# Central Nervous System Disease in Langerhans Cell Histiocytosis

Nicole Grois, MD, PhD, Bernhard Fahrner, MD, Robert J. Arceci, MD, PhD, Jan-Inge Henter, MD, PhD, Kenneth McClain, MD, PhD, Hans Lassmann, MD, PhD, Vasanta Nanduri, MD, MRCP, FRCPCH, Helmut Prosch, MD, and Daniela Prayer, MD, PhD for the Histiocyte Society CNS LCH Study Group*

Langerhans cell histiocytosis (LCH) is a rare disease of the monocyte-macrophage system. The clinical presentation ranges from a single bone lesion to widespread multiorgan involvement. The course is unpredictable, with a spectrum of spontaneous regression, chronic recurrences for years, or a rapidly fatal deterioration.[1,2] Because of the frequent involvement of the cranial bones and the hypothalamic-pituitary region (HPR) with diabetes insipidus (DI) as key manifestation, LCH has long been recognized to be closely related to the central nervous system (CNS).[3] In the past decade, a wide variety of other CNS findings have been described with magnetic resonance imaging (MRI) scans, with or without associated clinical neuroendocrine findings.[4-6]

The rarity of CNS LCH and the varied clinical presentation has impeded research in this field. The quality of the diagnostic examination and follow-up of patients who are scattered over the globe has been variable, leading to difficulties in comparing treatments and outcomes. Although the therapy of multisystem LCH has been subject to multicenter international clinical trials in the past 20 years, treatment experience in CNS disease is limited to anecdotal cases and small pilot studies. However, despite the problems associated with studying a rare disease with an unknown course and varied natural history, research in CNS LCH has made considerable progress in the past 2 decades because of the efforts of the LCH CNS study group of the Histiocyte Society (HS) and some single and multi-institutional collaborative efforts.

In this review, we provide a comprehensive description of the spectrum and course of MRI changes, the underlying neuropathology, the clinical pattern and course, and the risk factors for CNS LCH and the available therapeutic experience. This information stems from: (1) the database of the LCH Study Reference Center of the HS that comprises data on 308 patients with LCH with (intra)cranial lesions studied with MRI, including 153 patients with LCH-associated neurodegeneration registered in the HS LCH CNS study[7] and (2) a review of the relevant literature.

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| ARA-C | Cytosine arabinoside |
| CSF | Cerebrospinal fluid |
| CNS | Central nervous system |
| DI | Diabetes insipidus |
| FDG | Fluorodeoxyglucose |
| HPR | Hypothalamic pituitary region |
| HS | Histiocyte Society |
| IGIV | Imunoglobulin intravenously |
| LCH | Langerhans cell histiocytosis |
| MRI | Magnetic resonance imaging |
| PET | Positron emission tomography |
| T1WI | T1-weighted images |
| T2WI | T2-weighted images |
| VRS | Virchow-Robin spaces |

## Imaging Features

### Magnetic Resonance Imaging Findings and Differential Diagnoses

In the past 15 years, the knowledge and understanding of the brain MRI findings in patients with LCH has grown. In the LCH CNS Study Reference Center, a review of 935 MRI investigations in 308 patients with LCH was undertaken (D.P.) and resulted in the classification presented in the Table.

### Intracranial Tumorous Lesions (Figure 1)

The radiographic findings associated with DI have been described in detail in the past 2 decades. In the HPR, the characteristic features consist of enlargement of the pituitary stalk with potential progression to space-occupying tumors extending to the pituitary and hypothalamus. In DI, there is typically a "loss of bright spot" (ie, the lack of the physiologic hyperintense signal of the posterior pituitary on T1-weighted images [T1WI]), which correlates with the loss of antidiuretic hormone-containing granules.[8]

The LCH-associated pineal gland abnormalities comprise solid masses or cystic lesions. Grois et al found pineal gland lesions including cystic changes and enlargement in 63% of patients with LCH studied with MRI and an interesting association between pineal gland enlargement and enlargement of the pituitary stalk.[3] The co-existing changes in these 2 regions might be caused by their functional interactions, because both structures belong to the circumventricular organs that are located outside the blood brain barrier and changes also are observed in other diseases.[9]

From the St. Anna Children's Cancer Research Institute, Vienna, Austria (N.G., B.F.); Sydney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MA (R.A.); Texas Children's Cancer Center and Hematology Service, Houston, TX (K.M.); Center for Brain Research, Medical University of Vienna, Vienna, Austria (H.L.); Watford General Hospital, Watford Hertfordshire, United Kingdom (V.N.); Otto Wagner Spital, Department of Radiology, Vienna, Austria (H.P.); Department of Neuroradiology; Medical University of Vienna, Vienna, Austria (D.P.); and Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden (J-I.H.)

*List of members of the Histiocyte Society CNS LCH Study Group is available at www.jpeds.com (Appendix).

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**Table. Classification of magnetic resonance imaging changes on the basis of the findings in 308 patients with Langerhans cell histiocytosis patients and intracranial lesions studied with 935 magnetic resonance imaging investigations**

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| **Tumorous/Granulomatous lesions** |
| Granulomatous lesions of skull bones |
| Hypothalamic pituitary region |
| Posterior pituitary |
| Anterior pituitary |
| Pituitary stalk |
| Hypothalamus |
| Pineal gland |
| Choroid plexus |
| Meninges |
| Enhancing parenchmal lesions |
| **Non-tumorous/Non-granulomatous intracerebral lesions** |
| Dentate nucleus* |
| Cerebellar white matter* |
| Basal ganglia* |
| Brainstem, pons* |
| Supratentorial white matter |
| Virchow Robin spaces |
| **Atrophy** |
| Cerebellar atrophy |
| Midbrain atrophy |
| Supratentorial atrophy |

*Radiologic neurodegeneration

Other space occupying tumorous lesions occur rarely in the meninges, choroid plexus, and in the brain parenchyma. They can occur as single or multiple lesions with a signal intensity corresponding to soft tissue. Choroid plexus lesions are characterized by marked signal loss on T2-weighted images (T2WI) suggesting calcification.[10,11]

Parenchymal granulomatous lesions can show a random or vascular distribution pattern. The differential diagnosis includes craniopharyngioma, germ-cell tumor, sarcoidosis, other histiocytic diseases such as Erdheim Chester or Rosai Dorfman disease, and other rare entities.[11]

### Intracranial Non-Tumorous Lesions (Figure 2)

The second most frequent presentation of CNS LCH, excluding HPR disease, is a combination of pathologic changes in the cerebellum, basal ganglia, and/or pons with characteristic MRI patterns. Findings include symmetric, hyperintense signal changes on T2WI and hypo- or hyper-intense signals on T1WI in the cerebellar grey matter alone, extending to the surrounding white matter, or presenting as cerebellar atrophy, sometimes combined with T2-weighted hyperintense changes of the pons. In the basal ganglia, the abnormalities consist of hyperintense signals on T1WI and variable signal intensities on T2WI, usually involving the globus pallidum. Less frequently, the brain stem and forebrain are involved.[10-13] Prosch et al termed this pattern "radiological neurodegeneration."[14]

Apart from the extension of these so-called "neurodegenerative" lesions, there are 2 other types of parenchymal white matter changes: (1) the frequently found dilated Virchow-Robin spaces (VRS) and (2) the rare leukoencephalopathy-like pattern.

Dilated VRS are best seen on T2WI and can be barely visible with a width of approximately 2 mm. The role of VRS in the pathophysiology of CNS-LCH remains to be investigated. No biopsy samples to confirm histopathology were available from such lesions, but they might be consistent with either an active inflammatory process or the sequelae of an inflammatory process. Caution should be observed when evaluating VRS on MRI scans performed on modern 3 Tesla machines, because VRS are visible on high-field MRI in almost all patients.

The leukoencephalopathy-like pattern involves the cerebellar white matter, the pons, and the periventricular white matter and presents with symmetric patchy areas characterized by high signal intensity on T2WI and low signal intensity on T1WI without a clear vascular distribution.[11] The differential diagnosis of this pattern includes acute disseminated encephalomyelitis, acute multiphasic disseminated encephalitis, disseminated encephalitis, and diverse metabolic or degenerative disorders including leukencephalopathy caused by chemotherapy or radiation.[11] Atrophy is not a common finding and may be localized to the cerebellar hemispheres. However, atrophy can also be global, usually in patients with a progressive symptomatic course (Figure 3).[11,13]

## Experimental Imaging Studies

Positron emission tomography (PET) studies with the tracer fluorodeoxyglucose (FDG-PET) were reported in a few cases as showing an increased tracer uptake in tumorous lesions and lesions enhancing on MRI[15] and a decreased uptake in the cerebellum corresponding to lesions of a neurodegenerative pattern.[16,17-19] Single photon emission computed tomography with [$^{123}$I] 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane and [$^{123}$I]iodobenzamide, a method assessing the function of the nigrostriatal system, did not reveal any abnormality in a case with only neurodegeneration.

Proton magnetic resonance spectroscopy measures the concentration of neuronal metabolites. A decreased peak of N-acetyl-aspartate infratentorially was found in the same patient, reflecting neuronal damage and loss in the cerebellum in keeping with the neuropathologic findings.[16] The value of all these methods needs further exploration.

## Neuropathology

In 1979, Kepes provided a detailed treatise on the pathology of CNS lesions in LCH, on the basis of conventional examination of autopsy material and described lesions extending to the CNS from neighboring bones, meningeal involvement, and diffuse or circumscribed intraparenchymal lesions.[20] More than 2 decades later, the LCH CNS co-operative group reviewed brain samples of 12 patients with CNS LCH, applying modern immunocytochemical techniques, and correlated the findings to MRI changes and clinical findings.[21] There are 3 types of lesional patterns in CNS LCH. In the first, circumscribed granulomas within the brain's connective tissue spaces demonstrate a composition similar to LCH