Clinical features and difficulty in diagnosis of Langerhans cell histiocytosis in the hypothalamic-pituitary region

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Abstract. Langerhans cell histiocytosis (LCH) is a multi-organ disorder that rarely involves the hypothalamic-pituitary region (HPR). HPR-LCH presents with severe progressive pituitary dysfunction and its prognosis is poor. The definitive diagnosis of LCH is considerably difficult and complicated owing to the occurrence of several diseases with similar manifestations in the HPR and its location in the deepest portion of the anterior skull base, in close proximity to important normal structures, severely limiting the size of the biopsy specimen. Chemotherapy is the established treatment modality for LCH; hence, timely and accurate diagnosis of LCH is essential for early therapeutic intervention. We retrospectively reviewed clinical features and biopsy procedures in four patients with HPR-LCH (all female, 28–44 years old) from 2009 to 2020. Maximum diameter of supra-sellar lesions was 23–35 mm and 2 cases had skip lesions. All patients demonstrated central diabetes insipidus, hyper-prolactinemia, and severe anterior pituitary dysfunction. Two of the patients had progressive disease. Furthermore, four patients presented body weight gain, two visual disturbance, and two impaired consciousness. The duration from onset to diagnosis of LCH was 3 to 10 (average 7.25) years. In total, eight operations were performed until final diagnosis. The percentage of correct diagnosis by biopsy was 50% (4/8). Clinical features of HPR-LCH are very similar to those of other HPR diseases, and their symptoms are progressive and irreversible. Clinicians should consider repeated biopsy with a more aggressive approach if the lesion is refractory to steroid therapy, in order to ensure accurate diagnosis and appropriate treatment.

Key words: Langerhans cell histiocytosis, Hypothalamic-pituitary region, Clinical features, Biopsy, Accurate pathological diagnosis

LANGERHANS CELL HISTIOCYTOSIS (LCH) is a multi-system disorder and a rare disease characterized by the proliferation of abnormal Langerhans cells [1, 2]. LCH of the hypothalamus-pituitary region (HPR) is an extremely rare occurrence [3]. The magnetic resonance imaging (MRI) findings of HPR-LCH include absence of the hyper-intense signal in the posterior pituitary region [4], presence of high gadolinium enhancement, thickening of the pituitary stalk, and suprasellar mass lesion [5, 6]. These MRI findings are not specific to HPR-LCH. The manifestations of other inflammatory diseases of the HPR or neoplasms such as lymphocytic panhypophysitis, lymphocytic infundibulo-neurohypophysitis (LINH), sarcoidosis, germ cell tumors, Rathke’s cleft cyst, ectopic pituitary adenoma, craniopharyngioma, and meningioma are similar to those of HPR-LCH. The presence of Birbeck granules on electron microscopy images or positive immunohistochemical staining for the protein markers S100 and CD1a are instrumental in confirming the diagnosis of LCH [7]. However, the pathological features of LCH can also overlap with those of other inflammatory diseases. Moreover, performing biopsy of the HPR is difficult due to its deep location, proximity to important structures, and restrictions regarding the biopsy specimen size [8]. Proper protocols are therefore required to determine the appropriate biopsy approach and timing for the correct diagnosing LCH and establishing appropriate treatment strategies. Herein, we present the retrospective analysis of four patients with HPR-LCH (Table 1), discuss their clinical features, difficulties...
encountered in their diagnoses, and highlight the importance of early therapeutic intervention.

Materials and Methods

Twenty-one patients presented with central diabetes insipidus (CDI) and hypopituitarism and demonstrated absence of the hyper-intense signal in the posterior pituitary region, presence of high gadolinium enhancement, thickening of the pituitary stalk, and suprasellar mass lesion on MRI. They were biopsied and their pathological diagnoses were determined at Tokyo Women’s Medical University from 2009 to 2020. Of those 21 patients, 14 were pathologically diagnosed with lymphocytic hypophysitis, two with lymphocytic hypophysitis with Rathke’s cleft cyst, one with sarcoidosis, and four with LCH. All patients with LCH were females and their ages upon first presentation to our institute were 28 to 44 (average 38) years. All endocrinological evaluations were conducted using a water deprivation test and four hormone load tests: corticotropin-releasing hormone, thyrotropin-releasing hormone, luteinizing hormone releasing hormone, and growth hormone releasing peptide 2.

Informed consent was obtained from all the patients or their families. This study was approved by the Human Investigation Committee of the Tokyo Women’s Medical University and performed in accordance with the Declaration of Helsinki.

Results

Case description

Patient 1: A 36-year-old woman was referred to the department of neurosurgery for the biopsy of a suprasellar mass lesion. She presented with galactorrhea and amenorrhea due to hyperprolactinemia at the age of 27 years old, and was treated with oral dopamine agonists. She also conceived her second child at this stage. During pregnancy, she presented with polyuria and MRI demonstrated a mass lesion in the HPR. After delivery, she experienced general fatigue, drowsiness, an increase in body weight equaling 20 kg, and mild fever. The mass lesion showed homogeneous gadolinium enhancement, the high-intensity signal of the normal posterior pituitary gland was absent on T1-weighted imaging, and fluid-attenuated inversion recovery (FLAIR) MRI revealed perifocal edema in the bilateral hypothalamus, cerebral

| Patient No. | Age at onset to surgery | Approach | Diagnosis |
|-------------|-------------------------|----------|-----------|
| 1           | 2 years                 | TSS      | LCH       |
| 2           | 3 years                 | Trans-lateral ventricle | LCH |
| 3           | 7 years                 | Extended TSS | LCH |
| 4           | 10 years                | Trans-sphenoidal surgery | LCH |

* Upon first presentation to our institute.

TPS, thickened of pituitary stalk; CDI, central diabetes insipidus; Ad, adrenal axis; Th, thyroid axis; Gn, gonadal axis; GH, growth hormone; hP, hyperprolactinemia; BWG, body weight gain; LCH, Langerhans cell histiocytosis; TSS, trans-sphenoidal surgery.

+: cingulate gyrus, +++: left temporal lobe, pons, and right anterior horn of the lateral ventricle.
peduncles, and optic tract (Fig. 1a–c). Endocrine function testing revealed CDI, central hypoadrenalism, hypothyroidism, hypogonadism, severe growth hormone deficiency, and hyperprolactinemia. Her cerebrospinal fluid (CSF) tested negative for placental alkaline phosphatase (PLAP), which eliminated the possibility of a germ cell tumor. She presented with impaired short-term memory and lethargy just before the biopsy procedure. She underwent biopsy with the right frontotemporal craniotomy approach, since the mass was located posterior to the optic chiasm and the distance between the optic nerve and normal pituitary gland was too narrow to permit transsphenoidal surgery (TSS) (Fig. 1b). The pathological diagnosis of LCH was derived from CD1a and S100 positivity on immunostaining (Fig. 1d–g), since no other lesions were observed on bone scintigraphy. Consequently, she underwent chemotherapy treatment with vinblastine, prednisolone, and methotrexate regimen.

Patient 2: A suprasellar mass and skip lesion were detected in the cingulate gyrus on the MRI scan of a 44-year-old woman (Fig. 2a). She developed polyuria at the age of 42 years, followed by severe headache and impaired consciousness after 2 years. Endocrine function testing revealed CDI, central hypoadrenalism, hypothyroidism, hypogonadism, severe growth hormone deficiency, and hyperprolactinemia. Tumor markers of germ cell tumors (alpha-fetoprotein, human chorionic gonadotropin-beta, and PLAP) were absent in blood and CSF. She underwent biopsy with the TSS approach. A pathological diagnosis of pituicytoma was made based on the positive expression of GFAP, nestin and Olig2, and the absence of Rosenthal fibers and oncocytic changes (Fig. 2e–g). She underwent temozolomide therapy for 3 months; however, the tumor gradually increased in size (Fig. 2b). FLAIR MRI revealed perifocal edema in the bilateral hypothalami. Her consciousness deteriorated over the next 10 months. Thus, a second surgery was performed using the anterior interhemispheric approach in order to resect the suprasellar lesion (Fig. 2c). The pathological diagnosis of the second surgical lesion was LCH (Fig. 2h–j). Pulse steroid therapy was initiated (methyl prednisolone 1,000 mg per day for 3 days) after the diagnosis, which led to a reduction in the size of the residual tumors (Fig. 2d). She was treated with chemotherapy containing vinblastine, methotrexate, and prednisolone for adult-onset LCH after three courses of steroid therapy.

Patient 3: A 44-year-old woman presented with...
polydipsia and polyuria for 1 year. Gadolinium-enhanced MRI demonstrated a thickened pituitary stalk and skip lesion in the left temporal lobe (Fig. 3a). Endocrinological examinations revealed the presence of CDI, central hypothyroidism, hypogonadism, severe growth hormone deficiency, and hyperprolactinemia. The hypothalamic lesion was diagnosed as lymphocytic hypophysitis after TSS biopsy (Fig. 3e–g). Steroid pulse therapy and oral prednisolone were administered. Although the size of the hypothalamic and left temporal lesions were decreased at first (Fig. 3b), they subsequently underwent gradual enlargement (Fig. 3c). Moreover, her endocrine function worsened even further and she developed CDI, central hypoadrenalism, hypothyroidism, hypogonadism, severe growth hormone deficiency, and hyperprolactinemia. Moreover, multiple gadolinium-enhanced lesions appeared in the left temporal lobe, pons, and right anterior horn of the lateral ventricle after 7 years (Fig. 3d). A second biopsy was performed for the right lateral ventricle lesion via the anterior interhemispheric approach at another hospital, which yielded a pathological diagnosis of xanthogranuloma. Whole-body scanning was suggestive of a gallbladder lesion and cholecystectomy was performed. Finally, she was diagnosed as LCH based on the histopathological analysis of the cholecystectomy specimen and underwent vinblastine and prednisolone therapy.

Patient 4: A 28-year-old woman presented with polydipsia, polyuria, andamenorrhea. Endocrine

Fig. 2 Patient 2
Coronal and sagittal T1-weighted magnetic resonance images with gadolinium contrast enhancement show (a) heterogeneously enhanced lesions in the suprasellar region and cingulate gyrus at the initial diagnosis; (b) gadolinium enhanced lesions that were gradually enlarged (maximum diameter: 35 mm) 10 months after the first surgery; (c) after tumor removal via the anterior interhemispheric approach; and (d) shrinkage of the lesions after steroid pulse therapy. Photomicrographs of specimens obtained via trans-sphenoidal surgery (e–g) show no differentiation into astrocytes, no Rosenthal fibers, and no oncocytic changes in the plasma. S100 and glial fibrillary acidic protein (GFAP) positivity suggests in the diagnosis of pituicytoma. Photomicrographs of specimens obtained via the anterior interhemispheric approach (h–j) demonstrate immunohistological staining positivity for Langerin and CD1a, following a definitive diagnosis of Langerhans cell histiocytosis. Scalebar e–g: 50 μm, h–j: 20 μm. HE: hematoxylin-eosin.
examinations revealed the presence of CDI, central hypogonadism, and hyperprolactinemia. MRI revealed a gadolinium-enhanced suprasellar mass lesion and stalk thickening (Fig. 4a). PLAP was not detected in her CSF. The patient refused to undergo biopsy, and the suprasellar lesion grew larger after 7 years of hormonal replacement therapy (Fig. 4b). Endocrinological examinations revealed CDI, central hypogonadism, severe growth hormone deficiency, and hyperprolactinemia at that time. She underwent TSS biopsy and the lesion was diagnosed as lymphocytic hypophysitis (Fig. 4f, g). The mass shrank after steroid pulse therapy (Fig. 4c). However, this lesion recurred gradually after 3 years (Fig. 4d) and she developed bitemporal hemianopia despite being treated with an increased steroid dose. Her endocrine function worsened even further, and she developed CDI, central hypoadrenalinism, hypothyroidism, hypogonadism, severe growth hormone deficiency, and hyperprolactinemia (Table 1, Fig. 5) and she was required to have another hormone replacement therapy, hydrocortisone and Levothyroxine Sodium Hydrate. Hence, she underwent TSS again to facilitate the diagnosis of this lesion and reduction of the mass, in an attempt to improve her visual field disturbance. The sellar floor was opened widely to enable greater resection of the mass. The mass shrank (Fig. 4e) and her visual field disturbance improved after the extended TSS. The pathological findings of the second biopsy demonstrated invasion of CD1a-positive histiocytes into the normal gland, which resulted in the diagnosis of LCH (Fig. 4h–k). Fluorodeoxyglucose (FDG)-positron emission tomography demonstrated high FDG uptake in the superior mediastinum;
thus, chemotherapy (vinblastine, prednisolone, and methotrexate) was performed for multi-organ adult-onset LCH.

As shown in Table 1, all patients demonstrated CDI, hyper-prolactinemia, and severe anterior pituitary dysfunction, and two of them were progressive during the course of the disease. In addition, four patients presented body weight gain, two visual disturbance, and two impaired consciousness. The duration from onset to diagnosis of LCH was 3 to 10 (average 7.25) years. Two patients had enhanced lesions other than in the hypothalamic-pituitary region. A total of eight operations including four TSS, three open surgery, and one cholecystectomy were performed until final diagnosis. The percentage of correct diagnosis by biopsy was 50% (4/8).

**Discussion**

LCH is a relatively rare disease characterized by abnormal clonal proliferation and accumulation of antigen-presenting dendritic cells in multiple tissues and organs with a wide range of clinical manifestations and histological presentations. The dendritic cells found in the LCH lesions are precursor cells that originate from the bone marrow, travel to lesion sites, and differentiate into langerin-positive cells [1, 2].

LCH often involves multiple organs, especially extracranial sites. LCH can be classified into three types: a single system disease with good prognosis, a multi-system disease without the risk of organ involvement, and a multi-system disease accompanied by the risk of

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**Fig. 4** Patient 4

Coronal and sagittal T1-weighted magnetic resonance images with gadolinium contrast enhancement show (a) a thickened pituitary stalk at the first presentation; (b) gradual enlargement of the lesion over the next 7 years; (c) shrinkage of the lesion after biopsy via the trans-sphenoidal approach and steroid pulse therapy; (d) re-emergence of the lesion (maximum diameter: 23 mm) 2 years later; and (e) shrinkage of the lesion after extended trans-sphenoidal surgery. Photomicrographs of the surgical specimen obtained at the first biopsy reveal mainly T-cell and histiocyte invasion (f) with negative CD1a staining results (g). These pathological findings indicate that this lesion is lymphocytic hypophysitis. Photomicrographs of the surgical specimen at the second biopsy reveal similar findings for HE staining (h and i), but the partial expression of CD1a (j) and Langerin (k) led to the diagnosis of Langerhans cell histiocytosis. Scalebar f-h, and j: 50 μm, i and k: 20 μm. HE: hematoxylin-eosin.
organ dysfunction with the worst prognosis [3].

LCH of the hypothalamus-pituitary region (HPR) is an extremely rare occurrence [3]. The French national LCH registry had enrolled 1,236 LCH patients under 18 years old in 2010. Only four of the 1,236 LCH patients (0.32%) still had isolated HPR lesions after 5.1 to 10 years [9], In Howarth’s retrospective study, only two of the 314 (0.6%) patients with LCH had isolated HPR lesions during a 50-year period [10]. Patients often develop CDI and severe hypopituitarism as the initial manifestations of HPR-LCH [11]. Moreover, the MRI findings of a thickened pituitary stalk [5, 6] and absence of hyper-intensity of the posterior pituitary gland, are very similar to those of lymphocytic hypophysitis, germ cell tumors, and sarcoidosis. Thus, it is extremely difficult to distinguish LCH from these HPR diseases and diagnose it accurately using only the clinical features and MRI findings; hence, a tissue-based diagnosis is essential. Furthermore, only one of our four patients was diagnosed with LCH after the first biopsy, in which the condition was identified 9 years after onset. The other three patients required seven biopsies to establish a definitive diagnosis of LCH. Thus, making a relevant, accurate, and prompt diagnosis is the most important step in treating HPR-LCH.

Various clinical factors also contribute to the difficulty in diagnosing HPR. One such factor is the inhomogeneity in the degree of inflammatory change. Steroids can suppress inflammatory activity, even at doses that are sufficient to compensate for adrenal hypofunction. If a small specimen is obtained from a lesion that is treated with a steroid for suppressing inflammation, it can result in misdiagnosis. The pathological diagnosis of LCH is based on the evidence of transformation and proliferation of Langerhans cells, namely a pale eosinophilic cytoplasm, irregular and elongated nuclei with prominent nuclear grooves and folds, fine chromatin and indistinct nucleoli, and CD1a or Langerin positivity [12]. CD1a is a key immunohistochemical marker for the pathological diagnosis of LCH. However, the diagnosis should be based on S100 positivity if the results of CD1a and Langerin tests are unclear. Interestingly, the difference between the first and second pathological diagnoses in patient 4 was the absence and presence of CD1a positivity, respectively. This discrepancy in diagnosis may have arisen from the inflammatory activity level in the biopsied lesion. Although the second TSS biopsy was performed after steroid pulse treatment for hypophysitis, the specimen size was considerably greater than that obtained at the first biopsy, such that it reduced the mass, improved the bitemporal hemianopia, and enabled the observation of active inflammatory lesions. A BRAF V600E mutation was observed in approximately half of the patients with HPR-LCH, indicating that it has the potential to be used as a key LCH biomarker in the future [7].

Another clinical factor complicating diagnosis is the lesion depth. HPR lesions are in the deepest part of the
anterior skull base, which makes it challenging to access the lesion via a narrow corridor [7, 8]. Moreover, it is difficult to obtain a sizeable specimen because the HPR is surrounded by important structures, such as the hypothalamus, pituitary stalk, optic nerve, and superior hypophyseal artery. The greater the size of the resected biopsy specimen, the greater is the likelihood of complications owing to adjacent structure injury [7]. Thus, obtaining an adequately sized biopsy specimen is imperative for accurately diagnosing LCH, whilst avoiding complications arising from injury to the surrounding structures and choosing the appropriate approach (i.e. TSS or craniotomy).

Further complicating diagnosis is that several conditions apart from LCH are included in the differential diagnosis of mass lesions in the HPR, including germ cell tumors; sarcoidosis; ectopic pituitary adenoma; craniopharyngioma; meningioma; and inflammatory diseases, such as hypophysitis, which further includes autoimmune hypophysitis, lymphocytic panhypophysitis, and lymphocytic infundibulo-neurohypophysitis (LINH). Although germ cell tumors are common and resemble LCH, they can easily be diagnosed by assessing the tumor marker PLAP in the CSF [13]. CSF-PLAP was evaluated routinely in our patients with hypothalamic mass lesion and the results were negative in these four patients.

The symptoms and neuroimaging findings of HPR-LCH are often the same as those of LINH. Two of our four HPR-LCH cases demonstrated skip lesions, which may be one of the signatures of LCH. In general, however, distinguishing between the two conditions based on MRI findings alone is extremely difficult. As a consequence, pathological examination is essential for making the differential diagnosis. Rabphilin-3A is reportedly a highly reliable blood biomarker of LINH with a high sensitivity for detecting LINH [14]. This new biomarker may help in distinguishing between LIHN and LCH at the HPR. Diagnosing LCH is the most important step in its treatment for three reasons. First, LCH’s progression is relatively rapid, and LCH with multi-system involvement has a poor prognosis. The treatment protocol for LCH is nearly established and differs substantially from that of the other diseases. The Japan LCH Study Group proposed a regimen comprising vinblastine, methotrexate, and steroid [15]. Second, LCH is a progressive disease that can lead to irreversible changes in the adjacent normal structures and serious sequela due to inflammation and lesion growth. All four of our patients had severe endocrine dysfunction due to inflammation change, furthermore patients 2, 3 and 4 worsened progressively until final diagnosis. Their pituitary endocrine function might have been preserved if the LCH lesion had been detected earlier, followed by prompt intervention [16]. Four patients presented hyper-prolactinemia and body weight gain, two had consciousness deterioration, and two had visual disturbances. Those symptoms were attributed to the lesion infiltration and/or mass effect to stalk, hypothalamic-region, and optic nerve. We sometimes need to reduce the mass before symptoms become irreversible. Third, most patients with HPR-LCH eventually develop steroid resistance. Although the lesions shrank initially after steroid treatment, we should have been skeptical of the accuracy of the pathological diagnosis, since the lesion recurred or others were developed, despite increasing the steroid dose. Steroids are often effective against lymphocytic hypophysitis, including LINH. However, clinicians should doubt the accuracy of their initial pathological diagnosis and schedule another biopsy if the lesion responds poorly or becomes refractory to steroids.

In conclusion, clinical features of HPR-LCH are very similar to those of other HPR diseases, and their symptoms are progressive and irreversible. An accurate and prompt pathological diagnosis is essential for HPR-LCH, because the treatment for LCH differs from that for other inflammatory lesions or tumors occurring in this region. The biopsy procedure and correct diagnosis of HPR-LCH are quite difficult and challenging owing to the deep location, small biopsy specimen size, and low specimen inflammatory activity after steroid treatment. Clinicians, however, should not hesitate to perform biopsies repeatedly in a more aggressive manner including extended TSS or craniotomy to obtain a precise pathological diagnosis if the lesion increases in size, is refractory to steroids, or occurs at another location.

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Disclosure

The authors declare that there is no conflict of interest.
References

1. Berres ML, Allen CE, Merad M (2013) Pathological consequence of misguided dendritic cell differentiation in histiocytic diseases. *Adv Immunol* 120: 127–161.
2. Allen CE, Merad M, McClain KL (2018) Langerhans-cell histiocytosis. *New Engl J Med* 379: 856–868.
3. Fahrner B, Prosch H, Minkov M, Krischmann M, Gadner H, et al. (2012) Long-term outcome of hypothalamic pituitary tumors in Langerhans cell histiocytosis. *Pediatr Blood Cancer* 58: 606–610.
4. Fujisawa I, Asato R, Kawata M, Sano Y, Nakao K, et al. (1989) Hyperintense signal of the posterior pituitary on T1-weighted MR images: an experimental study. *J Comput Assist Tomogr* 13: 371–377.
5. Ghafoori S, Mohseni S, Larijani B, Mohajeri-Tehrani MR (2015) Pituitary stalk thickening in a case of langerhans cell histiocytosis. *Arch Iran Med* 18: 193–195.
6. Jian F, Bian L, Sun S, Yang J, Chen X, et al. (2014) Surgical biopsies in patients with central diabetes insipidus and thickened pituitary stalks. *Endocrine* 47: 325–335.
7. Huo Z, Lu T, Liang Z, Ping F, Shen J, et al. (2016) Clinicopathological features and BRAF(V600E) mutations in patients with isolated hypothalamic-pituitary Langerhans cell histiocytosis. *Diagn Pathol* 11: 100.
8. Jinguji S, Nishiyama K, Yoshimura J, Yoneoka Y, Harada A, et al. (2013) Endoscopic biopsies of lesions associated with a thickened pituitary stalk. *Acta Neurochir* 155: 119–124; discussion 124.
9. Kurtulmus N, Mert M, Tanakol R, Yarman S (2015) The pituitary gland in patients with Langerhans cell histiocytosis: a clinical and radiological evaluation. *Endocrine* 48: 949–956.
10. Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, et al. (1999) Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. *Cancer* 85: 2278–2290.
11. Brys ADH, Vermeersch S, Forsyth R, Velkeniers B, Bravenboer B (2018) Central diabetes insipidus: beware of Langerhans cell histiocytosis! *Neth J Med* 76: 445–449.
12. Harmon CM, Brown N (2015) Langerhans cell histiocytosis: a clinicopathologic review and molecular pathogenetic update. *Arch Pathol Lab Med* 139: 1211–1214.
13. Aihara Y, Watanabe S, Amano K, Komatsu K, Chiba K, et al. (2018) Placental alkaline phosphatase levels in cerebrospinal fluid can have a decisive role in the differential diagnosis of intracranial germ cell tumors. *J Neurosurg* 131: 687–694.
14. Iwama S, Sugimura Y, Kiyota A, Kato T, Enomoto A, et al. (2015) Rabphilin-3A as a targeted autoantigen in lymphocytic infundibulo-neurohypophysitis. *J Clin Endocrinol Metab* 100: E946–E954.
15. Imashuku S, Kudo N, Kaneda S, Kuroda H, Shiwa T, et al. (2011) Treatment of patients with hypothalamic-pituitary lesions as adult-onset Langerhans cell histiocytosis. *Int J Hematol* 94: 556–560.
16. Wnorowski M, Prosch H, Prayer D, Janssen G, Gadner H, et al. (2008) Pattern and course of neurodegeneration in Langerhans cell histiocytosis. *J Pediatr* 153: 127–132.