Paediatric Langerhans Cell Histiocytosis Disease: Long-Term Sequelae in the Hypothalamic Endocrine System

Elisa Vaiani^a Guido Felizzia^b Fabiana Lubieniecki^c Jorge Braier^b
Alicia Belgorosky^{a, d}

^aEndocrine Department, Hospital de Pediatría J.P. Garrahan, Buenos Aires, Argentina; ^bHemato-Oncology Department, Hospital de Pediatría J.P. Garrahan, Buenos Aires, Argentina; ^cPathology Department, Hospital de Pediatría J.P. Garrahan, Buenos Aires, Argentina; ^dEndocrine Department, Research Council of Argentina, Unidad de Investigación Garrahan – CONICET, Hospital de Pediatría Garrahan, Buenos Aires, Argentina

Keywords

Langerhans cell histiocytosis · Central diabetes insipidus · Pediatric endocrine dysfunction · Growth hormone deficiency

Abstract

Langerhans cell histiocytosis (LCH) is a disorder of the mononuclear phagocyte system that can affect almost any organ and system. The most common central nervous system (CNS) manifestation in LCH is the infiltration of the hypothalamic-pituitary region leading to destruction and neurodegeneration of CNS tissue. The latter causes the most frequent endocrinological manifestation, that is, central diabetes insipidus (CDI), and less often anterior pituitary hormone deficiency (APD). The reported incidence of CDI is estimated between 11.5 and 24% and is considered a risk factor for neurodegenerative disease and APD. Three risk factors for development of CDI are recognized in the majority of the studies: (1) multisystem disease, (2) the occurrence of reactivations or active disease for a prolonged period, and (3) the presence of craniofacial bone lesions. Since CDI may occur as the first manifestation of LCH, differential diagnosis of malignant diseases like germ cell tumours must be made. APD is almost al-

ways associated with CDI and can appear several years after the diagnosis of CDI. Growth hormone is the most commonly affected anterior pituitary hormone. Despite significant advances in the knowledge of LCH in recent years, little progress has been made in preventing long-term sequelae such as those affecting the hypothalamic-pituitary system.

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Introduction

Langerhans cell histiocytosis (LCH) is a disorder with elusive aetiology, of the mononuclear phagocyte system. Accumulation and clonal proliferation of immature dendritic cell (DC) immune-expressing antigens CD1a and CD207 and an inflammatory infiltrate characterize granulomatous lesions of LCH [1, 2]. Even though it was firstly considered an inflammatory disease, the discovery of clonality of the LCH cells [3], the permanent activation of the MAP kinase (K) pathway, especially secondary to BRAFV600E mutation [4], and the pathological DC precursor origin from lymphomyeloid progenitor cells [5] led to LCH being redefined as a probably “inflammatory myeloid neoplasia” [2, 6–8].

The annual incidence of LCH has been reported of 5–8 cases per million individuals <18 years per year, but the incidence rate decreases with age, from infancy to puberty [9–11]. It can affect almost any organ and system, with particular affinity for bone (80% of cases), skin (33%), and pituitary (25%). Other affected organs are the liver, spleen, haematopoietic system, and lungs (15% each), lymph nodes (5–10%), and the central nervous system (CNS) apart from the neurohypophysis (2–4%) [2, 12, 13].

The clinical presentation spans from a single organ, like bone or skin lesion, to a widespread multiorgan involvement. Additionally, clinical evolution is highly variable, and it can range from spontaneous regression, evolve with chronic recurrences over years, or present as a serious disease with rapidly fatal deterioration [2, 14, 15]. The disease is mainly unifocal and less frequently multifocal. Disseminated life-threatening forms predominate in infants.

Presently, LCH is classified as single-system (SS) disease (unifocal or multifocal) usually associated with a good prognosis or multisystem (MS) disease that has a poorer prognosis and/or chronic course. Additionally, MS disease is classified into 2 groups: MS with risk organs involvement such as the liver, spleen, and bone marrow (MS-RO+) and MS without risk organs involvement (MS-RO–). Of special interest to an endocrinologist, another group can be defined, that is, patients with SS or MS disease associated with risk of CNS involvement (central diabetes insipidus [CDI] and neurodegenerative disease [ND]) [16]. CNS risk factors will be detailed later on. The relationships between pathological DC and host tissues could determine the different phenotypes [17–19]. In addition, it has been speculated that the range of clinical phenotypes seen in LCH may be linked to the stage of precursor differentiation at which the pathological mutation in the MAPK pathway occurs [2]. This review aims to revise the relevant literature in hypothalamus-pituitary involvement in paediatric LCH patients, with special interest in endocrine findings, diagnosis, and treatment.

LCH: Hypothalamus-Pituitary Involvement

Clinical Phenotype, Histological Findings, and Neuroradiological Image Diagnosis

The most common CNS manifestation in LCH is the infiltration of the hypothalamic-pituitary region (HPR) by LCH granuloma, frequently leading to CDI and occasionally anterior pituitary hormone deficiency (APD) [19]. This usually occurs in the context of MS disease, and

importantly it has been associated with late-onset ND [20]. It has been reported that 76% of patients [15] with CDI developed radiologic ND changes when followed with brain MRI for years. In addition, at list, 25% of patients with radiologic ND will develop clinical neurodegeneration, such as progressive tremors, ataxia, dysarthria, dysmetria, learning disabilities, and behavioural abnormalities [15, 21].

Histopathological findings in LCH showed the identification of Langerhans histiocytosis cells and an inflammatory infiltrate, composed of macrophages, plasma cells, eosinophils, osteoclast-like multinucleated giant cells, and activated T cells [2, 13, 22]. Applying modern immunocytochemical techniques and in correlation with the MRI findings, 3 types of histological lesion patterns were determined in CNS LCH: (1) circumscribed granulomas in the brain's connective tissue space. (2) Diffuse granulomas occurring within the brain's connective tissue spaces, frequently associated with profound T-cell-dominated inflammation and severe neurodegeneration. (3) Neurodegenerative lesions characterized by lack of LCH cells and an inflammatory process, with CD8+ lymphocyte predominance, a nearly complete loss of neurons and axons, and gliosis [15, 19].

Interestingly, *BRAF* V600E-positive cells were identified in brain biopsy specimens from patients with LCH and neurodegeneration, supporting that manifestation of inflammation is driven by clonal, MAPK-activated myeloid cells in the CNS [23, 24]. CNS MRI with the administration of gadolinium is the method of choice to evaluate HPR [25]. In addition, CT, in selected circumstances, can provide complementary information when a detailed assessment of bone involvement is required [26].

In the presence of CDI, the disappearance of the hyperintense signal on MRI-T1-weighted images of the posterior pituitary is constant [27] but not specific to LCH [15, 28]. The latter can occur with or without thickened (>3 mm) pituitary stalk (PS) [15]. Thickening of the PS, also an unspecific sign, is the second most frequent finding and has the potential of progression to space-occupying tumours extending to the pituitary and hypothalamus and to the third ventricle floor [26]. Additionally, in patients with idiopathic CDI, thickening of PS has been significantly related to the development of further pituitary hormone deficits [26]. CNS germinoma, LCH, and lymphocytic infundibulo-neurohypophysitis are sometimes difficult to differentiate. Germ cell tumours can have an identical CNS MRI image with thickening of PS, as well as lesion extension to the third ventricle floor [28, 29]. In addition, in germ tumours, the absence of tumour cells in

the cerebral spinal fluid and/or tumour markers (beta human chorionic gonadotropin and alpha-fetoprotein) in the cerebral spinal fluid or blood makes differential diagnosis a great challenge. The PS size at CDI presentation is variable and can change over time. However, a normal PS thickness for years does not exclude the possibility of an occult germinoma or LCH [28–30]. A regression of the PS thickness is more consistent with a benign process such as LCH or infundibulo-neurohypophysitis and is an argument against PS biopsy even if the diagnosis remains unclear [29].

Empty sella and small or bulky pituitary gland for age are less common radiological abnormalities of HPR involvement in LCH [31–33]. In a study of a large single-institution paediatric LCH patients, there was a lack of correlation between measurements of pituitary gland height and endocrinopathy [33]. In contrast, in another study, patients who evolved with GH deficiency had a history of a smaller anterior pituitary gland [34].

Finally, dynamic MRI has been demonstrated to be informative regarding evolving pituitary hormone deficiency [35, 36]. In order to avoid a delay in the detection of active CNS LCH and neurodegeneration, regular neurological evaluation and whole-brain MRI scans are highly recommended during long-term follow-up of patients.

Hypothalamus Pituitary Deficiency

Central Diabetes Insipidus

CDI is the excretion of large volumes of hypotonic urine due to the defective production, transport, or secretion of the hormone arginine vasopressin (AVP) [26]. In LCH as it was previously stated, CDI is the result of destruction and neurodegeneration of axons and neurons in the hypothalamic supraoptic and paraventricular nuclei [30]. According to a recent review of the different aetiologies of CDI, LCH represents between 8 and 18% of all causes of CDI in patients <18 years [28]. Furthermore, CDI is the most frequent endocrinopathy associated with LCH [37]. It is considered an irreversible consequence of the disease, as complete resolution of CDI has been reported in rare isolated cases [38–40]. So far, neither conventional chemotherapy (vinblastine and prednisone) nor irradiation has been shown to be of significant benefit in the remission or prevention of CDI. In addition, radiotherapy may result in an anterior pituitary dysfunction, so it is not recommended any more. Rational therapeutic approaches are necessary in order to decrease the development of CDI. In the latest years, new therapies are currently under investigation [1, 2].

The incidence of CDI in the past was reported in up to 32–50% of the patients with LCH [40–42]. However, in the latest years, after the implementation of more aggressive and long treatments in MS disease, the reported incidence has significantly decreased, and it is estimated between 11.5 and 24% [9, 16, 38, 43–46]. Surprisingly, this is not the case in a recently study by Sagna et al. [47], since a higher incidence of CDI (74%) in a cohort of 23 LCH children was reported.

Three risk factors for development of CDI are recognized in the majority of the studies: (1) MS disease [16, 38, 45]. CDI frequency was reported as high as 40% when only MS disease was considered [38]. (2) The occurrence of reactivations or active disease for a prolonged period of time [16, 34, 45, 48, 49]. (3) The presence of craniofacial bone lesions: frontal bones, orbits, middle ears, and mastoids [34, 38, 48, 50]. However, this statement at the time of LCH diagnosis was not identified in the JLSG-96/02 study [43].

Persistent polyuria and polydipsia are CDI main symptoms and occur by the damage of >90% of vasopressin-producing neurons [26, 51]. Remarkably, in young children, severe hypernatremic dehydration, vomiting, constipation, fever, irritability, sleep disturbance, nocturia, failure to thrive, and growth retardation were reported [51]. A water deprivation test is necessary when water balance, osmolarity, and ionogram measurements are not conclusive. Generally, in the absence of symptoms, normally concentrated early morning urine is adequate to exclude CDI [10]. In addition, the presence of hyperglycaemia and hypercalcaemia must be ruled out [51].

Partial defects of posterior pituitary function have been also described. Dunger et al.'s [40] study showed abnormal response of urinary AVP to the water deprivation test in 5 of 21 (24%) patients with LCH in whom symptoms of DI were not manifest, indicating a partial defect. The explanation proposed was the increased sensitivity of renal vasopressin receptors. However, the measurement of plasma AVP was not useful in another study to identify partial deficiency of the posterior pituitary [35].

Another issue to consider is the possibility of a central adrenal insufficiency that could mask the manifestation of diabetes insipidus. Cortisol deficiency causes impaired renal free water clearance due to both vasopressin-dependent (stimulation of vasopressin secretion by CRH, the occurrence of renal sodium loss, and consequent volume depletion and decreased cardiac output) and vasopressin-independent (increase insertion of aquaporin channels in

Fig. 1. Kaplan-Meier analysis for the appearance of APD as a function of CA (**a**) at LCH diagnosis (log-rank test: a vs. b, $p < 0.02$), clinical forms (**b**): US, MS-RO- (LR), and MS-RO+ (MSR) (log-rank test: a vs. b, $p < 0.01$), and reactivation episodes (**c**) (log-rank test: a vs. b, $p < 0.01$) ([57], permission will be requested from HRP). APD, anterior pituitary hormone deficiency; CA, chronological age; LCH, Langerhans cell histiocytosis.

the renal collecting duct) mechanisms. Once glucocorticoid therapy is initiated, these mechanisms are downregulated resulting in polyuria and thus unmasking a DI [52–54]. Also, hypothyroidism can impair renal water excretion and masks a CDI [55].

More recently, the measurement of copeptin, the C-terminal segment of the AVP precursor peptide, during the water deprivation test or after arginine infusion has shown to be a promising tool in difficult diagnoses such as partial CDI [26]. However, the role of copeptin in the differential diagnosis of DI in children is still lacking. CDI could be diagnosed concomitantly or during follow-up especially within the first 5 years from LCH diagnosis [29, 33, 34, 38, 48, 56, 57].

Otherwise, CDI may occur as an isolated and inaugural manifestation of LCH. The reported incidence is variable, and according to the different cohorts report-

ed, the percentage ranged between 11 and 50% [28, 29, 43, 48, 56, 57]. The variability in incidence may be due to the fact that in some studies the definition of CDI as the first isolated symptom is not clearly addressed. When CDI occurs as an isolated event, a search for the aetiology is required. The differential diagnosis of the possible causes of CDI includes, in addition to LCH, germ cell tumours, craniopharyngioma or other tumoural lesions, autoimmune hypophysitis, inflammatory and vascular lesions, sarcoidosis, CNS malformations, genetic disorders, and last idiopathic CDI. As it was described in the Clinical Phenotype, Histological Findings, and Neuroradiological Image Diagnosis section, malignant oncological diseases which require prompt therapeutic intervention as germinoma must be differentiated from LCH, inflammatory, and “idiopathic” processes limited to the HPR [29].

Anterior Pituitary Deficiencies

APD are almost always associated with CDI and can appear several years after the diagnosis of CDI. Continuous monitoring is necessary to detect deficiencies that may evolve during the course of the disease. Established pituitary hormone deficiencies are mostly permanent [32].

Prompt diagnosis of APD is required to institute hormone replacement treatment. Highly variable percentage of developing APD was reported in LCH patients who had developed CDI with a range that goes from 14 to 81% with different follow-up times [9, 34, 38]. Median interval between CDI and first APD has been reported from 2.25 to 3.5 years [33, 44, 57, 58].

Occasionally, APD has been reported in patients without CDI [33, 58, 59]. A mass lesion in the HPR as well as radiation therapy (the latter is no longer used in LCH) are also known to be a risk factor for developing APD [58].

In a recent study [57], we could define 3 significant predicted variables of APD in a group of LCH paediatric patients with CDI. We found that APD was more frequent when (1) LCH was diagnosed at an older age (2), the clinical forms were US or MS-RO–, and (3) patients had less reactivation episodes. Figure 1 shows Kaplan-Meier analysis and the comparative log-rank test that revealed a significant difference for the appearance of APD for age at LCH diagnosis ($p < 0.02$; Fig. 1a), low-risk clinical forms (US and MS-RO–) ($p < 0.01$; Fig. 1b), and absence of reactivation episodes during the long-term follow-up ($p < 0.01$). We speculated that older age at the diagnosis of LCH could be explained by a delay in the diagnosis of this heterogeneous disease and, consequently, a deferral in treatment initiation. In this line, Marchand et al. [28] study reported a high percentage (81%) of APD in a group of 26 paediatric patients who presented CDI as the initial presentation of LCH during a median time of 1 year from onset of CDI.

The more frequent involvement of US or MS RO– versus MS-RO+ in the APD group may suggest a different pathogenic origin of DC (misguided myeloid differentiation) [6], defining different clinical presentations. Furthermore, Donadieu et al. [34] study stated that the more severe forms of LCH were not associated with pituitary involvement. Finally, contrary to what was previously published [15, 45], in our study, patients with a lower frequency of reactivations had a significantly higher risk of APD. The reason of this discrepancy is not well understood. A possible explanation of this finding could be related to an undiagnosed subclinical activity of LCH disease in this group of patients with CDI and APD.

Other factors such as early decline in growth rate with a loss of >1.5 SDS in height and a decrease in anterior pituitary height on MRI have been reported to be associated with GH deficiency [58]. Growth hormone is the most commonly affected hormone of the anteropituitary and has been recognized and reported since long [33, 58–60]. However, it is important to note that LCH patients may have growth retardation due to chronic disease, spinal involvement, and prolonged steroid therapy in addition to growth hormone deficiency. Haupt et al. [38] reported a cumulative risk of being diagnosed with growth retardation of 17.6% after 14 years from LCH diagnosis. In addition, Donadieu et al. [34] reported a cumulative 5- and 10-year risks of GH deficiency, in a group of paediatric LCH patients with CDI, of $36.7 \pm 4.5\%$ and $53.7 \pm 5.2\%$, respectively.

Other anterior pituitary hormones can be affected in a variable proportion and commonly in association. In accordance with LCH adult patients [32, 61, 62], Nanduri et al. [33] and Sagna et al. [47] reported GH and gonadotropin deficiencies (D) as the more frequent most common endocrine deficiencies seen after CDI. In the Argentinean paediatric cohort [57], GHD (45.4%) and thyroid hormone D (34%) were the most frequent APD associated with CDI, followed by gonadotropins D (27%) and corticotrophin-releasing hormone (ACTH) D (9%). In accordance with other reports [28, 34], ACTHD was the least frequent of APD. Panhypopituitarism has been found less frequently [12].

Thyroid hormone deficiency can also occur secondary to infiltration of the thyroid by Langerhans cells [32, 63, 64]. Moderately hyperprolactinaemia which can be attributed to PS infiltration has been occasionally reported [29, 47]. However, it has not been studied systematically in the different reports.

The occurrence of the involvement of the different pituitary lineages is actually not clear. It is important to take into account that evaluation of anterior pituitary deficiencies is sometimes a complex issue. It often depends on the criteria of each group of researchers to define the normality of hormonal measurements. In addition, very few studies have reported patients with complete evaluation, it means, the prevalence of some deficiencies is probably underestimated [47].

Hypothalamic abnormality with increased appetite resulting in hyperphagia and secondary obesity has also been reported [33, 56, 65]. Development of central precocious puberty or early puberty during LCH has been rarely reported. Nanduri et al. [33] reported 1 boy with LCH who had an early onset of puberty requiring treatment

Table 1. Clinical characteristics of pituitary compromise in LCH paediatric patients in recent years

Patients, <i>n</i>	Age at LCH D, yr	CDI, <i>n</i> (%)	CDI D, prior and after LCH D (<i>n</i>)	APD, <i>n</i> (%)	APD, time from LCH D, yr	APD			LH/FSH, <i>n</i>	ACTH, <i>n</i>	hyper- prolactin
						GH, <i>n</i>	TSH, <i>n</i>				
Nanduri et al. [33]	275	nd	Prior (occasionally) After within 5 years (49)	21 (7.6) (1*)	3.5 (0–11.8)	21	5**	7**	3*	nd	nd
Haupt et al. [38]	182	4.3±4.1	Prior/at D (14) After D (29)	17*** (9.3)	– (0–13)	nd	nd	nd	nd	nd	nd
Donadieu et al. [58]	589	2.8 (0.08–18.4)	nd	61 (10.3) (4*)	nd	61	23**	17**	10*	nd	nd
Amato et al. [56]	46	3.9 [†] (1.4–20)	Prior D (3) At/after D (7)	4**** (8.6)	(0–8) [‡]	4	0	1**	0	Normal	Normal
Grois et al. [15]	1,741	nd	At D (102) After D (110)	–	–	–	–	–	–	–	–
Maria Postini et al. [44]	121	4.13 (0.03–15)	At/after D (14)	8 (6.6)	2.24 (1.24–5.24)	7	2 (1p isolated)	nd	nd	nd	nd
Rigaud et al. [9]	1,478	3.2 (IQR: 1.2–7.9)	nd	129 **** (8.7)	–	–	–	–	–	–	–
Chow et al. [46]	70	3.2 (0.1–15.4)	At D (4) After D (9)	5**** (7)	5.91 (0.04–7.05)	4	1	2	3	nd	nd
Vaiani et al. [57]	435 [#]	2.32 (IQR 1.74–4.11)	Prior D (7) At D (27) After D (30)	23**** (5.28)	2.58****	20	15 (3 p isolated)	9*	4*	nd	nd
Sakamoto et al. [43]	317	3.1±3	Prior D (25) After D (25)	–	–	–	–	–	–	–	–

Data are expressed in mean (X ± SD)/median (range) and percentage (% of total LCH patients). nd, not described; IQR, interquartile range; LCH, Langerhans cell histiocytosis; *n*, number; yr, years; D, diagnosis; CDI, central diabetes insipidus; APD, anterior pituitary deficiency; GH, growth hormone; TSH, thyroid-stimulating hormone; LH/FSH, gonadotropins; ACTH, corticotropin; *p*, patient. * Number of patients without CDI. ** All in association with other APD. *** Number of patients with growth failure. **** All patients associated with CDI. [‡] Data of the 145 patients with pituitary disease. [†] Data of the 10 patients with pituitary involvement. [#] LCH patient population at the time of patient recruitment for the study.

with a gonadotropin-releasing hormone analogue for a period of 20 months. Another reported case was a 7.5-year-old girl with multisystem LCH, CDI, GH deficiency, and central hypothyroidism who developed central precocious puberty [66]. Finally, Table 1 describes the frequency of pituitary involvement in the latest paediatric series.

Treatment with rhGH

Braunstein et al. [67] first reported the good response to human growth hormone in 5 children with MS-RO-disease and growth hormone deficiency. In 1998, Howell et al. [68] reviewed 82 patients with growth hormone deficiency and LCH who were enrolled in the Kabi (Pharmacia & Upjohn) international growth database. In a 3-year period, patients with GH deficiency showed a response to rhGH similar to that seen in children with other causes of GH deficiency, including idiopathic deficiency. Nanduri et al. [33] analyzed growth in 21 GH-insufficient patients with MS disease. The treatment with rhGH improved growth significantly. However, 18 patients, who reached adult height, did not attain their target height, and this result is in accordance with other studies [34, 56]. Furthermore, also the control group (LCH without GH deficiency) did not reach their target height, suggesting that rhGH treatment alone may not be sufficient to normalize final stature in this group of patients. However, Donadieu et al. [58] reported normal median final height among non-GH-deficient LCH patients and considered that the lower final height of the rhGH-treated patients was due to the severe growth delay that most GH-deficient patients had prior to rhGH treatment. The earlier the treatment is started, the more likely the patient will attain full growth potential [33, 50].

Importantly, no increase in the recurrence rate of the underlying disease was observed [33, 67–69]. In the study of the French cohort [34], 19 new LCH events occurred among 12 out of 47 patients treated with rhGH. The first relapses in these 12 patients occurred after a median of 1.4 years on GH therapy (range 0.3–6.9 years). Interestingly, among patients with pituitary involvement, the relapse rate was not significantly influenced by GH deficiency or rhGH therapy, arguing against a deleterious effect of GH therapy on LCH disease activity. The study by Howell et al. [68] reported 1 case of benign intracranial hypertension and in addition, though it could not be directly attributed to rhGH treatment, in 1 patient that had pre-existing ataxia, this worsened during rhGH treatment. Nevertheless, in reference to this study, it must be taken into account the fact that the reliability of informa-

tion could be questioned since the data obtained from an international database depend on accurate diagnosis and reports by different researchers.

In the French cohort study [34], 8 out of 10 patients with neurodegenerative LCH received replacement therapy with rhGH, but only 3 patients received this treatment before the onset of neurological symptoms, arguing against a deleterious effect of GH therapy. In relation to this, in an experimental animal model, it has been proposed that neurodegenerative LCH could be a consequence of an active BRAF V600E mutation in microglia cells [24]. Even more, BRAF V600E mutation in humans has been considered one of the risk factors for ND [20]. On the other hand, it is well known that GH and insulin-like growth factor-1 (IGF-1) exert trophic effects on neuronal regeneration in the CNS through activation of the signalling pathway, MAPK/ERK pathways, among others. Positive effects of GH/IGF-1 administration on neuroregeneration have been shown in animal models. However, there are few clinical studies in human subjects on the possible beneficial effects or not of exogenous rhGH administration in ND [70].

Conclusion

LCH is a heterogeneous disease, and the paediatrician must suspect it for prompted diagnosis and treatment. It is well known that CDI is the most common endocrinological manifestation. In addition, it has been proposed that CDI, among other factors, such as craniofacial lesions, can be considered to carry a greater risk of developing neurodegenerative changes.

Despite the significant advances in the knowledge of LCH and the clinical improvements achieved in recent years, little progress has been made in preventing long-term sequelae such as those affecting the HP system. More specific treatments that can prevent neurohypophyseal compromise are necessary.

Treatment with rhGH in GH-deficient patients has been reported to be successful and safe. However, it would be important to carry out clinical research protocols to evaluate the effect of rh rhGH on the prognosis and clinical outcome of ND in this group of patients.

Finally, in case of isolated CDI, recommendations consist of a close follow-up of the patients, for possible underlying LCH localization among other diagnoses. The detection of easily accessible lesions for biopsy is important to avoid the risk of CNS biopsy. It must include a clinical, biochemical, and radiological evaluation. MRI

exams should be performed every 3 months for the first year and then extended at 6-month intervals at least for the first 2 years after the diagnosis of CDI. Importantly, as the clinical signs of LCH may become evident years after the diagnosis of CDI, patients should be informed about new symptoms and manifestations. APD should be addressed particularly in LCH paediatric patients associated with CDI, in order to start hormone replacement treatment as early as possible to improve long-term quality of life.

Conflict of Interest Statement

Alicia Belgorosky is an Associate Editor of the journal. The other authors have no conflicts of interest to declare.

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Author Contributions

E.V. has written the manuscript. G.F. and J.B. have contributed with the revision of the onco-haematological aspect. F.L. has contributed with the revision of the pathological aspect. A.B. has contributed intellectually and in the revision of the whole manuscript.

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