

## Central Nervous System Disease in LCH

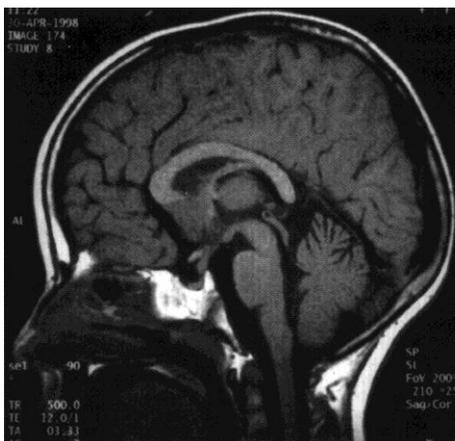
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Overview of Langerhans cell histiocytosis in the central nervous system

The very early descriptions of Langerhans cell histiocytosis (LCH) provide evidence that the central nervous system (CNS) is commonly involved in this disease. In 1893, Hand reported a case of "polyuria and tuberculosis." In retrospect, this patient presented with diabetes insipidus (DI), skull lesions, and exophthalmos, typical for LCH. Diabetes insipidus is the hallmark of involvement of the hypothalamic-pituitary region and is the most common and best recognized feature of CNS disease in LCH.

During the last few years, magnetic resonance imaging (MRI) has become readily available. More LCH patients with lesions in the skull or with DI are investigated with this modern imaging technique. Unexpectedly, an increasing number of patients are diagnosed with lesions in other parts of the brain, apart from the hypothalamic-pituitary region, some even before any clinical symptoms develop.

### What is CNS LCH?

Three major clinical groups of CNS LCH can be distinguished, but the occurrence of more than one type of lesion in the same patient is common. The classification of the lesions according to their MRI appearance is given in Table 1.



Hypothalamic pituitary involvement (type IV) is seen in about 10 percent of LCH patients. The incidence ranges from 5 to 50 percent in the different reports, according to the various stratification systems or treatment approaches. Polyuria and polydipsia as symptoms of posterior pituitary dysfunction are the most frequent finding in about 90 percent of patients with morphological changes in this region. However, other endocrine deficiencies like growth failure, precocious or delayed puberty, amenorrhea, hypothyroidism, or hypocortisolism resulting from anterior pituitary failure, are seen in about 50 percent of the DI patients. In rare cases of hypothalamic tumors, disturbances of appetite and social behavior with binge or rage attacks and dysregulation of sleep or temperature may be seen.

MRI findings comprise a thickening of the pituitary stalk (type IV a), a loss of the normal hyperintense signal of the posterior pituitary on T1-weighted images (bright spot), partial or completely empty sella (type IV b), or mass lesions (type IV c) [Figures 1 and 2].

Extraparenchymal space-occupying lesions (type III) derive from the meninges [Figure 3] or choroid plexus and mostly occur in patients with concomitant lesions in the hypothalamic-pituitary axis but may also be associated with neurodegenerative lesions. Symptoms depend on the site and size of the lesions and include headaches, seizures, vomiting, papilledema, optic nerve compression, or other focal symptoms but also are influenced by the presence of additional CNS lesions.

Pineal gland changes (type III d), i.e., increased size for age or cystic changes [Figure 1] are found in almost 60 percent of patients in whom the pineal gland region can be adequately assessed. The relevance of this finding is not known yet; however, it is remarkable that in a control study in 39 patients

without LCH who underwent MRI for various indications, only 5 percent of pineal gland changes were detected.

MRI lesions (type I, II, and VI) in patients with a neurodegenerative syndrome are mainly located in the cerebellum, pons [Figure 4 and 5], basal ganglia [Figure 6], or in the cerebral gray and white matter [Figure 7]. This type of disease is observed in about 1 percent of the overall LCH population but might develop in 10 percent of the LCH patients with DI. The symptoms range from subtle tremor or coordination problems to severe ataxia, dysarthria, and dysphagia, sometimes combined with intellectual impairment or behavioral changes. Eventually progressive neurological degeneration renders the patients wheelchair bound and severely disabled and may lead to a fatal deterioration in the worst cases.

Neuropsychological sequelae are frequently seen in LCH patients with CNS changes on MRI. Global cognitive deficits, as well as more specific changes in memory, concentration/attention, and perceptual-organizational changes have been observed.

### What are the histopathological findings?

Biopsies of cerebellar lesions (type I and II) showed perivascular rarefaction or histiocytes and gliosis, including Bergman gliosis, loss of Purkinje cells but not histiocytes of LCH phenotype. The extraparenchymal lesions (type III) revealed fibroxanthomatous changes also without Langerhans cell phenotype, but some findings were similar to the histology of juvenile xanthogranuloma.

These lesions appear like "burnt-out" lesions that lost the classical histology of LCH. In biopsies from hypothalamic-pituitary lesions (type IV a, c) and in meningeal masses, typical LCH lesion microscopies were found. Kepes et. al. provided a comprehensive overview of the histopathology of CNS LCH in 1979.

Table 1. CLASSIFICATION OF CNS LESIONS IN LCH ACCORDING TO THEIR MRI MORPHOLOGY (MODIFIED AND UPDATED FROM GROIS, ET. AL. "CENTRAL NERVOUS SYSTEM DISEASE IN LANGERHANS CELL HISTIOCYTOSIS." HEMATOLOGY/ONCOLOGY CLINICS OF NORTH AMERICA, vol. 12, no. 287, 1998.)

TYPE	N	%
<b>I a</b> White matter lesions - enhancement	34	40
<b>I b</b> White matter lesions + enhancement	15	18
<b>II a</b> Gray matter lesions - enhancement	36	42
<b>II b</b> Gray matter lesions + enhancement	4	5
<b>III a</b> Extraparenchymal dural based	22	26
<b>III b</b> Extraparenchymal arachnoidal based	2	2
<b>III c</b> Extraparenchymal plexus choroidal based	630/52	7
<b>III d</b> Pineal gland changes	58	
<b>IV a</b> Abnormal stalk width	59	69
<b>IV b</b> (Partial) empty sella	17	20
<b>IV c</b> Hypothalamic mass lesions	17	27
<b>V a</b> Atrophy, diffuse	11	13
<b>V b</b> Atrophy, localized	8	12
<b>VI a</b> T1 and T2 high-signal intensity - enhancement (therapy related?)	20	24
<b>VI b</b> T1 and T2 high-signal intensity + enhancement (therapy related?)	1	1

## Who is at risk of developing CNS LCH?

In the LCH study reference center in Vienna, Austria, 1329 patients are registered. Based on this large population, we analyzed the risk factors for the development of DI, the hallmark of CNS disease. We found that patients with multisystem LCH with multiple skull lesions and lesions in the skull base, in particular with involvement of the eye and ear bones, have a risk of DI at almost 40 percent, as opposed to 4 percent in single-system patients without such "CNS-risk lesions."

Fourteen out of 1329 study patients (1 percent) were found to have neurodegenerative lesions on MRI; all 14 patients had lesions in the cerebellum. In 11 of these, DI preceded the detection of other CNS abnormalities. In all 14 patients, "CNS-risk" lesions were present, and 13 of them were found to have changes of the pineal gland. Three patients are still free of neurological symptoms for a couple of years after the diagnosis of MRI changes. However, 7 patients exhibit significant neurological symptoms.



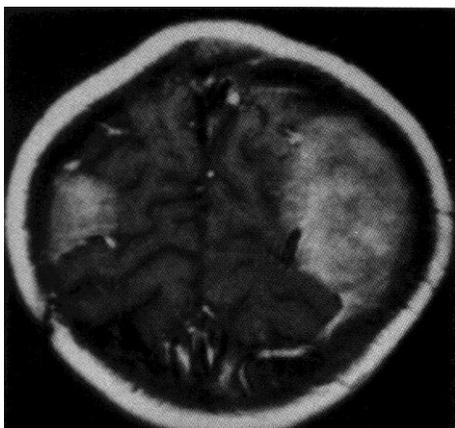
## What causes CNS LCH?

Analogous to the uncertainty regarding the etiology of LCH in general, the causes of CNS LCH remain completely enigmatic. Why in some patients does the disease remain restricted to the hypothalamic-pituitary, whereas others develop mass or neurodegenerative lesions? What factors influence the evolution of the different types of CNS disease? Speculations on a triggering event include an infectious process, a paraneoplastic phenomenon, an immunological imbalance, an autoimmune process, and/or an error of metabolism. What is the role of the pineal gland changes?

Understanding of the causes of the histopathological or MRI morphological changes seen in LCH CNS patients is essential for the development of therapeutic interventions.

## How can it be treated?

No general recommendations concerning treatment are possible at this point. The individual strategy is dependent on the type and site of the lesions and the state of LCH outside the CNS.



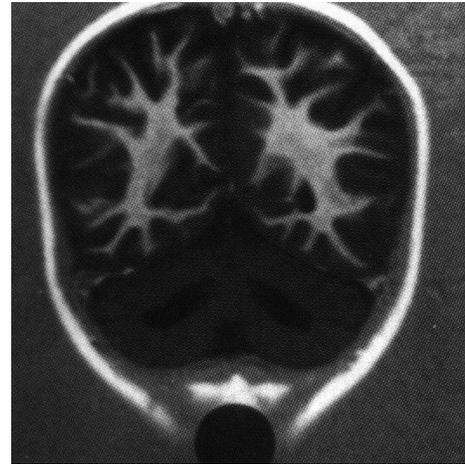
The appropriate management of patients with DI is dependent on the disease state of LCH outside the brain and on the cerebral MRI. In patients with known LCH and longstanding DI who do not show a thickened infundibulum on MRI, no specific therapy is needed, but regular evaluations as outlined in the protocol should be performed. In the case of new-onset DI with an infundibular thickening, active LCH must be assumed, and systemic therapy should be considered, even in the absence of LCH activity outside the brain.

Radiotherapy should be reserved for growing mass lesions that fail to respond to systemic therapy. Cases of isolated DI with an infundibular thickening on MRI without a history of

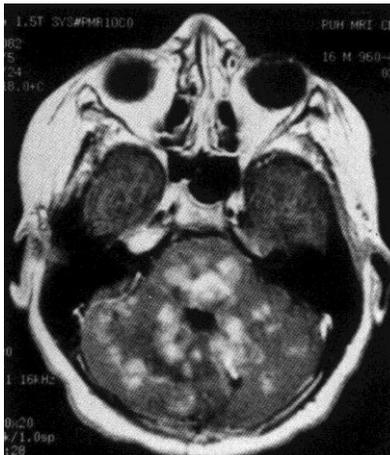
LCH and a negative diagnostic workup for LCH should have serum and CSF studies for aFP ( $\alpha$ -fetoprotein) and should be followed closely. A stereotactic biopsy is strongly recommended in case of an increase of the infundibular width to rule out malignant tumors (e.g., dysgerminoma).

Space-occupying tumors may need to be completely or partially resected if they exert a mass effect. Chemotherapy with agents of established efficacy in systemic LCH that are known to cross the blood brain barrier might be beneficial in cases of a diagnosis of active LCH in such masses. Local irradiation might be another option when a radical surgery is not possible.

Apart from these mass lesions, radiation therapy rarely seems indicated in CNS LCH. Irradiation of the hypothalamic-pituitary region does not seem to be the method of choice, considering the potential endocrine sequelae and the small chance of reversal of established DI. There was no case observed in which manifest DI reversed, independent from the applied therapy. However, the high risk of such patients to develop neurodegenerative CNS LCH stresses the need of systemic treatment.



Therapy for patients with neurodegenerative lesions remains a dilemma. The lack of understanding of the pathogenesis of neuronal injury and gliosis in neurodegenerative CNS LCH has impeded the employment of specific therapeutic modalities. So far, no single drug or regimen applied in patients with such lesions has shown a convincing positive effect. Steroids have shown transient improvements only in some patients. In others, various agents including etoposide (VP-16), 2CdA, interferon- $\alpha$  or intravenous immunoglobulins, cyclosporine, or retinoic acid were used for different periods without a clear effect.



However, it has to be emphasized that these experiences derive from single cases only. To date, no regimen has been tested in a standardized manner in a greater number of patients, nor have the pre- and post-treatment situations been assessed and documented accurately in a comparable way. In the retrospective LCH CNS study in three patients with significant lesions on MRI who are under observation between three months and six years, no overt neurological problems have been reported yet. The majority of patients with neurodegenerative disease experienced a progressive neurological deterioration and are significantly disabled. Four of these patients died.

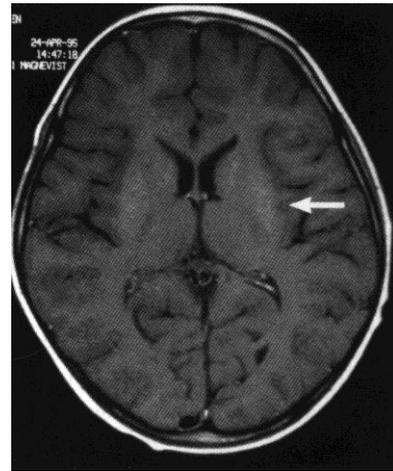
In the desperate case of this disease, new experimental treatment approaches seem to be warranted. This has to be done with an organized approach. In 1998, the Histiocyte Society initiated a prospective international study for LCH CNS disease, which comprises a thorough diagnostic program and guidelines for the treatment of the various types of CNS LCH, including a treatment option for neurodegenerative disease.

### **Diagnostic program**

It is the main goal of the prospective LCH CNS study to introduce and implement a standardized diagnostic program for all patients with CNS disease, to be able to compare the different disease courses.

Also, biological material for research projects to study the pathophysiology of the underlying process will be collected.

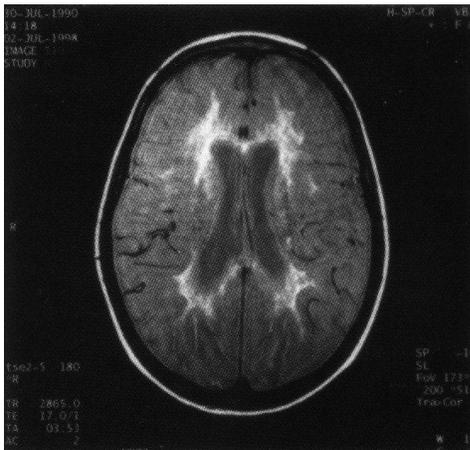
The diagnostic program should be performed at standardized intervals as specified for the individual patient groups in the protocol. The following studies are requested: Serial MRI should be performed according to the MRI instructions of the protocol. All MRIs should be reviewed centrally by the study neuroradiologist. All patients should undergo standardized, formal neuropsychometric and motor-efficiency tests and neurophysiological tests. Laboratory studies at diagnosis of CNS disease should include basic immunological and virological studies. Serum and EDTA (ethylenediaminetetraacetic acid) blood should be frozen and saved for future research purposes.



Endocrine evaluation should be done in all patients with DI, growth failure, or other evidence of hormonal dysfunction. Cerebrospinal fluid (CSF) should be obtained at diagnosis of CNS involvement and at specified intervals in patients with neurodegenerative disease. Additional CSF should be frozen for research studies. A 24-hour-urine collection should be performed for the determination of melatonin levels in all patients at diagnosis.

Brain biopsy may be necessary in mass lesions, often combined with a curative surgical approach. In neurodegenerative lesions, biopsies are rarely indicated in the context of a history of LCH outside the CNS. The tissue samples should be processed according to the biopsy instructions of the protocol and should be reviewed by the study reference pathologist.

### Cooperation is the Watchword



CNS LCH is a rare but potentially devastating manifestation of an orphan disease. Progress can only be made by international cooperation. If you take care of a patient with this disease, please have him/her registered, and please participate in this study.

The CNS LCH study protocol is available at the LCH study reference center: *(Editor's Note - The CNS LCH study protocol closed, effective 9/20/02. As of this date, no replacement protocol is available from the Histiocyte Society.)*

## LCH Study Reference Center

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Fax: +43-1-40170-430  
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### Suggested References

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3. Hand A. "Polyuria and Tuberculosis." *Arch Pediat*, vol. 10, 1893, pp. 673-675.
4. Kepes JJ. Histiocytosis X in *Handbook of Clinical Neurology*, eds. Vinken PJ, Bruyn GW., 1979, pp. 93-117.

Figure 1. Sagittal section, T1-weighted: inhomogenously thickened pituitary stalk (type IV a), small anterior pituitary lobe (IV b), missing bright spot, cystic pineal gland change (type III d), and atrophy of the upper vermis (V a)

Figure 2. Coronal section, T1-weighted, contrast enhanced: thickened enhancing pituitary stalk (type IV a) with impingement of the optic chiasm (arrow).

Figure 3. Axial section, T1-weighted, contrast enhanced: bilateral dural-based enhancing mass lesions (type III a)

Figure 4. Coronal section, inversion-recovery sequence: CSF-intense dark holes in the region of the cerebellar dentate nuclei and the adjacent white matter (type I. and II b)

Figure 5. Axial section, T1-weighted, contrast enhanced: multiple enhancing lesions in the cerebellum and pons (type I and I b)

Figure 6. Axial section, T1-weighted: bilateral symmetric areas of high-signal intensity in the basal ganglia (type VI a)

Figure 7. Axial section, FLAIR sequence: Hyperintense symmetric periventricular lesions involving the deep white matter (type I a)