

# Langerhans' cell histiocytosis

**Author: Doctor Jean Donadieu<sup>1</sup>**

**Creation Date: June 2001**

**Update: May 2003**

**Scientific Editor: Professor Loïc Guillevin**

<sup>1</sup>Hôpital Trousseau, Service d'hématologie et d'oncologie pédiatriques 26, avenue du Docteur Arnold Netter, 75571 Paris cedex 12, France. [j.donadieu@invs.sante.fr](mailto:j.donadieu@invs.sante.fr)

[Abstract](#)

[Key-words](#)

[Definition-History](#)

[Diagnosis criteria](#)

[Epidemiological data](#)

[Clinical description](#)

[Etiology](#)

[Biological diagnosis](#)

[Assessment of disease extension](#)

[Survival, prognostic factors](#)

[Classification](#)

[Sequelae](#)

[Treatment](#)

[Questions not resolved and comments](#)

[References](#)

## Abstract

*Langerhans cell histiocytosis refers to the oligoclonal proliferation of Langerhans cells that occurs in children and young adults. Prevalence is estimated at 1/200,000/year in children. Clinical presentation is variable, ranging from a single location in the bone to severe multivisceral involvement (i.e lungs, bone marrow, liver, spleen) leading to dysfunction of vital organs. Diagnosis is always based on cytological or histological examination. Management is still controversial. Whereas local forms require only limited care, some severe forms may resist to chemotherapy. Multicentric protocols have been organized to improve the understanding of the physiopathogenesis and also because of the multiple treatments and types of patient management. They should be helpful to guide therapeutic strategies and to progress in the treatment of the more severe forms.*

## Key-words

Langerhans cell histiocytosis

## Definition-History

The clinical identification of Langerhans' cell histiocytosis began at the end of the 1800s. Hand (1893), Kay (1905), Schüller (1915), Letterer (1924) and Siwe (1933) were the first to describe different clinical forms of the disease. The link between these pathologies and the eosinophilic granuloma described by Smith (1865), foreshadowed in 1940 by Farber, was finally identified by Lichtenstein in 1953. The definition of this group of diseases is thus based

on morphological criteria detected by light microscopy and the term 'histiocytosis X' was proposed. The relationship between these syndromes and the proliferation of Langerhans' cells (LC) - described by Langerhans in 1868 - was demonstrated in 1973 by Nezelof and Basset. The name, Langerhans' cell histiocytosis (LCH), was logically adopted and the criteria of diagnostic certainty were defined by The Histiocytosis Society in 1987 [1] (see **Table 1**).

**Table 1: Diagnosis criteria**

| LCH        | criteria  |
|------------|---|
| Presumed   | light microscopy histology  |
| Probable   | light microscopy histology and 2 of the following markers:<br>a) adenosine triphosphatase b) protein S-100<br>c) a-D-mannosidase<br>d) peanut agglutinin (PNA)                  |
| Definitive | light microscopy histology and at least 1 of the 2 following factors:<br>a) Birbeck's granules by electron microscopy<br>b) labeling of CD1a antigen (T6) on pathological cells |

### Epidemiological data

In children, the diagnosis can be made from birth to adolescence with a peak frequency from the first year of life to 3 years. The incidence is estimated to be 1/200,000 children under 15 years old/year, the prevalence to be 1/50,000 with a M/F sex ratio of 2/1 [2]. In France, 40-50 new cases have been diagnosed per year over the past 10 years [3]. The epidemiology of the disease in adults is less well known. Cases, some very severe, have been reported but it is difficult to estimate their incidence. The largest series of adults were reported by lung specialists with [the pulmonary localization of the disease](#) apparently associated with heavy smoking [4, 5].

### Clinical description

The clinical spectrum of LCH is very broad. Different localizations are affected initially and at relapses. The most common are the following:

#### **Bone involvement**

It can be isolated or multiple. The symptoms that orient the diagnosis towards LCH are pain, painless swelling and, sometimes, a pathological fracture. The discovery can also be made on X-rays ordered for an intercurrent event (trauma). The typical image is a punched-out cavity in a long or flat bone. Sometimes, the radiological aspect is disquieting, with cortical outcropping, and a periosteal reaction radiologically suggestive of Ewing's sarcoma. Local complications can be among the most evident symptoms: spinal cord compression, instability of the spine, ocular compression, dental instability.

#### **Cutaneous involvement**

The usual skin involvement occurs during the first months of life, presenting as

papulosquamous lesions, sometimes petechial, disseminated, initially affecting the scalp, the major folds and the thorax. At first, these lesions are suggestive of eczema or seborrheic dermatitis, affections that are much more common. The persistence of the involvement and its spread should lead to taking a biopsy. More rarely, the auto-involutive cutaneous histiocytosis of Hashimoto- Pritzker, which affects only newborns, is observed. It consists of small papulonodular lesions, isolated or multiple, violaceous, and can sometimes resemble varicella lesions; a biopsy is required to confirm its diagnosis. The evolution is usually spontaneously favorable.

#### **Hematological involvement**

The presence of a few proportion of histiocytic Langerhans' cells (HLC) in the bone-marrow smear, commonly used as a definition of hematological involvement, may be found in non aggressive presentation of the disease. Dysfunction of hematopoiesis, mainly anemia and/or severe thrombopenia, rarely neutropenia, is the most appropriate feature of hematological involvement. Hemophagocytic syndrome could be associated.

Anemia and thrombopenia can also be associated with hypersplenism or be further accentuated by it.

#### **Pulmonary involvement**

This aspect is responsible for the interstitial syndrome, nodular images and localized pneumothorax. The functional respiratory consequences can be very marked. Chest radiography can detect these lesions but pulmonary computed tomography (CT) scan seems to be a more sensitive examination. Today, the diagnosis is based on bronchoalveolar lavage (BAL) [6]. Lung biopsy is recommended only within the framework of an etiological study after failure of other procedures, but not for the assessment of disease dissemination. Some forms are secondarily complicated by pneumothorax and/or pulmonary fibrosis.

#### **Hepatic involvement**

It is useful to distinguish acute involvement, often multivisceral, resulting from a first episode of the disease, from chronic involvement with sequelae. Acute involvement can be manifested by simple hepatomegaly, but can also lead to cytolysis and/or hepatocellular insufficiency with parenchymatous infiltration by LCH. In this case, treatment can be effective and cure the hepatic involvement. Chronic involvement consists of

sclerosing cholangitis, which is complicated in the intermediate term by biliary cirrhosis and finally hepatic failure. This involvement corresponds histologically to fibrosis, predominantly of the bile ducts, without any LCH infiltration. No specific treatment of the disease can even diminish this fibrosis and the hepatic prognosis seems to be independent of LCH [7].

#### ***Pituitary involvement***

The posterior and anterior lobes are affected. The most common symptomatology is diabetes insipidus, but it is important to recall the possibility of a deficit of growth hormone and/or TSH (thyroid-stimulating hormone). These hormonal deficits can appear several years after the diagnosis and justify prolonged monitoring of these patients with particular attention paid to their growth (height). Diabetes insipidus can precede other signs of the disease or appear during the course of its evolution.

#### ***Neurological involvement***

LCH can be responsible for a cerebral tumor or parenchymatous infiltration. The site of this rare localization is usually the cerebellum, but hemispheric involvement has been observed. The clinical consequences of this localization are not unexpected (intracranial hypertension, localization signs, ataxia).

#### ***Gastrointestinal tract involvement***

Rare but probably underestimated, this involvement can be limited to a localized focal infiltration of the digestive mucosa with no nutritional repercussion or be responsible for severe serous diarrhea. Involvement of the buccal mucosa, which often precedes the more generalized gastrointestinal tract disease, should prompt a complete endoscopic work-up.

#### ***Numerous other involvements***

Can be present: spleen, lymph nodes, subcutaneous tissues overlying a bony lesion, urinary tract, eye (uveitis) ...

Classically, these different involvements are associated in the distinct nosological entities.

#### ***Eosinophilic granuloma***

Has only uni- or multifocal bone involvement; it has a favorable outcome without treatment or with local therapy.

#### ***Letterer-Siwe disease***

Which affects mainly newborns, has multivisceral involvement: skin, liver, spleen, lung. Its prognosis is pejorative, sometimes irrespective of the treatments.

#### ***Hand-Schüller-Christian***

Disease affects children over 2-3 years old and associates diabetes insipidus, cranial bone cavities and exophthalmia. This progressive form is only rarely life-threatening, even if several attacks occur.

These descriptions help us classify the patients but numerous intermediate forms exist. More than a third of the patients suffer relapses of LCH during which new symptoms are acquired. The total number of relapses is generally less than 3, but 5% of the patients experience more than 4 aggravating crises.

Some adult clinical forms have presentations similar to those of children. The forms of young adults and smokers are somewhat different. A cough and fever lead to the discovery of interstitial or micronodular images with honeycombing [4, 5]. The diagnosis can be provided by BAL, but a transbronchial or lung biopsy is preferable. Associated lesions are rare. The evolution upon stopping smoking is usually favorable, sometimes combined with simple corticotherapy.

The observations of LCH associated with other malignant tumors are worrisome and are probably not coincidental. An article published in 1992 reported on 91 patients: 31 with lymphoma, 25 of which were Hodgkin's disease; 22 leukemias; and 30 solid tumors, 12 of which were lung cancers. Concerning lymphomas and solid tumors, the diagnoses were usually made simultaneously, unlike the leukemias, which were usually preceded by histiocytosis [8].

Thus, it seems that the malignant tumor-histiocytosis association is more frequent than chance would allow. Other than the responsibility of etoposide (VP-16) in secondary myeloblastic leukemias - highly probable in certain cases [9] but excluded in others - at present, no clear explanation can account for this disease association.

The presence of constitutional diseases in patients with LCH differs from the general population. However, because of the very broad diversity of the responsible syndromes (malformations of the kidney, the central nervous system ...), no recurrent association can be described [10]. The observation of homozygous twins with LCH also raises the question of a genetic factor.

#### ***Etiology***

LC originate in the bone marrow and are derived from CD34-positive stem cells. Experimental argument plays to consider as monocyte as a precursor of LC. They express certain number of surface phenotypic markers, among which the

most important are the major histocompatibility complex (MHC) class II molecules and the antigen CD1a. With their dendrites, they cover 25% of the entire cutaneous surface, even though they represent only 5% of the dermal cells [11].

From the skin, they migrate via the lymphatics to the paracortical zones of lymph nodes to assure their function: presenting antigens to T lymphocytes. Unlike monocytes and macrophages, their antigen-presenting capacity takes precedence over their phagocytic activity. This function is diminished under the action of ultraviolet (UV) rays, the primary etiological agents of skin cancers.

In contrast to LC, found exclusively in the skin, Malpighian mucosa and the lungs, the cells of LCH can infiltrate all organs: liver, spleen, gastrointestinal tract, central nervous system, bone. The specific expression of adhesion molecules could be at origin of these particular localizations. Studies have shown the unexpected expression of CD2, normally found only at the surface of T lymphocytes, and the variable presence of CD11a and CD11b [12]. In addition, other membrane markers differentiate between LC and the cells of LCH, notably the expression of 3 markers: PNA, placental alkaline phosphatase (PLAP) and the interferon- $\gamma$  receptor.

It has been shown that the cells of LCH have a markedly diminished antigen-presenting function compared to normal LC from the same subject. Indeed, the proliferation of allogeneic lymphocytes in the presence of the cells of LCH from a child with a disseminated form was much lower than that observed in the presence of LC from the skin of the same patient [11]. The monoclonality of LCH, including the forms with a clinically benign evolution, has been demonstrated by the study of chromosome X inactivation [13].

LCH could arise secondary to a somatic mutation of a gene with, as a consequence, clonal proliferation of the cells of LCH. The absence of parallelism between the severity of the disease and monoclonality is quite remarkable, albeit difficult to interpret.

The cells of LCH are able to synthesize a number of cytokines, including interleukin 1 (IL1), tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and granulocyte/macrophage-colony-stimulating factor (GM-CSF), which can explain certain systemic signs of the disease, for example, fever and cachexia. Large quantities of GM-CSF have been detected in the cytoplasm of the cells of LCH; the children with severe forms of LCH have higher levels of circulating GM-CSF than control

subjects, thereby suggesting an autocrine role for GM-CSF in LCH [14].

The role of infection has been advanced many times and associations have been found with cytomegalovirus, herpesvirus type 6, Epstein-Barr virus and the human immunodeficiency virus. However, to date, a causal role of these infections has never been demonstrated.

### Biological diagnosis

The diagnosis is always made based on histological or cytological examination. Examination of a fine-needle biopsy can be sufficient for the diagnosis [15]. The cells of LCH are large with an excentric, kidney-shaped or 'coffee-bean' nucleus. They are often associated within lesions with inflammatory cells: eosinophils, lymphocytes and macrophagic cells in bone and lymph nodes.

A confirmed diagnosis can only be made if the cells are labeled with anti-CD1a antibodies. This study can be conducted on frozen cytological samples and, since recently, on samples fixed with formol or, preferentially, Bouin's solution [11]. The detection of protein S-100 is less informative because it, like peanut lecithin antigens or  $\alpha$ -D-mannosidase, is not specific to LC. The search for Birbeck's granules by electron microscopy is another possibility, highly specific, but more time consuming and costly.

### Assessment of disease extension

The discovery of LCH imposes such a work-up. This evaluation aims not only to know the status of the patient at the time of diagnosis but it helps guide therapeutic decision-making. It should comprise a careful physical examination with ear, nose and throat (ENT), and stomatological examinations, minimal biological analyses (hemogram, hepatic function tests, inflammatory markers, blood and urine osmolarities) and a radiological assessment of disease dissemination: skeletal radiography, bone scintigraphy, chest X-ray and abdominal ultrasonography.

For multivisceral involvement and as a function of the initially affected sites, other examinations are recommended: bone-marrow studies with search for CD1-positive cells, BAL, thoracic CT scan, cerebral MRI when the pituitary is involved...

### Survival, prognostic factors

In the French retrospective study, the actuarial survival at 4 years was 90% (95% confidence interval (CI): 86-94%) [3]. This rate was obtained for a patient population in which 16% had organ dysfunction (liver, bone marrow, lung), which is a

marker of disease severity. It is obviously difficult to compare this value with those obtained for other patient populations for which this percentage can exceed 50% [2, 16-35]. Appreciation of prognostic factors hinges on this methodological bias. Nevertheless, the concordance among different studies that found the following elements clearly pejorative should be noted:

- the diagnosis made in a young child (especially before the age of 1 year);
- liver, bone-marrow, lung and/or digestive involvement;
- dysfunction of 1 of the 3 vital organs, *i.e.*, liver, lung or bone marrow;
- the total number of organs involved is > 3.

The DAL group [24] and French retrospective [3] studies demonstrated the highly pejorative value of a poor initial response to treatment (after 3 months or even 6 weeks). It should be noted that pituitary involvement is a protective factor for survival.

### Classification

The oldest classification, that of Osband, considered 3 variables: age (older than 2, yes/no), the total number of organs involved (< 4, yes/no) and organ dysfunction (yes/no). Subsequently, the DAL group developed a classification system with 4 groups: unifocal bone involvement alone, multifocal bone involvement alone, soft-tissue involvement without organ dysfunction, presence of organ dysfunction [24]. The Histiocyte Society recommended a simplified classification that took into account a single variable: the number of organs involved (1 or 2 organs: localized forms; at least 3 organs: multisystemic forms) [36].

### Sequelae

LCH has sequelae that occur months or even years after disease onset and are associated with the progressive fibrosis of the tissues involved. Indeed, one of the objectives of treatment is to limit their frequency and severity. Their frequency ranges from 10 to 50%, depending on the series. It varies clearly according to the initial stage of the disease, with 7% for unifocal bone involvement to about 40% for forms with initial organ dysfunction [3].

Orthopedic sequelae are the most common and are predominantly present in forms with multifocal bone involvement: vertebra plana, kyphosis-scoliosis, bone deformations, functional or esthetic disorders, bite anomalies, loss of teeth. In multivisceral forms, the endocrine sequelae (diabetes insipidus) are common, and

often already present at diagnosis. It should be noted that no local (radiotherapy) or general treatment has obtained regression of diabetes insipidus in these patients [37].

Other sequelae are rarer: retarded growth, growth-hormone deficiency, hypoacusis, ataxia or psychomotor sequelae due to neurological involvement.

Hepatic sequelae are particularly severe, with the appearance of sclerosing cholangitis. The latter usually occurs within 2 years following diagnosis and thereafter progresses alone towards secondary biliary cirrhosis, even when the histocytic disease is no longer evolving [7]. The same holds true for pulmonary involvement, which progresses towards fibrosis and chronic respiratory insufficiency [38].

### Treatment

At present, the treatment of LCH is still controversial, due to the rarity of the disease and the absence of a universally accepted standard. Although the greater majority of eosinophilic granulomas disappear spontaneously, without treatment or with only local therapy, the severe multivisceral forms require much more heavy-handed management, usually referred to oncology-hematology departments.

### Drugs used

Numerous substances have been successfully administered to LCH patients since the 1960s: vinblastine, vincristine, steroids, methotrexate, chloraminophen, cyclophosphamide, 6-mercaptopurine, VP-16 and, more recently, cyclosporin A, interferon- $\alpha$ , aracytine and 2-deoxychloroadenosine.

Of all these drugs, the combination of vincristine and steroids is the most often reported with very diverse therapeutic regimens (dose, duration of treatment).

VP-16 has been the object of several studies [19] since 1985, and appears to be effective in this setting. However, its potential long-term leukemogenesis is worrisome, but probably concerns < 1% of the patients receiving this drug [9]. The observations of leukemias following VP-16 use means that it should be prescribed prudently, since no clear-cut superiority has been demonstrated compared to other chemotherapies.

### Indications of treatments

The intensity of treatment should be modulated according to the presentation of the disease. It is useful to distinguish local forms and multivisceral forms.

*In local forms*

Bone lesions, singular or few in number, usually do not require treatment, other than the biopsy or cytopuncture needed to confirm the diagnosis and possibly curettage or local injection of corticosteroids for pain [39]. Radiation therapy [40], previously widely used, is contraindicated because of the risk of secondary cancer. It can, nonetheless, be used when the lesion threatens the functional prognosis (vertebral involvement with spinal cord compression, for example).

Cutaneous involvement, provided that the assessment of disease extension is negative, benefits from local caryolysine (nitrogen mustard) application [41].

Within the French LCH study group, case-by-case evaluation of certain localized forms indicated that systemic treatment was required, in particular, for: ENT involvement because of the risk of deafness, multiple bone lesions without involvement of other organs (provided that worrisome functional symptoms were present) and widespread cutaneous involvement resistant to local therapy. In these cases, the treatment of choice was the combination of vinblastine and steroids.

*In multivisceral forms (> 2 organs involved)*

The risk of dying is high for these patients, who have a 4-year survival rate of 60-80% [3, 24]. Even if a spontaneous remission can be hoped for in these forms, consensus has been reached to administer systemic therapy to these patients. However, the choice of first-line treatment remains to be established: the aggressive DAL HX 83 protocol [24], which combines 4 drugs (steroids, vinblastine, VP-16 and 6-mercaptopurine) or the more conservative approach, which combines vinblastine and steroids. This question is being addressed by The Histiocyte Society LCH II trial, which is an international, randomized, open, phase III trial that is now recruiting subjects.

*In patients resistant to first-line systemic therapy*

Experimental approaches currently under study  
These attempts concern small groups of patients identified not only by their original presentations but also their poor responses to first-line therapy with at least vinblastine and steroids. The prognosis for these patients is dismal, with an expected 4-year survival rate not exceeding 50%.

*a) Immunomodulating therapies*

- Interferon- $\alpha$ : the first promising results have not been confirmed.

- Cyclosporin A: the first publication on cyclosporine treatment of LCH appeared in 1991 [42]. The 3 patients treated entered remission but were taking other drugs concomitantly (cortico- and chemotherapy). Subsequent studies have not confirmed that good result.

*b) New chemotherapies*

2-Deoxychloroadenosine is a purine-base analogue, similar to 6-mercaptopurine. A case report describing its efficacy against a refractory multivisceral form has been published [43]. These encouraging results have not been confirmed in other situations and a well-structured therapeutic trial is needed to evaluate the real contribution of this drug.

*c) Bone-marrow transplantation*

Intensive chemotherapy followed by allogeneic or autologous bone-marrow transplantation might be a therapeutic option for severe chemoresistant forms. As of today, 4 allogeneic grafts and 2 autologous transplantations have been reported in the literature with 4 successes and 2 failures [44]. This type of therapy, whose potential contribution is being evaluated, would be proposed to patients who fail to respond to conventional treatments.

**Questions not resolved and comments**

The construction of a homogeneous, reproducible definition of this pathology has barely pushed back the questions raised by it. How can we bring together the highly diverse profiles of LCH, from the spontaneous cure to resistance to all therapies, from the isolated involvement of one bone to the generalized dissemination to the majority of organs? The possibility of cloning LC, the autocrine role of certain cytokines (TNF $\alpha$ , GM-CSF) and the modulation of adhesion-molecule expression on LC are at the core of ongoing research [12-14].

LCH is a rare disease, with a heterogeneous clinical presentation and often unpredictable outcome. Although the localized forms require limited management, the severity of the multivisceral forms with organ dysfunction and the small number of patients afflicted, justify the use of new drugs and the organization of international, multicentric therapeutic trials. Progress must be made in understanding the pathogenic mechanisms of this disease so as to adapt therapies accordingly. The formulation of a diagnostic and therapeutic protocol would enable a rational and homogeneous treatment strategy to be devised and to better understand the etiopathogenetic mechanisms at work, with the

objective of improving the prognosis for the severe multivisceral forms.

## References

1. Histiocyte society: Writing Group of the Histiocyte society. 1987. Histiocytosis syndrome in children. *Lancet*. II :1181-1191.
2. Cartensen H., Ornvold K. 1993. The epidemiology of Langerhans cell histiocytosis in children in Denmark 1975-1989. *Med Pediatr Oncol* 21: 387-8.
3. French Langerhans Cell Histiocytosis Study Group. 1996. French retrospective survey of Langerhans cell histiocytosis : 348 cases observed between 1983 and 1993. *Arch Dis Child.*, 75:17-24.
4. Schonfeld N., *et al.* 1993. Clinical and radiologic features, lung function and therapeutic results in pulmonary histiocytosis X. *Respiration* 60: 38-44.
5. Brauner M.M., Grenier P., Mouelhi M.M., Mompoin D., Lenoir.P. 1989. Pulmonary histiocytosis X: evaluation with high resolution CT. *Radiology* 172: 255-258.
6. Refabert L., Rambaud C., De Blic J. 1995. Intérêt du lavage broncho-alvéolaire au cours de l'histiocytose X de l'enfant. *Journées Parisiennes de Pédiatrie*. Flammarion eds , Paris. 259-266.
7. Zandi P., Panis Y., Debray D., Bernard O., Houssin D. 1995. Pediatric liver transplantation for Langerhans' cell histiocytosis. *Hepatology* 21: 129-133.
8. Egeler R.M., *et al.* 1993. Association of Langerhans cell histiocytosis with malignant neoplasms. *Cancer* 71: 865-873.
9. Haupt R., *et al.* 1993. Acute myeloid leukemia after single agent treatment with etoposide for Langerhans'cell histiocytosis of bone. *Am J Pediatr Hematol Oncol.* 15: 255-257.
10. Sheils C., Dover G.J. 1989. Frequency of congenital anomalies in patients with histiocytosis X. *Am J Hematol*; 31: 91-95.
11. Emile J.F., Donadieu J., Thomas C., Brousse N. 1995. L'histiocytose Langerhansienne. Données récentes sur le diagnostic et la physiopathologie. *Ann Pathol* 15: 252-259.
12. Graaf J., *et al.* 1994. Langerhans cell histiocytosis: expression of leukocyte adhesion molecules suggests abnormal homing and differentiation. *Am J Pathol* 144: 466-472.
13. Willman C.L., Busque L., Griffith B.B. 1994. Langerhans' cell histiocytosis (histiocytosis X) A clonal proliferative disease. *N Engl J Med* 331: 154-160.
14. Emile J.F., *et al.* 1993. Immunohistochemical detection of granulocyte macrophage colony stimulating factor in Langerhans's cell histiocytosis. *Histopathology* 23: 327-332.
15. Elsheikh T., *et al.* 1991. Fine needle aspiration cytology of LCH (eosinophilic granuloma) of bone in children. *Diagn Cytopathol* 7: 261-266.
16. Avery M.E., McAffe J., Guild H.G. 1957. The course and prognosis of reticuloendotheliosis: a study of 40 cases. *Am J Med* 22: 636-642.
17. Berry D.H., Gresik M.V., Humphrey G.B. 1986. Natural history of histiocytosis X: a Pediatric Oncology Group study. *Med Pediatr Oncol* 14: 1-5.
18. Broadbent V. 1986. Favourable prognostic features in histiocytose X: bone involvement and absence of skin disease. *Arch Dis Child* 61: 1219-21.
19. Ceci A., *et al.* 1993. Langerhans cell histiocytosis in childhood: results from the Italian Cooperative AIEOP CNR-HX '83 study. *Med Pediatr Oncol* 21: 259-264.
20. Chomette G., Auriol M., Ragot J.P., Guilbert F. 1987. Histiocytose X des maxillaires. I. Etude anatomo-clinique à propos de 61 cas. *Rev Stomatol Chir Maxillofac* 88: 334-338.
21. Daneshbod K., Kissane J.M. 1978. Idiopathic differentiated histiocytosis. *Am J Clin Pathol* 70: 381-386.
22. Dimentberg R.A., Brown K.L. 1990. Diagnostic evaluation of patients with histiocytosis X. *J Pediatr Orthop* 10: 733-741.
23. Egeler R.M., de Kraker J., Voute P.A. 1993. Langerhans-cell-histiocytosis (histiocytosis X); 20 jaar ervaring in het Emma Kinderziekenhuis, 1969-1988. *Ned Tijdschr Geneesk* 137: 955-960.
24. Gardner H., *et al.* 1994. Treatment strategy for disseminated Langerhans cell histiocytosis. DAL HX-83 Study Group. *Med Pediatr Oncol* 23: 72-80.
25. Greenberger J.S., Crocker A.C., Vawter G., Jaffe N., Cassady J.R. 1981. Results of treatment of 127 patients with systemic histiocytosis. *Medicine (Baltimore)* 60: 311-317.
26. Komp D.M. 1981. Long-term sequelae of histiocytosis X. *Am J Pediatr Hematol Oncol* 3: 165-168.
27. Lahey M.E. 1975. Histiocytosis X - comparison of three treatment regimens. *J Pediatr* 87: 170-183.
28. Leavey P., Varughese M., Breatnach F., O'Meara A. 1991. Langerhans cell histiocytosis - a 31 year review. *Ir J Med Sci* 60: 271-274.
29. Mac Lelland J., *et al.* 1990. Langerhans cell histiocytosis: the case for conservative treatment. *Arch Dis Child* 65: 301-330.
30. Nezelof C., *et al.* 1979. Disseminated histiocytosis X. Analysis of prognostic factors

based on a retrospective study of 50 cases. *Cancer* 44: 1824-1838.

31. Oberman H.A. 1961. Idiopathic histiocytosis. A clinico-pathologic study of 40 cases and review of literature. *Pediatrics* 8:307-327.
32. Raney R.B. Jr, D'Angio G.J. 1989. Langerhans' cell histiocytosis (histiocytosis X): experience at the Children's Hospital of Philadelphia, 1970-1984. *Med Pediatr Oncol* 17: 20-28.
33. Rivera-Luna R., *et al.* 1988. Langerhans cell histiocytosis: clinical experience with 124 patients. *Pediatr Dermatol* 5: 145-150.
34. Sims D.G. 1977. Histiocytosis X, follow-up of 43 cases. *Arch Dis Child.* 52: 433-440.
35. Toogood I.R.G. 1979. Prognostic criteria, treatment and survival in disseminated histiocytosis X *Aust Paediatr J* 15: 91-95.
36. Ladisch S., *et al.* 1994. LCH-I: a randomized trial of etoposide vs, vinblastine in disseminated Langerhans cell histiocytosis. *The Histiocyte Society. Med Pediatr Oncol* 23: 107-110.
37. Dunger D.B., *et al.* 1989. The frequency and natural history of diabetes insipidus in children with Langerhans cell histiocytosis. *N Engl J Med*, 1989; 321: 1157-1162.
38. Loire R., Brune J. 1993. Les lésions évoluées graves de l'histiocytose X pulmonaire. A propos de 3 transplantations. *Rev Mal Respir* 10: 223-228.
39. Wirtschaffer J.D., Nesbit M., Anderson P., Mc Chain K. 1987. Intralesional methylprednisolone for Langerhans'Cell histiocytosis of the orbit and cranium. *J Pediatr Ophthalmol Strabismus.* 24: 194-197.
40. El Sayed S., Brewin T.B. 1992. Histiocytosis X: does radiotherapy still have a role ? *Clin Oncol (R Coll Radiol)*; 4: 27-31.
41. Sheehan M.P., Atherton D.J., Broadbent V., Pritchard J. 1991. Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. *J Pediatr* 119. 317-321.
42. Mahmoud H.H., Wang W.C., Murphy S.B. 1991. Cyclosporine therapy for advanced Langerhans cell histiocytosis. *Blood* 77: 721-725.
43. Saven A., Figueroa M.L., Piro L.D. 1993. 2-Chlorodeoxyadenosine to treat refractory histiocytosis X. *N Engl J Med* 329: 734-735.
44. Greinix H.T., Storb R., Sanders J.E., Petersen F.B. 1992. Marrow transplantation for treatment of multisystem progressive Langerhans cell histiocytosis. *Bone Marrow Transplant* 10: 39-44.