EXPERT OPINION

Medical management of langerhans cell histiocytosis from diagnosis to treatment

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Introduction: Langerhans cell histiocytosis (LCH) is a heterogeneous disease, involving the accumulation of langerhans cells in various organs. The physician's perception of the disease varies considerably depending on their experience, the presentation of the disease or the short-term treatment outcome. As this disease is very rare, only a limited number of large surveys exist in the literature and many aspects of the management of patients remain obscure or controversial.

Areas covered: An expert opinion on the diagnosis and medical management of LCH is presented in this paper. The diagnostic procedures, including differential diagnosis, initial clinical workup and criteria for initiating therapy are reviewed, as well as disease evaluation criteria and therapeutic approaches. Controversial issues in the medical management of LCH patients (aged less than 18 years) are also briefly discussed.

Expert opinion: Further fundamental and clinical research is still needed in this field. Progress may be expected from collaborations organized at national and international levels, among collaborative groups and expert networks. Collections of tissue and blood samples in biobanks must also be organized. New international protocols will be opened to patient accrual and represent an opportunity to further develop global research.

Keywords: clinical workup, diagnosis, follow-up, guidelines, Langerhans cell histiocytosis, therapy

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1. Introduction

Langerhans cell histiocytosis (LCH) is a heterogeneous disease, involving the accumulation of langerhans cells in various organs. It may affect any organ or system of the body, but those more frequently affected are bone (80% of cases), skin (33%) and the pituitary (25%). Other organs involved are the liver, spleen, the hematopoietic system and the lungs (15% each), lymph nodes (5 – 10%) and the central nervous system (CNS) excluding the pituitary (2 – 4%). The natural history of the disease is also extremely heterogeneous, ranging from a self-healing lesion to a disease involving several organs with life-threatening consequences, while some lesions may be responsible for permanent sequelae. The physician's perception of the disease varies considerably depending on their specialty and experience, the presentation of the disease or the short-term treatment outcome. But whatever the initial point of view of the treating physician, a global approach to the management of LCH is recommended. However, as this disease remains very rare, only a limited number of large surveys exist in the literature [1-5], and many aspects of the management of patients remain obscure or controversial. A multidisciplinary approach is warranted in all cases, to coordinate the care needed for this systemic disease and its associated morbidity. This short text proposes to summarize the major issues related to the medical management of the disease in order to provide a consistent body of data.

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Article highlights.

- Langerhans cell histiocytosis is a rare multisystemic disease.
- The diagnostic needs a concordance of clinical radiological histological findings.
- Initial workup is a two-step procedure.
- The first step of the workup procedure is a thorough clinical examination followed by few routine tests.
- The second step of initial workup is based on organ evaluation if suspected by the first-step screening.
- Therapy is adapted to the extension of the disease.
- First-line therapy, if necessary, is associated vinblastine and steroid.
- Scoring system helps physicians for therapeutic evaluation.
- B raf mutations have a high frequency in LCH.

This box summarizes key points contained in the article.

2. Diagnosis of langerhans cell histiocytosis

In addition to clinical and radiological features, the diagnosis of LCH is based on histological and immuno-phenotypic examination of a biopsy of lesional tissue. The biopsy should be taken from the most accessible organ: skin if involved. In the case of multiple skeletal involvements, the bony lesion that is most easily accessible and felt to be active and representative should be chosen for biopsy. The main diagnostic feature is the morphologic identification of the characteristic LCH cells, but positive staining of lesional cells with CD1a and/or Langerin (CD207) is required for a definitive diagnosis [6-9]. Electron microscopy is no longer recommended since it has been shown that the expression of Langerin fully correlates with the presence on electron microscopy of Birbeck granules, which was previously one of the criteria required for definitive diagnosis. There are very few exceptions; however, in organs such as the liver, Birbeck granules are not present and CD1a and/or Langerin may be negative [10].

In some rare situations, where the location of the only lesion means that the risk of biopsy may outweigh the need for a definitive diagnosis, the risk versus benefit of biopsy should be carefully considered. This is the case in patients with involvement of a vertebral body without adjacent soft tissue involvement, such as cases of isolated involvement of the odontoid peg, for example. However, if the decision to omit or postpone a biopsy is made, every effort should be made to consider other clinical conditions that might lead to a similar radiological finding and close follow-up is warranted.

3. Differential diagnoses

Diagnosis should always be based on concordant clinical–radiological–pathological evidence, and the physician needs to be aware of possible alternative diagnoses. Thus, typical bone lesions (such as a punch-out lytic lesion on the skull) can mimic a dermoid cyst, a vertebra plana can mimic an Ewing's sarcoma and typical cysts in the lung can be a leiomyosarcoma. Even infiltration of histiocytes on a skin biopsy with CD1a staining can result from scabies rather than LCH. The list of potential alternative diagnosis is long and largely depends on location and the specific organ involved (**Table 1**). When considering the diagnosis of LCH, the physician must be cautious and keep in mind the necessity to carefully evaluate clinical, radiological and pathological data in order to determine whether the disease presented by the patient is really consistent with LCH.

4. Evaluation of the extent of disease at diagnosis or during episodes of reactivation

Once a diagnosis of LCH has been ascertained, it is important to do a careful clinical workup for each individual patient in order to decide on the therapeutic approach.

The first step of this evaluation is a review of the complete medical history including special reference to the nature and duration of symptoms. Specific symptoms to be actively looked for are pain, swelling, skin rashes, otorrhea, irritability, fever, loss of appetite, diarrhea, weight loss or poor weight gain, growth failure, polydipsia, polyuria, changes in activity level, dyspnea, smoke exposure, and behavioral and neurological changes. Examination should be performed at each follow-up visit in order to assess response to therapy, investigate possible disease progression or reactivation, as well as to detect sequelae.

The second step of this evaluation is a routine paraclinical screening. In the absence of a specific biological marker of disease activity, the list of mandatory paraclinical tests is limited and includes a complete blood count, liver tests (including albumin, bilirubin, gamma glutamyl transpeptidase, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT)), erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, a chest X-ray and bone X-ray. Usually, a radiographic skeletal survey is performed at diagnosis, whereas in cases of disease reactivation, X-rays are focused on the anatomic region(s) with clinical symptoms. Abdominal ultrasound may be useful in babies; however, the liver and spleen size should be evaluated clinically.

Other techniques such as technetium scintigraphy [11], positron emission tomography (PET) scan [12], whole-body magnetic resonance imaging (MRI) [13] have been proposed, but remain not currently recommended. In order to decide which of these techniques to employ, two broad principles may be considered: the principle of parsimony, which advocates for strictly the minimum number of examinations needed in order to make a medical decision; and the principle of exhaustivity, which tends to use all available techniques in order to have an exhaustive count and description of all anatomic involvement in the disease. To resolve this dichotomy, it is important to assess what added value, in terms of patient care and treatment decisions, arises from the detection of

Table 1. Differential diagnosis for manifestations of langerhans cell histiocytosis.

Involvement	Manifestation	Possible other condition
Skin	Vesicles and bullae (most common in early infancy)	Erythema toxicum Herpes simplex Chickenpox infection
	Dermatitis (most frequently scalp, diaper or axilla, may occur up to late infancy)	Seborrheic dermatitis (eczema; usually no petechiae and marked scaling)
	Nodules	Mastocytosis Juvenile xanthogranuloma Neuroblastoma Infant leukemia
	Pruritus (more common), Petechiae (uncommon)	Scabies (other family members may be affected) [62] Dermatopathic nodes and dermatopathic lesions [63]
Bone	Vertebra plana	Ewing sarcoma Septic osteomyelitis Chronic relapsing multifocal osteomyelitis (CRMO) Leukemia Lymphoma Aneurysmal bone cyst Juvenile xanthogranuloma Myeloma (only described in adults) Osteoporosis
	Temporal bone	Chronic otitis media Mastoiditis Cholesteatoma Soft tissue sarcoma
	Orbit	Acute infection (preseptal cellulitis) Dermoid cyst Rhabdomyosarcoma Neuroblastoma Pseudoinflammatory tumor
	Other lytic lesions of the long bones	Parasitosis like difilariosis [64] Osteomyelitis Chronic relapsing multifocal osteomyelitis Aneurysmal bone cyst Bone angiomatosis (Gorham disease) Fibrous dysplasia Atypical mycobacterial infection Osteogenic sarcoma Ewing's sarcoma
Lung	In particular systemic symptoms and cavitated pulmonary nodules	Pneumocystis Carinii cavitated infection Mycobacterial or other pulmonary infections Sarcoidosis Bronchiolar-alveolar carcinoma (only described in adults) Lymphangio-Leiomyosarcoma (only described in young adult women) Septic emboli
Pituitary	Central diabetes insipidus	Dysgerminoma Idiopathic central diabetes insipidus [65,66]
Liver	Jaundice with direct hyperbilirubinemia Hypoalbuminemia	Chronic destructive cholangitis Metabolic disease Hepatitis Neoplasia obstructing biliary tract Inherited deficient conjugation of bilirubin Toxic (Reye syndrome) Chronic inflammatory bowel disease Neonatal hemochromatosis
Anemia Thrombocytopenia	Hematophagocytic syndrome with hepato splenomegaly	Familial Hemophagocytic Lymphohistiocytosis [67]

any given lesion, particularly bone extensions. To our best knowledge, no study has demonstrated that disease outcome is related to the total number of locations of the disease in the body. Indeed, the anatomic site itself (particularly for bone involvement), the volume of associated soft tissue involvement and degree of local destruction have a more clear impact on disease outcome that the actual number of bones involved. Lastly, it is important to consider that all 'new' techniques have a cost for the health system and may add to radiation exposure or inconvenience to the patient, such as general anesthesia for whole-body MRI in young children. The conclusion of this scientific debate has not yet been reached, but so far, the parsimony principle is commonly recommended. The only exception to date is the complete bone X-ray survey, which is still recommended at diagnosis for all patients.

Whatever the final choice to evaluate the bone lesions in a patient with LCH, it is very strongly not recommended to change the method of evaluation during the course of a given patient, as it may lead to discrepancy between assessments. It is important also to consider, during follow-up, limiting the evaluation to the anatomic region initially involved.

The third step of the evaluation process is targeted imaging or specialized clinical assessments for precise evaluation of specific involvement. A history of polyuria or polydipsia requires an early-morning urine sample for determination of specific gravity and osmolality, a blood electrolytes test and a water deprivation test, if possible. Other suspected endocrine abnormalities (i.e., short stature, growth failure, hypothalamic syndromes, precocious or delayed puberty) need a complete endocrine workup.

Bicytopenia, pancytopenia or persistent unexplained single cytopenia requires analysis of hemophagocytic biological features (coagulation, including fibrinogen, triglycerides and ferritin), bone marrow aspiration and trephine biopsy to exclude causes other than LCH.

Liver dysfunction requires abdominal ultrasound and the advice of a hepatologist. Liver MRI currently appears preferable to retrograde cholangiography in cases of frank liver dysfunction (liver enzymes > 5 times normal and/or bilirubin > 5 times normal range). Liver biopsy is only recommended if there is clinically significant liver involvement and if the test results will affect treatment decisions (i.e., to differentiate between active LCH and sclerosing cholangitis).

In case of abnormal chest X-ray or symptoms/signs suggestive of lung involvement, or lung findings not characteristic of LCH, or suspicion of an atypical infection, a lung evaluation is needed using high-resolution computed tomography (HR-CT) or, preferably, low-dose multi-detector HR-CT if available, and also a lung function test (if age appropriate). Bronchoalveolar lavage (BAL) may be useful to exclude other condition such as infections and may offer in addition to HR-CT, a positive argument for LCH involvement if the case of false-positive CD1a staining is excluded [14]. Finally, lung biopsy is useful if the diagnosis is not ascertained by another method. Vertebral lesions require MRI of the spine to exclude spinal cord compression and to assess for soft tissue masses. Any visual or neurological abnormalities need neurological and neuropsychometric assessment. Aural discharge or suspected hearing impairment/mastoid involvement requires a formal hearing assessment, MRI of the head and HR-CT of the temporal bone. Unexplained chronic diarrhea, failure to thrive, or malabsorption requires endoscopy with multiple biopsies.

4.1 Cranial MRI in LCH patients

To date, MRI of the head is not recommended for all patients with LCH, but only for those patients with neurological symptoms, pituitary dysfunction or patients with skull or facial bone lesions. If performed, the MRI protocol must be able to investigate the entire brain, the hypothalamus–pituitary axis and all craniofacial bones. The aim of the MRI is to systematically seek any neurodegenerative involvement and/or tumorous lesions and meningeal involvement [15,16]. The use of an intravenous contrast agent (gadolinium chelate) is mandatory. The following protocol is recommended: axial and sagittal T_1-weighted slices of the entire brain, fine T_1-weighted sagittal slices focused on the pituitary gland (3 mm/ 0.3 mm or below), axial T_2-weighted and fluid attenuated inversion (FLAIR) slices (except in patients aged less than 1 year) of the entire brain. The option 'contrast by magnetic transfer' is not recommended. However, if this is used, the same technique must be used at each subsequent evaluation and this information must be specified on the report. After injection of the gadolinium agent, the MRI scan should be performed according to data obtained from the first series (T_1-weighted slices): fine sagittal slices of the pituitary and coronal slices of the brain. Additional sequences may be taken if indicated.

Regarding the frequency of routine MRI surveillance in cases with positive findings at the initial MRI scan, the following recommendations are offered. If a CNS lesion has been identified, it is suggested to repeat the examination after 6 weeks (in symptomatic patients and those with tumorous lesions) and at 3 months. A decision to conduct further images should be made on the basis of the results of the first two examinations. In case of clinical hypothalamic dysfunction or neurodegenerative findings on MRI, even in the absence of symptoms, it is suggested to perform a second MRI after 1 year and then at 2, 4, 7 and 10 years. If after 10 years there is no clinical deterioration, further MRI is recommended only upon clinical indication.

5. Definition of organ involvement/definition of risk organs, CNS risk organ and special sites in langerhans cell histiocytosis

Once a diagnosis of LCH is determined in one organ by histopathology, it is not mandatory to confirm the involvement of other organs using a pathology method. The definitions

of organ involvement are listed in Table 2. Among all organs potentially involved in LCH, some organs are considered as risk organs. In medicine in general, the term 'risk organ' means that in a patient with disease involvement in one organ, there is a higher risk of complication than in patients who do not have involvement in that 'risk organ.' In LCH, there are two different meanings included in the word 'risk': the risk of death and the risk of a neurodegenerative complication.

The organs or systems in which disease involvement may lead to death are well defined in the literature; in children the main one is the hematological system, which almost always is associated with spleen and liver involvement [2,3,5,17]. The lung has been considered for several years as a 'vital' risk organ, and there is general agreement that lung involvement can considerably worsen the prognosis and is, therefore, a mortality risk for the patient [14,18]. However, lung involvement is, in children, rarely the sole cause of death, and when it is a cause of death, it is almost always for 'mechanical complications' not accessible to any systemic therapy, such as untreatable pneumothorax [19]. This is why lung involvement is no longer considered a 'risk organ' in clinical trials for LCH [20].

The CNS risk lesion, also coined a 'special site,' is a more recent concept [21] and has been used in the Histiocyte Society protocol LCH III. The risk involved here is the development of a neurodegenerative LCH, which is a dramatic and irreversible complication associating a clinical symptomatology and typical MRI features [22,23]. The literature does not define this risk directly, and to date two aspects have been reported. First, diabetes insipidus (DI) – that is, pituitary involvement – is associated with neurodegeneration such that about 95% of clinical neurodegenerative syndrome cases have DI; the risk of neurodegeneration in patients with DI is approximately 15% compared with 1% in patients without DI [24]. Second, there is a statistical association between disease involvement in certain organs and occurrence of DI [21,24,25]. By extension, these organs have been considered as 'CNS risk lesions' based on the assumption that DI is a surrogate marker of neurodegenerative histiocytosis [21]. Among the studies that have addressed this question [21,24,25], head bone involvement was shown to be always associated with the occurrence of DI. However, two studies had considered all skull bones together [24,25], while another study evaluated the facial bones separately from vault bone [21], excluding vault bone from the definition of special sites, even if involvement of the same occipital bone or frontal bone could be considered either as a vault lesion or as a skull base lesion. The association of pneumothorax and sclerosing cholangitis with DI was found in one study [24], but not evaluated in others. Finally, one study excluded patients with inaugural DI (i.e., DI onset before or at the same time as extra-pituitary involvement), despite the fact that they represent 50% of DI cases [21]. Indeed, the definition of CNS risk organ is not consensual and remains an extrapolation of epidemiological studies. So far, neurodegenerative lesion in LCH cannot be predicted at the diagnosis of LCH by any method in a reliable way.

6. Clinical classification

LCH has been classified in several ways and several synonyms have been used such as eosinophilic granuloma, Hand-Schuller-Christian syndrome, Letterer–Siwe syndrome, Hashimoto–Prizker syndrome, all of which are quite frequently used. In actual fact, the border between different disease entities is not strict, and so far, despite the heterogeneous presentation of the disease, it is still pertinent to consider LCH as a unique disease with various extensions and various outcomes. As several reactivations may occur during the course of the disease, the extension of the disease through the body may increase from initial presentation to the maximal extent. The current classification differentiates single system disease and multisystem disease. This classification is applied at diagnosis of the disease, even if the final extent of the disease may be different [26]. In single-system LCH (SS-LCH), one organ or system is involved such as unifocal bone (single bone), multifocal bone (more than one bone), skin, lymph node (not the draining lymph node of another LCH lesion), lungs, hypothalamic–pituitary/CNS or others such as thyroid or thymus. In multisystem LCH (MS-LCH), two or more systems are involved that may include 'risk organs' (hematopoietic system, spleen and/or liver) or not (for example skin and bone, or skin and pituitary).

6.1 Evaluation of disease activity

LCH can cause both acute complications and permanent sequelae. At least 10 separate organs can be directly involved (bone, skin, liver, spleen, lung, hematopoietic system, pituitary, brain, lymph nodes, mucosa) while others can be affected by proximity. Some involvements appear to be almost irreversible once they are observed. Indeed isolated pituitary involvement can constitute both a reactivation of disease, when it occurs late in the course of the disease, and at the same time, a permanent consequence. A single bone involvement can be highly symptomatic, with dramatic local consequences (such as deafness in the case of a massive temporal bone lesion) while multiple bone lytic lesions in silent anatomic areas may have no consequences. Finally, the healing 'speed' of bone lesions depends on the criteria used to evaluate it. Our understanding of this important aspect is based on several studies published in the 1980s [27,28].

Disease activity is currently assessed using the criteria employed in Histiocyte Society randomized trials [2,3]. The more recent assessment system is semi-quantitative, with the following four categories [18]: non-active disease, active disease-better, active disease-stable and active disease-worse. The drawbacks of this system are that, by definition, each assessment is based on a comparison of the situation before and after therapy (or over a 6-week interval) and the lack of reliable definition of the disease activity in involved organs.

A disease activity score system, tested on a sample of 650 patients, has been published [29] and is a useful tool to

Table2. Definition of organ involvement in langerhans cell histiocytosis.

Criteria
Bone involvement
General bone involvement: All radiological documented lesions, usually considered as LCH lesions
An abnormality on Tc Bone scan or an MRI hypersignal, not correlated with symptoms, and not correlated with an X-ray image is not considered bony disease!
Skin involvement
Any rash documented by histological examination
or any lesion (erythematous and crusted macules, papules or nodules, with or without ulceration, or petechiae, or seborrhea-like picture) compatible with the diagnosis, if LCH is confirmed by biopsy of another organ
Mucosae involvement
Oral involvement with lesions in the oral mucosa, gums
Genital or anal involvement
Pituitary involvement
Any pituitary hormone deficiency
or tumor appearance in the hypothalamic pituitary axis
Ear involvement
Ear involvement with external otitis, otitis media or otorrhea
Hematopoietic involvement
Mild
Hemoglobin between 10 and 7 g/dl (not due to other causes, e.g., iron deficiency)
Or thrombocytopenia with platelets between 100,000 and 20,000/mm^3
Severe
Hemoglobin < 7 g/dl. Exclude iron deficiency or other causes
Or platelets < 20,000/mm^3
Liver involvement (the patient can show a combination of these symptoms)
Enlargement > 3 cm below the costal margin at the mid-clavicular line, confirmed by ultrasound
or dysfunction documented by: hyperbilirubinemia > 3 times normal, hypoalbuminemia (< 30 g/dl), γ GT increased > 2 times normal,
ALT(SGPT) - AST(SGOT) > 3 times normal, ascites, edema
or intra hepatic nodular mass
Spleen involvement
> 3 cm below the costal margin at the mid-clavicular line, confirmed by ultrasound
Lung involvement
Typical imaging (nodules or cysts) on CT scan
Any atypical aspect needs to be explored by BAL or biopsy in order to have histopathological/cytological diagnosis
Central nervous system (CNS) involvement
Tumoral: All intracerebral expansive lesions predominantly affecting the brain or meninges
Neurodegeneration on MRI: MRI imaging compatible with neurodegenerative disease[1], i.e., abnormal signal intensity localized in the dentate nuclei or cerebellum or cerebral atrophy *not* explained by corticosteroids
Clinical neurodegeneration: Presence of suggestive symptoms (either cerebellar syndrome or learning difficulty) with compatible MRI imaging
Eye involvement
Orbital involvement with proptosis or exophthalmos
Anatomic involvement of the eye

assess disease response, especially in cases of systemic disease (**Table 3a**).

However, this scoring system is accurate neither for lung involvement nor for monitoring sequelae. CT scanning is now a very accurate method for evaluating the anatomic extension of the disease although the anatomic lesions, categorized roughly as cysts or nodules, can be disseminated in a various proportion at various locations. In order to offer a simple ranking, a semi-quantitative score has been proposed (**Table 3b**) [30,31]. In addition to the disease activity score, a sequelae score has been proposed and correlated with quality of life (**Table 3c**) [32].

Altogether, the use of such scoring systems offer a global and reliable approach to determine the activity of the disease and may aid the physician in making treatment decisions as proposed in **Table 3a, 3b and 3c.**

Lastly, neurodegenerative presentation must be monitored, using the International Cooperative Ataxia Rating (ICAR) scoring system [33], which has been used in the US, France and UK [32,34,35], while the Japanese cooperative group had used a scale derived from multiple sclerosis named EDSS [36].

7. Treatment: what are the options?

7.1 Local therapy

Bone lesions: The decision regarding orthopedic or physiotherapy treatment options must be taken in conjunction with an orthopedic surgeon. Complete excision of bone lesions (curettage) may be indicated if the bone lesion is small (< 2 cm) and this approach may offer a complete treatment. By contrast, the complete excision of large lesions is not indicated since it may increase the size of the bony defect and the time to healing; it may also result in permanent skeletal defects. Depending on lesion size and aspect, intra-lesional injection of methylprednisolone can be used [37]. Immobilization of a limb has to be considered. Vertebra plana 'per se' is not an indication for orthopedic corset, and only appropriate and expert physiotherapy should be considered.

Skin lesions: Topical steroids are often suggested in standard textbooks but their efficacy has never been proven. Moreover, most LCH patients with cutaneous involvement (either isolated or in the context of MS-LCH) are diagnosed only after unsuccessful treatment with local steroids. Skin involvement may usually be controlled by topical nitrogen mustard (mechlorethamine hydrochloride) application [38]. These topical treatments can be applied to the external auditory tract, in case of local lesion [39].

Lung: Pneumothoraces are treated by standard techniques such as drainage and pleurodesis. Pleurectomy should be avoided in patients for whom lung transplantation may ultimately be an option.

Ear nose and throat: In case of temporal bone lesions and recurrent otorrhea, secondary cholesteatoma can be considered [40].

Table 3a. Langerhans cell histiocytosis – systemic score [29].

Variable	Modality	Score
Bone (a)	Pain	1
	No pain	0
Bone (b)	Compressing other organs (orbit or spine)	2
	No compression	0
Fever (> 38.5 °C)	Yes	1
	No	0
Lung: iconography	Pneumothorax	2
	Interstitial lesion on chest X-ray film or lung CT scan	1
	Normal chest X-ray film or lung CT scan	0
Lung: function	Mechanical ventilation or PFT > 50%	5
	Supplemental oxygen or PFT between 50 to 80%	2
	No dysfunction, no cyanosis, no supp. Oxygen	0
Skin: area	25%	2
	5 – 25%	1
	Below 5%	0
Soft tissue tumor (including CNS)	5 cm max diameter	2
	2 – 5 cm max diameter	1
	0 – 2 cm max diameter	0
Nodes (> 2 cm)	Yes	1
	No	0
Liver	Below umbilicus	2
	Enlarged above umbilicus	1
	Not enlarged	0
Spleen	Below umbilicus	2
	Enlarged above umbilicus	1
	Not enlarged	0
Liver (enzymes)	> 10 N	2
	3 N to 10 N	1
	< 3 N	0
Liver (gamma GT)	> 10 N	2
	3 N to 10 N	1
	< 3 N	0
Albumin	Perfusion required in past week	3
	No perfusion but < 30 g/l	1
	> 30 g/l	0
Platelet: requirements in past week	More than 2 transfusions	4
	1 or 2 transfusions	3
	Low platelet count, no transfusion	2
	Normal count	0
Red cells: requirements in past week	More than 2 units	4
	1 or 2 units	3
	Hb below 10 g/dl, no transfusion	1
	Hb equal or above10 gr/dl	0

The score is calculated after collection of the clinical information, a chest X ray, a complete blood count, albumin level, SGOT, SGOT and gamma GT.
N: Maximal normal value for the laboratory.

7.2 Systemic therapy

Many drugs are used in LCH, from nonsteroidal anti-inflammatory drugs (NSAIDS), steroids, to cytostatic drugs such as vincristine, vinblastine, VP-16 (etoposide), 6 mercaptopurine (6-MP), methotrexate, cytarabine and cladribine. To this list can be added many drugs considered as immuno-therapeutic agents (interferon alpha, anti TNF-alpha, ciclosporin A, thalidomide, etc.) and various other drugs such as imatinib, retinoids and bisphosphonates.

Unfortunately, most of the drugs used in LCH have been evaluated in very low numbers of patients, usually in special, potentially biased, circumstances. The degree of evidence of efficacy is usually poor.

In the last 20 years, a limited number of therapeutic trials have been set up: three in the Western world under the auspices of the Histiocyte Society (LCHI [2], LCHII [3] and LCH III, which are not yet published) and one in Japan [41]. None of these trials had included adults [42].

These studies have provided the following observations:

1) The most frequently reported regimen is the association of vinblastine with a steroid. This therapy has been used

Table 3b. Lung score evaluated by the high-resolution CT scan.

Estimation of the proportion of cysts by field:		Estimation of the proportion of nodules by field:	
0 no nodules		0 no nodules	
1 < 25% or rare		1 < 25% or rare	
2 25 – 50% or intermediate		2 25 – 50% or intermediate	
3 > 50% or high		3 > 50% or high	
Right	**Left**	**Right**	**Left**
Upper		Upper	
Medium		Medium	
Lower		Lower	

To establish this score, the chest was divided into six fields: upper, medium and lower and left and right. For each field, and both for nodules and for cysts, the score was 0 if no lesion, 1 if the proportion of lesions was between 1 and 25% of the surface (or consider as rare), 2 if the proportion of the lesions was between 26 and 50% (or consider as intermediate) and 3 if the proportion of lesions was above 50% (or consider as high) [30,31]. This score correlates with lung function.

since 1972 and so far all reports have shown that, for most of the cases, it is a safe and efficient therapeutic option. Late effects of this treatment are very limited in children. The use of this combination is more controversial in adults and more frequent short term side effects are reported, such as peripheral neuropathy

2) VP-16 added to a combination of vinblastine, steroid and 6-MP did not provide any additional effect in patients with risk organ involvement or MS-LCH [2,3]
3) Methotrexate, in addition to a combination of Vinblastine steroid and 6-MP did not bring any addition benefit for patients with risk organ involvement or MS-LCH (LCH III protocol, unpublished results)
4) In patients with MS-LCH, a 12-month maintenance therapy period limited the rate of reactivation compared with 6 months of maintenance therapy (LCH III protocol, personal communication)
5) The combination of vincristine, steroid, and cytarabine provides comparable results to the combination of vinblastine, steroid, and 6-MP [41]
6) Cladribine monotherapy is effective for non-risk-organ disease that is refractory to standard therapy except in cases of hematological dysfunction [43]
7) Cladribine in association with cytarabine is effective in patients with hematological dysfunction that is refractory to standard therapy [44].
8) Hematopoietic stem cell transplantation is a therapeutic option if risk organ involvement is present, refractory to other salvage therapeutic approaches [45]

Because of its simplicity and low toxicity, compared with other drugs used in association, the use of NSAIDs has to be emphasized too [46].

7.3 Front-Line treatment

The most frequently used systemic therapy is based on vinblastine 6 mg/m^2 intravenous (i.v.) bolus once every 7 days (once a week) for 6 weeks, along with prednisone at 40 mg/m^2/day given orally in three divided doses for 4 weeks and then tapered over the following 2 weeks. After the first 6 weeks of treatment, disease status should be evaluated and treatment continued accordingly. Usually, in cases of disease progression, patients must switch to salvage therapy. By contrast, in cases of complete response, patients continue with maintenance therapy, while in the intermediate situation, a second course of 6 weeks of vinblastine plus steroid is administered, with a further evaluation undertaken at the end of this second course. Given that the risk of reactivations is high in many forms of LCH, and in line with as-yet-unpublished results of the LCH III protocol, treatment should continue for up to a total of 12 months with vinblastine 6 mg/m^2 i.v. bolus every 3 weeks, along with prednisone at 40 mg/m^2/day given orally in three divided doses for 5 days. The immunosuppressive drug 6-MP at a dose of 50 mg/m^2 is added if a risk organ is present at diagnosis. An acceptable modification to this protocol is to avoid steroids in cases of DI (as steroids interfere with water balance) and to use more frequent vinblastine pulses in the maintenance therapy in case of minor reactivation between pulses provided every 3 weeks. Vinblastine with steroid is efficient as a front-line therapy for tumoral processes of the CNS [47].

The association of vincristine, cytarabine and steroid, as proposed by the Japanese cooperative group [41], represents a therapeutic alternative to the combination of vinblastine and steroid. Whatever the systemic therapy, prophylaxis against *Pneumocystis carinii* is recommended during the treatment period.

7.4 Salvage therapy

Refractory disease in patients with hematological and/or liver dysfunction is a rare but life-threatening situation [5,17]. Such patients need to be referred to a trained team, that is, a team with a medical experience of both intensive chemotherapy and LCH. Therapeutic options (although the evidence is quite

Table 3c. Score sequel [32].

	Score	
Hormones DI	3	Panhypopituitarism and/or hypothalamic syndrome not correctable with hormone replacement
	2	Partial anterior pituitary deficiency *and* diabetes insipidus on replacement therapy
	1	Diabetes insipidus on replacement therapy
	0	No pituitary deficiency
Cerebellar syndrome [33]	3	Severe ataxia (scale > 40) or other motor disability
	2	Moderate ataxia (scale 20–40)
	1	Mild ataxia (scale < 20)
	0	No ataxia
Intellectual deficiency	3	Severe learning difficulty (IQ < 70) and/or severe behavioral/psychological problems impairing function and not correctable by treatment
	2	Moderate learning difficulty (IQ 71–79) and/or behavioral/psychological problems correctable by treatment
	1	Mild learning difficulty (IQ 80–89) and/or mild behavioral/psychological problems not requiring treatment
	0	No intellectual deficiency
Ear function	3	Severe bilateral hearing loss, not correctable with aids
	2	Moderate bilateral hearing loss, partially correctable by aids
	1	Mild bilateral or moderate/severe unilateral loss correctable with aids
	0	No hearing loss or mild unilateral hearing loss, no aids required
Lung = dyspnea NYHA	3	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest./requiring lung transplant
	2	Patients with marked limitation of activity; they are comfortable only at rest
	1	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion
	0	Patients with no limitation of activities; they suffer no symptoms from ordinary activities
Dysmorphie facial - teeth	3	Gross facial or orthodontic abnormality and/or scarring requiring repeated or major surgery
	2	Moderate facial or orthodontic abnormality and/or scarring correctable with surgery
	1	Mild facial or orthodontic abnormality and/or scarring not requiring any surgery
	0	No abnormality
Liver	3	Liver function extremely poor/requiring liver transplant
	2	Moderate liver function decrease/jaundice permanent
	1	Mild cholangitis – no liver dysfunction
	0	No liver dysfunction
Obesity	3	Pathological obesity – BMI > 35
	2	Obesity – BMI 30 – 35
	0	BMI < 30
Vision	3	Bilateral blindness – not correctable
	2	Mild bilateral blindness or unilateral severe blindness
	1	Mild unilateral blindness
	0	No abnormality
Other: in text		

This score can be applied at each follow-up visit and is correlated with quality of life.

limited) may include the chemotherapy combination of cladribine and cytarabine [44] as a second-line treatment, and even hematopoietic stem cell transplant after reduced-intensity conditioning regimen as a third-line option [45]. Indications for the combination of cladribine and cytarabine in France have been limited to patients with a systemic disease activity score above 5 and who progress after initial therapy with a classical regimen comprising at least six pulses of vinblastine and 6 weeks of therapy. In this group of patients, the survival rate was very low (about 30%) until the use of cladribine and cytarabine and is now as high as 85% (LCH S 2005 protocol – personal data).

In contrast to the situation of failure in patients with risk organs, the possibility of disease progression in patients without risk organ involvement (e.g., bone or mass lesion in the CNS) can be managed by cladribine monotherapy [43].

7.5 Radiotherapy

Radiotherapy is an efficient method to treat a bony lesion or a CNS mass lesion. However, this method has two limitations: first, it is only a local therapy, which means that the systemic course of the disease is not controlled by this approach; and second, there is a frank increased risk of secondary malignant tumor, as observed in several surveys and case reports. With regard to the ALARA (as low as reasonably achievable) safety principle, there is always an alternative therapy.

7.6 Adults

So far, the medical management of adults is not based on therapeutic trial but on small survey [42]. In adult, the dose of vinblastine is commonly adapted (as the maximum dose per pulse is no more than 10 mg), while peripheral neuropathy is a more frequently observed compare with children.

7.7 Neurodegenerative complications

Neurodegenerative complications are complex situations and such patients need to be managed by a multidisciplinary team, involving a physician trained in LCH, a neurologist, a reeducation specialist and, commonly, a endocrinologist, with the help of social workers.

Several therapeutic approaches have been attempted and can be proposed: retinoic acid (survey of 10 patients [35]), the combination of vincristine and cytarabine (survey of 8 patients [34]), immunoglobulin (4 patients including 2 asymptomatic and a case report [36,48]) and more recently infliximab [49]. The best result that can be expected from such regimens is the stabilization of neurological symptoms. So far, intensive therapy, including autologous bone marrow transplant, radiotherapy, high-dose methotrexate or steroids, has never shown any effect, not even a stabilization of the course of neurodegeneration, and should be avoided.

8. Indications for therapy and evaluation

MS-LCH with risk organ involvement (hematopoietic system/liver/spleen, regardless of additional organs involved). A systemic therapy is always recommended. The use of a systemic scoring system [29] is very useful in this situation in order to objectively determine the response to therapy.

MS-LCH and SS-LCH without risk organ. The indication of systemic therapy should be based on the presence or absence of clinical symptoms and/or patient complaints, and on the size and site of the disease. In the absence of symptoms or threat to organ function, the decision is more controversial. Some may decide that a systemic therapy should be used in all MS-LCH without risk organ involvement and some may even decide to treat all patients with skull lesions, or lesions localized at the skull base (but the latter are commonly responsible for symptoms).

There is no consensus regarding duration of maintenance therapy. However, the results of the unpublished LCH III protocol offer a first answer and demonstrate than a duration of 12 months limits the total number of reactivations.

8.1 Isolated lung involvement

The impact of systemic therapy on the lung is not well documented in children or adults, and pneumologists do not consider systemic therapy as the standard approach [14,18]. In adults, smoking cessation and stopping exposure to cigarette smoke in daily life is always mandatory. This recommendation may be considered for teenagers. There is no information about the impact of passive smoking exposure on children. However, isolated lung involvement can be very challenging due to the risk of severe acute complications such as pneumothorax or acute cardiopulmonary arrest.

8.2 Diabetes insipidus and pituitary involvement

In our experience, as in the experience of several groups [50], DI is almost never reversible even if the needs of desmopressin may change during the life of the patient. However, a case report had shown that cladribine provided soon after DI onset may reverse DI [51]. Diabetes insipidus in our experience, as well as in the conclusion of a UK study [50], is not considered as an indication for systemic therapy, except if it is associated with a mass lesion of the hypothalamus–pituitary axis. However, some authors had recommended to start a systemic therapy in case of isolated CDI [23]. In cases of growth hormone deficiency, there is no contraindication to treat a patient with LCH, even with active disease, using growth hormone therapy, if the latter is fully indicated. Indeed, there is no evidence to link an increased risk of LCH reactivation or any peculiar side effects with growth hormone therapy [52].

8.3 Treatment evaluation

All therapy needs to be carefully monitored. The evaluation needs to be focused on the target organs, those for which the initial therapy was started. Whatever the methods and criteria used to assess the response, a treatment period of 6 weeks is important to respect before assessing response [5,17] but some assessments can be delayed for the lung or for bone.

A general disease activity score (**Table 3a**) is a clear aid for therapeutic evaluation, in order to check for serious, potentially lethal, threats. If the score remains low (i.e., below 5), the disease is not life-threatening. In case of a high disease activity score (above 5), the possibility of switching to a salvage therapy must be considered within the trained team, associating both the experience of LCH and the management of high-dose chemotherapy, like in acute myeloid leukemia. Persistence of very aggressive local disease, if the local activity of the disease may be ascertained, can justify a switch to monotherapy with cladribine.

Usually, bone reconstruction is a very long process and persistence of X-ray bone lesions is rarely a good reason to modify the therapeutic schedule. Lung involvement is commonly assessed by CT scan although it is important to note that the density of cysts is rarely altered by therapy and should not be used to guide treatment.

9. Treatment options in case of reactivation

The choice of treatment options for disease reactivation is based on the same principles as for initial disease [53]. The options for reactivations of SS-LCH (skin, bone, other) include a 'wait and watch' approach, local therapy (as above), NSAID for bony disease and vinblastine plus steroid. Radiotherapy is no longer recommended due to potential

long-term sequelae. In case of a multisystemic reactivation of a SS-LCH, treatment should follow the options for MS-LCH including systemic therapy.

Reactivation after systemic therapy. If the reactivation is after completion of treatment, re-induction with vinblastine plus steroid may be effective, and there may be no need to switch to an alternative therapy.

9.1 Management of permanent consequences

Although LCH is a mostly benign and treatable disease, it can result in sequelae affecting various involved tissues [25]. Some sequelae may be present at diagnosis or even precede diagnosis, while other may become manifest later. It is thus important to keep monitoring these patients at least until growth is completed and possibly further into adult life. The most common long-term consequences are endocrine and growth, auditory and orthopedic. Neurocognitive, pulmonary and liver sequelae are rare but cause major morbidity. A scoring system for sequelae has been developed in order to observe disease evolution, and its adaptation to incorporate liver sclerosing cholangitis and morbid obesity is proposed [32].

So far, the management of long-term sequelae is not specific to LCH and all therapeutic options, like growth hormone therapy, liver or lung transplantation must be considered according to current medical practice.

9.2 Follow-up; duration and frequency

With regard to the heterogeneity of the disease, a standard follow-up schedule appears difficult to propose and we wish to provide only some principles.

The first principle is the use of a coordinated multidisciplinary approach. This means that each patient needs to be followed by the referring physician during the course of their disease and that evaluation and/or therapy of a particular clinical situation need to be addressed by a competent specialist.

The second principle is to follow the patient for a sufficient duration, which has been considered as at least 5 years after the last therapy or the last activation of the disease in the absence of systemic therapy.

The frequency of the follow-up is necessarily adapted to each particular situation. If the patient is receiving a systematic therapy, this frequency is adapted to the treatment schedule. In the absence of systemic therapy or in the absence of symptomatology, we consider that the routine number of consultations should be 4 during the first year after diagnosis, 2 in the second and third years and 1 each for years 4 and 5.

10. Expert opinion

LCH is a rare disease potentially resulting in death or with permanent sequelae. The burden of therapy may also be extremely heavy: there are still lots of reasons to continue to develop fundamental and clinical research in this field.

Indeed, in 2010 the team of Barrett Rollins reported a very important discovery that about 50% of the tumoral tissues of LCH patients bear a somatic mutation of the B raf oncogenes [54]. A lot of complementary research remains to be done in order to understand how such mutations may lead to disease as observed in many other conditions including malignant disease (melanoma, colon carcinoma, papillary thyroid cancer [55-57]) and benign conditions such as naevi [58]. Nevertheless, this discovery may have a clear potential impact if we consider the possibility of treating LCH with the new class of B raf inhibitors [59]. However, many steps need to be made from this discovery to the clinical use of these new drugs including a determination of the group(s) of patients who may benefit from B raf inhibitor treatment.

Progress may be expected from collaborations organized at national and international levels, among collaborative groups and expert networks. Collections of tissue and blood samples in biobanks have to be organized too. New international protocols will be opened to patient accrual and represent an opportunity to develop global research [60,61].

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