 
of pineal cysts and enlarged pineal glands in patients 
with LCH remains a nonspecific but striking observa-
tion; this may reflect direct pineal infiltration by LCH 
or hyperplasia of the gland. Biopsy of a pineal-gland 
tumor in one patient revealed LCH infiltration and 
indicated that an association between HPR and pi-
 neal gland involvement in LCH, as observed in ger-
 minoma (36). However, in the absence of a histologic 
proof in the other patients, whether the morphologic 
appearance (size, solid vs cystic) of the pineal gland is 
related to the disease is unclear.

Intra-axial brain parenchymal changes showed dif-
ferent patterns. The second most frequent presenta-
tion of CNS LCH, apart from extra-axial HPR dis-
 ease, was involvement of the cerebellum, basal 
ganglia, and pons. Clinically, this pattern of involve-
ment was associated with a neurodegenerative syn-
drome of highly variable severity and course. The 
symptoms ranged from subtle tremor to profound 
disabilities, including ataxia, dysarthria, and psy-
chomotor deterioration. Some patients with follow-
up studies initially presented with slight hyperin-
tensity of the dentate nucleus on T1WI; this 
appearance was followed by development hypointen-
sity or hyperintensity on T2WI, with subsequent 
extension of T2 hyperintensity to the perinuclear white 
matter over months or years. Some patients with significant 
neurologic impairment ultimately developed 
CSF-intensity holes in the cerebellum. In 13 
patients, T1WI hyperintensity limited to the dentate 
nucleus persisted for years without neurologic dete-
rioration. From the few cases that we were able to 
follow up, neurologic impairment seemed to become 
clinically apparent when the signal-intensity abnor-
mality extended into the cerebellar white matter.

These infratentorial changes were frequently asso-
ciated with T1WI hyperintensity of the basal ganglia. 
Others have also reported this pathologic MR ap-
pearance of the basal ganglia and cerebellum (9, 37). 
The pathologic signal intensity in the basal ganglia 
and dentate nucleus of the cerebellum resemble the 
pattern of multiple-system degeneration. However, 
the term multiple-system atrophy, as defined by Gil-
man et al (38), does not seem to be entirely adequate 
in the neurodegenerative form of LCH. Multiple-
ystem atrophy is a sporadic progressive neurodegen-
erative disorder with Parkinson-like, pyramidal, cer-
bellar, autonomic or bladder dysfunction, with 
involvement of the nigrostriatal system. Even if some 
these clinical criteria are fulfilled, overt autonomic 
dysfunction has not been reported in LCH CNS; in 
addition, the onset of complaints before the 3rd de-
cade of life has been defined as an exclusion criterion 
for multiple-system atrophy (38, 39). The neuro-
pathologic changes in multiple-system atrophy consist of 
cyttoplasmic glial inclusions with neuronal cell loss, 
reactive astrogliosis, and microgliosis (40, 41). The 
only available biopsy specimens in CNS LCH, derived 
from mainly the cerebellum have shown loss of Pur-
kine cells with gliosis. Cyttoplasmic inclusions have 
not been reported so far.
The white matter changes that we observed consisted of two patterns: a vascular pattern and a leukoencephalopathy pattern. In the vascular pattern, enlarged VRSs were identified in the deep white matter of the hemispheres on T2WIs. They ranged from barely visible (corresponding to a width of about 2 mm) to markedly enlarged and contrast enhancing, following the distribution of the perivascular spaces. Because enlarged VRSs are not necessarily pathologic and because they are seen with many other conditions (42–47), T2WIs were evaluated in an age-matched control group of children without LCH or vascular or seizure disorders. Interestingly, accentuated VRSs on T2WIs were considerably more common in LCH patients than in control subjects.

This vascular pattern was found incidentally in neurologically asymptomatic patients, in severely impaired patients, and in patients with and those without other CNS findings. Perivascular spaces that surround the penetrating arteries have been recognized as the lymphatic clefts of the CNS (48). Thus, they are involved in CNS immune responses to viral infection and autoimmune diseases (49, 50). Widening of these spaces leads to the imaging pattern of pronounced VRSs. In patients with LCH, pronounced VRSs may indicate an underlying cerebral immune process. They may also be secondary to cerebral atrophy, but severe atrophy was seen in only a few patients and always localized to infratentorial regions. The enhancement observed in eight patients might be attributed to breakdown of the BBB, which was possibly caused by LCH infiltration or a collapse of the immune defense mechanisms in the VRSs.

The leukoencephalopathy pattern was seen in severely disabled patients only. Imaging showed diffuse or patchy, usually symmetrical, involvement of the white matter without a clear vascular distribution. In most cases, supratentorial lesions were confluent and predominantly periventricular, with blurred margins. Breakdown of the BBB was present in a few severely disabled patients. In two patients, T2WIs showed a leukoencephalopathy-like pattern, while enhancing vascular structures were seen on T1WIs. Thus, the two described imaging patterns may possibly correspond to different manifestations of the same process. Regarding the leukoencephalopathy-like pattern, the differential diagnoses includes acute disseminated encephalomyelitis, acute multiphasic disseminated encephalitis, and disseminated encephalitis (51). Other differential diagnoses include diverse metabolic or degenerative disorders (52) and leukoencephalopathy secondary to chemotherapy and/or radiation therapy (53–55). Interestingly, 10 patients in our series had not received therapy before such white matter changes were diagnosed; therefore, these lesions seem to have been related to LCH rather than treatment. Associated changes in the infratentorial white matter may have been due to Wallerian degeneration primarily, as they were predominantly associated with degenerative lesions of the dentate nucleus.

Changes similar to those seen in the dentate nucleus are known to occur in a variety of neurodegenerative diseases. The dentate nucleus seems to be a cardinal target in corticobasal degeneration (56), hereditary dentatorubral-pallidoluysian atrophy, Machado-Joseph disease (57), and progressive supranuclear palsy (58). In children, T2 prolongation in the dentate nucleus may also indicate infantile neuronal dystrophy or Krabbe disease, whereas T2 shortening in the pallida suggests Hallervorden-Spatz syndrome (59, 60). Additionally, degeneration of the dentate nucleus may be an inconstant part of different hereditary ataxias; when present, it is associated with poor prognosis (61). Degenerative changes of the cerebellum are also known to develop in paraneoplastic syndromes (62, 63). However, antineuronal antibodies, which were identified in other paraneoplastic syndromes (64), have not been detected in LCH so far (6). Furthermore, cerebellar degeneration and atrophy are typical features of metabolic diseases such as mitochondrial abnormalities in the cerebellum in conjunction with loss of Purkinje cells and spongiform degeneration of the cerebellar white matter, as seen in Kearns-Sayre syndrome (65) and myoclonus epilepsy with ragged red fibers (66). MR changes of the basal ganglia and the dentate nucleus are also the morphologic hallmark in cerebrotendinous xanthomatosis (67).

We found that involvement of the brain stem (particularly the pons) with intraparenchymal LCH was associated with poor prognosis (68). About 88% of patients with brain stem involvement had severe neurologic impairment. All but two patients who died had brain stem lesions. All patients with a vascular or leukoencephalopathy-like pattern that extended to infratentorial regions experienced rapidly progressive neurologic deterioration.

Atrophy was not a common finding in our series. Global atrophy was diagnosed in only seven individuals (all with several follow-up studies). Although it was infrequent and may be regarded as of questionable clinical importance, it was in these patients with CNS LCH and therefore retained in the classification system. Localized atrophy that mirrors irreversible tissue loss most frequently involved the cerebellar hemispheres and was always associated with a symptomatic, progressive neurodegenerative syndrome.

Conclusions

The wide spectrum of intracranial findings in LCH patients can be classified into four major groups according to their anatomic topography and signal-intensity pattern. Group 1 includes osseous lesions in the craniofacial bones and/or skull base with or without soft-tissue extension. Group 2 is an intracranial and extra-axial disease in the hypothalamic-pituitary region; meninges; and other circumventricular organs, including the pineal gland, choroid plexus, and ependyma. Group 3 is intra-axial parenchymal disease in the gray matter or white matter, with a striking symmetry of the lesions and a clear predominance of a neurodegenerative pattern in the cerebellum and basal ganglia. Group 4 is localized or diffuse atrophy.
These cranial and intracranial manifestations of LCH-associated CNS disease occur in typical patterns or combinations that may be suggestive of LCH, even in the absence of a history of LCH or extracranial signs or symptoms of LCH. Isolated diabetes insipidus with morphologic changes in the HPR should always prompt a careful diagnostic search for other intracranial and extracranial LCH-specific lesions. Also, a neurodegenerative syndrome with lesions in the cerebellum and basal ganglia or poorly marginated and symmetrical white matter changes in the absence of typical signs or symptoms of leukoencephalopathy should lead to the differential diagnosis of LCH followed by an adequate diagnostic evaluation.

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