Central Nervous System Manifestations of Langerhans Cell Histiocytosis in the Pediatric Population

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Authors: M. De La Hoz Polo¹, M. Rebollo Polo², J. Muchart López², C. Fons², O. Cruz Martinez²,¹ Barcelona/ES,²Barcelona/ES  
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Learning objectives

To illustrate and to describe the different radiological manifestations of Langerhans Cell Histiocytosis in the Central Nervous System using MRI

Background

Langerhans cell hystiocitosis (LCH) is a rare disease secondary to an abnormal deposit in different tissues of abnormal dendritic cells similar to Langerhans cells.

The clinical presentation can range from a solitary bone lesion to a multisystemic disease. Central nervous system (CNS) involvement, revealed by diabetes insipida, is well known since the original description of the disease.

Two different types of CNS lesions are recognized nowadays, first, **Tumor-like lesions**, secondary to Langerhans cells infiltrates, which most common manifestation would be the pituitary infiltration, but also can have a intraparenchymal supratentorial location, and cases have been described affecting the brainstem or cerebellum.

And secondly, **Neurodegenerative CNS lesions**, that have been described more recently, related to cognitive decline. This Neurodegenerative disease is the second most frequent presentation of CNS LCH, excluding the hypothalamic-pituitary disease, is a combination of pathologic changes in the cerebellum, basal ganglia, and/or pons with characteristic MRI patterns. It has a progressive course that varies in severity. It is not usually the initial or only manifestation of the disease, but usually appear several years after the initial diagnosis.

Neurodegenerative symptoms range from asymptomatic cases or mild to disabling situations , but also manifest with ataxia, gait disturbances, spastic diparesis, dysarthria and cognitive regression.

The cause may be related to inflammatory or autoimmune paraneoplastic syndrome, however, the precise pathophysiology is unknown

Findings and procedure details
We reviewed all the MRI of patients clinically diagnosed with Langerhans Cell Histiocytosis looking for the findings described in the current literature.

According to the "Histiocyte Society", the radiological manifestations of LCH in the CNS can be classified into:

1. Intracranial extra-axial lesions
   a. Hypothalamic-pituitary axis
   b. Other locations
      • Meninges
      • Choroid plexus
      • Pineal gland

2. Intracranial intra-axial lesions
   a. Intraparenchymal lesions
   b. Neurodegenerative disease
   c. Other findings: Virchow-Robin spaces dilated

**Group 1: Intracranial extra-axial lesions:**

a. Hypothalamic-pituitary axis:
   • Diabetes insipidus is the hallmark of infiltration in the hypothalamic-pituitary region, and is seen in as many as 25% of all patients with LCH or in as many as 50% of patients with multisystem disease. There is typically a "loss of bright spot" (i.e., the lack of the physiologic hyperintense signal of the posterior pituitary on T1-WI) which correlates with the loss of antidiuretic hormone-containing granules (*FIGURE 1*). It can also manifest as infiltrating masses in these regions, that can reach big sizes, simulating other primary tumors in these regions as germinomas or craniopharyngiomas (*FIGURE 2*).

b. Other locations: Less commonly, single or multiple lesions can be observed in the meninges, choroid plexus and pineal gland.
   • Meninges: Meningeal involvement manifests as space-occupying lesions. In RM this masses are iso-hyperintense in T1 and hyperintense on T2WI, with variable contrast enhancement. Most frequently the meningeal
infiltration may be due to intracranial extension of bone lesions (*FIGURE 3 and 4*).

- **Choroid plexus**: The lesions of the choroid plexus, when large, can cause obstruction and hydrocephalus and can simulate plexus papillomas (*FIGURE 5*).
- **Pineal gland**: Cysts and enlargement of the gland in patients with HCL have been described (*FIGURE 6*). This may reflect infiltration by histiocytes or glandular hyperplasia, although no histological data are available.

**Group 2: Intracranial intra-axial lesions**

a. **Intraparenchymal lesions or tumor-like lesions**: They manifest as rounded masses with abnormal signals that are iso- hypointense to gray matter on the T1 and hyperintense on T2WI. These areas show intense contrast enhancement and have well-demarcated edges and often surrounding by edema and can produce mass effect (*FIGURE 7*). Its distribution may be random or follow a pattern of vascular distribution.

b. **Neurodegenerative disease**: The following patterns of involvement in MR have been described:

- **Dentate Nuclei** appears as well delineated curvilinear areas displaying a moderate T2 hypointense and T1 hyperintense signal. On coronal images involvement of the cerebellar white matter displayed an evocate "butterfly wings" appearance in which the T2 hypointense and T1 hyperintense signal of the dentate nuclei areas are better individualize (*FIGURE 8 and 9*).
- **Involve**ment of the white matter of the cerebellum appears as hyperintense areas on T2 and FLAIR, symmetrical, without contrast enhancement. Frequently associated with altered signal of dentate nuclei. In severe cases it can spread to the cerebellar peduncles, pons and bulb (*FIGURE 8*).
- **In the basal ganglia**, the abnormalities consist of bilateral, symmetrically increased signal on T1WI with and variable signal intensities on T2WI, usually involving the globus pallidum, and without contrast enhancement (*FIGURE 10*).
- **Leukoencephalophathy-like pattern** manifest as poorly defined hyperintense areas in the cerebral periventricular white matter, pons and cerebellar white matter, without mass effect or gadolinium enhancement (*FIGURE 11*). These areas are characterized by high signal intensity on T2WI and low signal on T1WI without a clear vascular distribution.
- **Cerebellar and supratentorial atrophy** is one of the most non-specific findings described in CNS-LCH. It has been described that the cerebellar atrophy appears to correlate with the severity of the cerebellar symptoms (*FIGURE 12*). When it affects the corpus callosum can be either diffuse or predominate in the posterior part of the corpus callosum (*FIGURE 13*).

c. **Other findings**:
• The Virchow-Robin spaces (VRS) dilated are best seen on T2WI and can be barely visible with a width of approximately 2mm. The role of VRS in the pathophysiology of CNS-LCH remains to be investigated, but they might be consistent with either an active inflammatory process or the sequelae of an inflammatory process.

Images for this section:

**Fig. 1:** 4 years old male patient with clinical onset of diabetes insipidus, and skin lesions diagnosed with HCL. Brain magnetic resonance imaging (MRI). (A) Sagittal T1 FLAIR sequences showing absence of normal hyperintense neurohypophysis (black arrow). (B, C) Coronal T1 FSE and Axial SPGR image after administration of paramagnetic contrast, shows a 5mm nodule with high contrast uptake in the upper part of the pituitary stalk (arrow in B and C).
Fig. 2: Female patient diagnosed with LCH and DI at 2 years old. At 11 years of age referred with intense headaches. She underwent brain MRI. (A, B) Coronal and sagittal T1 image after contrast administration, shows a mass occupying the entire sellar and suprasellar region (asterisk in A and B) extending to the hypothalamic region.

Fig. 3: 3 years old male who debuted with extensive craniofacial bone lesions that progressed despite medical therapy. (A) Coronal T1 fat-suppressed FSE and paramagnetic contrast, shows multiple bone lesions that destroy the roof and the left side of orbit (arrows) (B) Axial contrast SPGR shows a bone lesion in the left portion of the frontal bone with rupture of the internal table and epidural extension with meningeal involvement (arrow). (C) Coronal T2 FLAIR shows the incidentally discover, alteration of the signal of the cerebellar dentate nuclei and surrounding white matter (arrow).
Fig. 4: Extraaxial and leptomeningeal LCH granulomas. Coronal contrast-enhanced slice with space occupying dural manifestations on the left convexity and bilateral on the tentorium.
**Fig. 5:** Axial T2-WI image show bilateral hypointense(calcified) lesions in the choroid plexus (arrow) in a patient with LCH
Fig. 6: Sagittal contrast-enhanced T1-weighted MR image obtained after an intravenous injection of gadolinium depict small foci of pathologic enhancement in the cerebral peduncles (arrowhead), as well as cystic nodular enhancement and enlargement of the pineal gland (arrow).
Fig. 7: Axial contrast enhance image showing multiple sharply demarcated enhancing lesions in random distribution
**Fig. 8:** Coronal Flair T2WI (a) and T1WI (b) in a 17-year-old man presenting a severe cerebellar ataxia. The dentate nuclei areas appear as well-delineated curvilinear T2 hypointense and T1 hyperintense areas (arrowheads). The cerebellar white matter involvement displays a “butterfly wings” appearance (arrows).

**Fig. 9:** Axial images in 9-year-old asymptomatic boy with a 7-year history of LCH. Top row, show the hyperintense appearance of the dentate nuclei (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 nuclei and the lentiform nucleus (white arrows).
**Fig. 10:** Course of signal intensity alteration in the basal ganglia in a patient with LCH. 
A, Axial T1-weighted images show mild hyperintense signal intensity alterations limited to the pallidum. B, Three years later, prominent hyperintense signal intensity alterations involve the pallidum and the putamen.

**Fig. 11:** (A and B) Axial T2 FLAIR and (C) Axial T2 FSE. A symmetrical signal alteration of periventricular and occipital periatrial white matter (arrows) is seen, compatible with leukoencephalopathy-like pattern.
Fig. 12: Course of cerebellar atrophy in patient with LCH. Sagittal T1-weighted images show mild cerebellar atrophy at the time of the diagnosis of ND-LCH (A). Seven years later the atrophy is more pronounced (B).

Fig. 13: 4 years old male patient with LCH and diagnosis of DI. (A) Sagittal T1 FLAIR, made at the time of diagnosis showing a corpus callosum with a normal morphology and thickness for the patient's age. (B) Sagittal T1 FLAIR, 5 years after the diagnosis of HCL, shows thinning of the corpus callosum, more marked on its posterior part and splenium (arrows).
Conclusion

CNS involvement in LCH in children varies according to published series, and its frequency is probably underestimated.

The DI is the most common manifestation, followed by other much less common as neurodegenerative disease, space-occupying lesions in extra-axial location and intraparenchymal lesions.

Before a patient with DI in whom the MR shows infiltration of the hypothalamic-pituitary axis it is mandatory to look for other intra/extracranial findings to rule out LCH.

The presence of a neurodegenerative process in a pediatric patient who curse with involvement of the dentate nucleus and/or the basal ganglia and white matter involvement, should propose the differential diagnosis with HCL.

Correlation of the clinical and neuroimaging findings allows suggesting the diagnosis of CNS-LCH involvement.

Personal information

References


