Journal of Pediatric Sciences

SPECIAL ISSUE : *"Pediatric Oncology"*

Editor:

Jan Styczynski

Department of Pediatric Hematology and Oncology
Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

Langerhans Cell Histiocytosis in childhood

Judit Müller

Journal of Pediatric Sciences 2010;2(3):e28

How to cite this article:

**Muller J. Langerhans cell histiocytosis in childhood.
Journal of Pediatric Sciences. 2010;2(3):e28.**

REVIEW ARTICLE

Langerhans Cell Histiocytosis in childhood

Judit Müller

Abstract: *Histiocytoses are rare and heterogeneous group of disorders in childhood. The clinical presentation of Langerhans cell histiocytosis (LCH) is highly variable, from asymptomatic to clinically significant symptoms and consequences. As it can involve nearly every organ of the body, the clinical manifestations depend on the site of the lesions, on the organs and systems involved and whether their function is affected. The most common sites of involvement in LCH are bone, skin, lymph nodes, lung, bone marrow and hypothalamic-pituitary region. The classical presentation of LCH is a unifocal bone disease, previously known as eosinophilic granuloma. LCH can be divided according to disease extent: single- or multi-system disease. There is very high chance of spontaneous resolution and favourable outcome for single-system disease involving the skin or bone. In many cases, no therapy or only local therapy is enough. For patients with multi-system disease currently systemic therapy is the treatment of choice. The goal of treatment is to relieve clinical symptoms, to increase survival and prevent complications. Currently cooperative international trials of the Histiocyte Society are used for treatment of LCH based on 'risk group stratification' with therapeutic agents have generally paralleled those used for the treatment of malignancies. There is no standardized therapy for chronic relapsing, acute refractory and progressive disease, some alternative approaches have been tested. Childhood LCH is a well treatable disease and the survival rate is high. This article summarizes the classification, pathophysiology, diagnostic criteria, different clinical manifestations, treatment possibilities, prognosis and long-term sequelaes of LCH in children.*

Keywords**:** *histiocytosis X, Langerhans cell histiocytosis, pediatric oncology*
Received: *28/03/2010; Accepted: 29/03/2010*

1. Inroduction

Histiocytoses are rare and heterogeneous group of disorders in childhood. The various manifestations of these diseases were first recognized as having common link by Lichtenstein in 1953 and given the name histiocytosis X (1). The letter X referred to the unknown nature and cause of the disease. Now the recommended term is Langerhans cell histiocytosis (LCH), because of the typical morphological characteristics of the Langerhans cell (LC) described by Paul Langerhans in 1868 (2). Although several histiocytic disorders are known, in this article the focus is on LCH: classification, pathology, clinical presentation and treatment are discussed.

Judit Muller
2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary

Corresponding Author: Judit Müller, Ph.D.
2nd Department of Pediatrics
Semmelweis University, Tuzolo utca 7-9,
Budapest, H-1094
Phone: (*36)(1) 215 1380
Fax: (*36)(1) 210 6979
e-mail: muller@gyer2.sote.hu

2. Classification

The Writing Group of the Histiocyte Society defined the diagnostic criteria in 1987. The classification system has a pathologic basis because the ultimate diagnosis of all the childhood histiocytoses rests on the findings of pathologic examination. The classification replaces the eponyms histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schüller-Christian syndrome, Hashimoto-Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, LCH, type II histiocytosis and the generic term non-lipid reticuloendotheliosis. The different forms are grouped into three classes: LCH (Class I.), non-LC histiocytosis (Class II.) and malignant histiocytosis (Class III.), seen in table 1. Under the definitive name LCH, the disease was designed as Class I of the histiocytic disorders (3).

Table 2. shows the contemporary classification of histiocytic disorders by the World Health Organization

(WHO), based on the lineage of lesional cells and biological behaviour. This nosology is related to the ontogeny of histiocytes (macrophages and dendritic cells of the immune system) (4).

Table 1. Classification of childhood histiocytoses

[Chu T. et al: Histiocytosis syndromes in children: Lancet 1987; 1:208-209.]

Class I.	Langerhans cell histiocytosis (LCH)
	Eosinophilic granuloma
	Hand-Schüller-Christian syndrome
	Letterer-Siwe disease
Class II.	Histiocytoses of mononuclear phagocytes other than Langerhans cells
	Haemophagocytic lymphohistiocytosis (familiar or reactive)
	Rosai-Dorfman disease
	Juvenile xanthogranuloma
	Reticulohistiocytoma
Class III.	Malignant histiocytic disorders
	Acute monocytic leukaemia (FAB M5)
	Malignant histiocytosis
	True histiocytic lymphomas

Table 2. The WHO classification of neoplastic disorders of histiocytes and dendritic cells

Class	Syndromes
Dendritic-cell related	Langerhans cell histiocytosis Xanthogranuloma
Macrophage related	Familial and reactive hemophagocytic lymphohistiocytosis (genetic or sporadic) Sinus histiocytosis with massive lymphadenopathy
Malignant disorders	Monocyte related, monocytic leukemia Dendritic-cell related Localized or macrophage related Disseminated (malignant histiocytosis)

3. Pathology and pathophysiology

LC is an important component of the immune system. It is a mononuclear cell of bone-marrow origin that belongs to the dendritic cell family and potent antigen-presenting cell. LCH is characterized by an accumulation of the LC together with different types of inflammatory cells, causing infiltration of the affected tissues. The LCH cells are actively proliferating, they have a round rather than dendritic shape, however, functionally defective in antigen presentation, show a deviant regulation of cell division and the tissue distribution of the disease is quite different from the normal distribution of the LC (5, 6). The morphology of LCH lesion and the clinical signs and symptoms of disease suggest that cytokines may be important in the pathogenesis of the disorder. The close proximity of T cells and LC suggested that the "cytokine cascade" in the lesions resulted from autocrine and paracrine amplification of signals between cell types. This cascade can be linked directly to the development of LCH through recruitment, maturation, and proliferation of LCH cells. The cytokines studied are known to be involved in the development of other characteristic features of LCH, such as fibrosis, necrosis, and osteolysis. T cells and LCH cells are the major local sources of cytokines, which are involved in recruitment and survival of LCs, as well as in their maturation into effector cells contributing to LCH pathogenesis (7-9). The cells of LCH demonstrate the phenotypic characteristics of normal LC, including S100 positivity, CD1a (OKT6) expression, and Birbeck granules (10, 11). However, in contrast to normal LCs, the cells of LCH also express leukocyte adhesion molecules, such as CD11 and CD14, typically expressed in greater density on phagocytic histiocytes (12, 13). The diagnosis of LCH is confirmed by characteristic morphology (Figure 1.) and immunohistochemical expression of CD1a, S-100 (Figure 2.) and CD207 (Langerin) or the presence of Birbeck granules seen by electron microscopy. Langerin is a relative newly recognized monoclonal antibody directed against a type II transmembrane C-type lectin associated with Birbeck granules (14). Langerin expression is present in most cases of LCH. Immunohistochemical determination of Langerin and CD1a may be used to separate LCH from other histiocyte proliferations. Nowadays, electron-microscopic confirmation of the presence of Birbeck granules is rarely used (15).

4. Ethiology

The ethiology of the disease in unknown, and it has been variously classified as neoplastic process, reactive disorder to viral infections, dysfunction of lymphocytes and cytokines; genetic factors; cellular adhesion molecules; and their combinations (7, 16-23). LCH is usually considered a sporadic, non-hereditary disorder. Nevertheless, familiar clustering has been described in a limited number of cases (24-27). One report from Sweden suggests an increased rate of diagnosed histiocytosis in children conceived using in-vitro fertilization (28). A national study in the UK and Ireland proved that two from 94 cases of LCH were reported to have been conceived by in-vitro fertilization (29).

5. Diagnosis

Although clinical findings may be suggestive of the disease, biopsy of suspect lesions is obligatory. The diagnosis of LCH must be set up histopathologically. The Writing Group of the Histiocyte Society identified three levels of confidence in the diagnosis of LCH (3).

1. *A presumptive diagnosis*. This is in a patient with disease clinically consistent with LCH and with histology consistent with the diagnosis.

2. *A diagnosis.* This is established when the histology is consistent with LCH and lesional cells are shown to express S100 and/or α-D-mannosidase activity.

3. *A definitive diagnosis*. This is established when histology is consistent with a diagnosis of LCH and the lesional cells are shown to express CD1a or to have intracytoplasmic Birbeck granules on electron microscopy.

The Writing Group of the Histiocyte Society has developed guidelines to assist in the diagnosis and evaluation of LCH (30). Donadieu et al initiated a quantitative scoring system for LCH disease activity, which is an objective tool for assessing disease severity, both at diagnosis and during follow-up and treatment (31).

6. Clinical presentation

The clinical presentation of LCH is highly variable, from asymptomatic to clinically significant symptoms and consequences. As it can involve nearly every organ of the body, the clinical manifestations depend on the site of the lesions, on the organs and systems involved and whether their function is affected.

The most common sites of involvement in LCH are bone, skin, lymph nodes, lung, bone marrow, liver, spleen, central nervous system (hypothalamic-pituitary region) and gastrointestinal tract. LCH can be divided into two broad categories according to disease extent: single-system (SS) or multi-system (MS) disease.

The historic eponyms of eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease are all examples of the clinical spectrum of LCH but not specific disease entities (32).

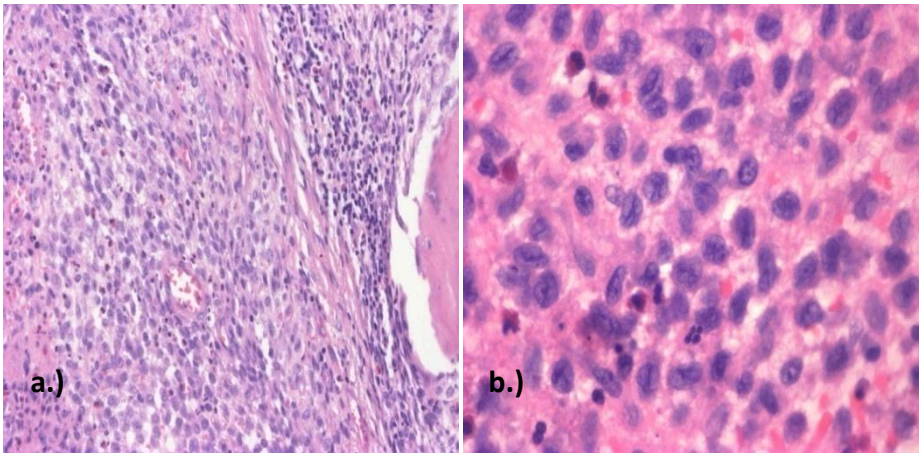

Figure 1. Typical histological manifestation of a bony eosinophilic granuloma [hematoxylin-eosin stain, original magnification x20 (a.), x60 (b.)]

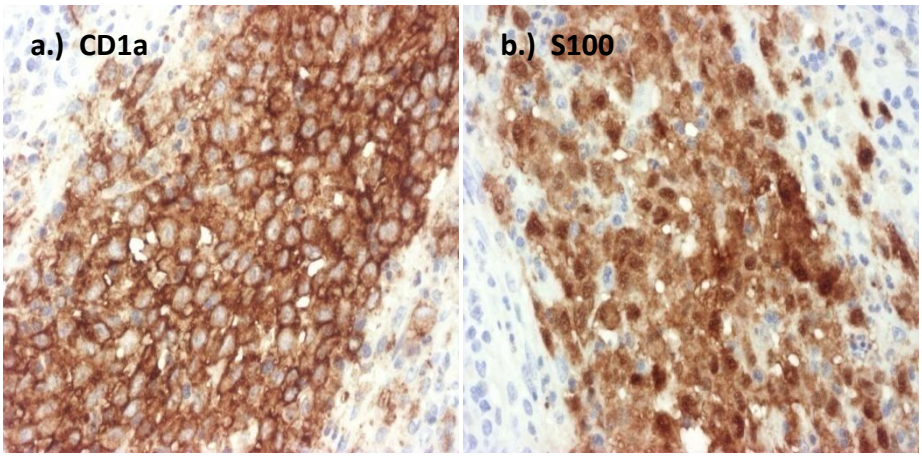

Figure 2. Langerhans cells show strong immunoreactivity for CD1a (a.) and S100 (b.)

Single-system LCH

Patients who have SS involvement should be further subcategorized based upon the number of sites involved: unifocal or multifocal (MF).

The classical presentation of LCH is SS unifocal *bone* disease, previously known as eosinophilic granuloma (33). Presentation is usually a painless lump w/o soft tissue swelling, frequently ascribed to trauma. The classical radiologic finding of bone involvement on plain x-ray is a punched-out lytic, radiolucent lesion (Figure 3.).

The skull being the bone affected most often, followed in frequency by the long bones of the upper extremities and then the flat bones (ribs, pelvis, and vertebrae) (Figure 4.). Osteolytic lesions of long bones can lead to pathological fractures. Lesions of the orbit may present with proptosis and the mastoid with swelling and chronic aural discharges, and can mimic mastoiditis. Purulent otitis media may occur and may be difficult to distinguish from infectious etiologies. Long-term sequelae, including deafness, are reported. Mandibular involvement gives the typical appearance of "floating teeth" within the lytic lesion and is often associated with soft tissue swelling (34). The small bones of the hands and feet are rarely affected (35). In the spine, the lytic process can result in compression and collapse of the vertebral body, causing vertebra plana. LCH is the commonest cause of vertebra plana in children and an associated soft tissue mass may result in significant neurologic impairment due to cord or nerve-root compression (36, 37).

About 15% of children with SS bony disease may be found to have more than one site of involvement at the time of

initial diagnosis (29). Hand-Schüller-Christian disease, the clinical triad of skull lesions, diabetes insipidus (DI) and exophthalmus, is the classical form of MF SS bony disease. In 1921, Hand proposed that his earlier reported patient and those published by Christian and Schüller represented a single entity (38).

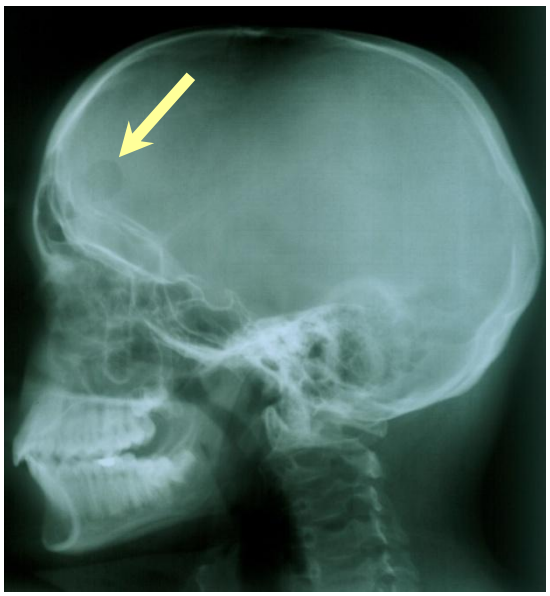

Figure 3. X-ray shows a well-circumscribed punched out lytic, radiolucent lesion in the frontal bone

Skin is the second most commonly affected organ, after bone. In the skin, LCH often simulates seborrhoic dermatitis, with irritation, erythema in the scalp. Other skin manifestations include papules, vesicles, crusted plaques, nodules and purpuric nodules (39). Patients commonly present with a "diaper rash" that is refractory to usual treatments. LCH should be considered whenever seborrhoic dermatitis or diaper dermatitis fails to respond to therapy, or keeps recurring. Patients with skin-only LCH may have spontaneous regression, regression and reactivation in skin or progression, particularly in the infant, to disseminated, sometimes fatal disease. Hashimoto–Pritzker disease (congenital self-healing reticulohistiocytosis) is an uncommon, skin-only LCH associated with spontaneous involution (40). Unfortunately, cuteneous LCH either as SS disease or as part of a MS disease presents a broad spectrum of symptoms and thus is often misdiagnosed.

Lymph nodes draining involved bone or skin may be affected, but occasionally LCH may occur in isolated nodes. The lymphadenopathy is smooth, non-tender and firm. Cervical lymph nodes are affected most often and may reach massive size (41, 42).

Multi-system LCH

For therapeutic purposes MS LCH is divided into two categories based on the risk of mortality from disease. Risk LCH includes all children with disease in two or more organs including visceral organ. Presence (MS-RO+) or absence (MS-RO-) of organ dysfunction of risk organs (bone marrow, spleen, liver and lung) should be determined (43). The disseminated forms are more common in younger ages, MS-RO+ disease most commonly presents under the age of one year with an extensive skin rash and failure to thrive (44). MS disease may demonstrate especially aggressive behaviour in very young children. The eponymous Letterer-Siwe disease classically refers to the infant with diffuse rash, gum disease, hepatosplenomegaly, bone lesions, and often pancytopenia (45). It represents less than 10% of cases of LCH , in this rapidly-progressing form LCs proliferate in many tissues.

In children ***pulmonary*** involvement usually manifests itself as part of MS LCH, isolated pulmonary lesions are unusual. In adults, smoking is invariably associated with pulmonary involvement with LCH. In children under 10 years old disease can regress spontaneously. In older children, pulmonary features are more like those of adults, and progress to a multicystic appearance. Some patients are asymptomatic, diagnosed incidentally because of lung nodules on radiographs; others suffer from tachypnoe, dyspnoe and chronic cough. The acute changes observed in the lung include the development of micronodular infiltrative disease, bullous formation, spontaneous pneumothorax and pleural effusions not attributable to infection (46, 47).

Involvement of the ***central nervous system*** (CNS) occurs in 23-35% of children with LCH, has always been a well-recognized manifestation, often part of MS disease. Histopathologically, LCH may involve the pituitary and hypothalamus by direct extension from a focus in the sphenoid bone. However, histiocytic proliferation also may begin in the brain (48). DI can be sign for LCH due to hypothalamic pituitary axis involvement. DI is the most frequent and well-known CNS manifestation of LCH, which mostly requires life-long hormone replacement therapy. The frequency of DI varies considerably between 10% and 50%. Patients with MS disease and craniofacial involvement at diagnosis, in particular of the "ear," "eye," and the oral region carry a significantly increased risk to develop DI during their course. This risk is augmented when the disease remains active for a longer period or reactivates (49).

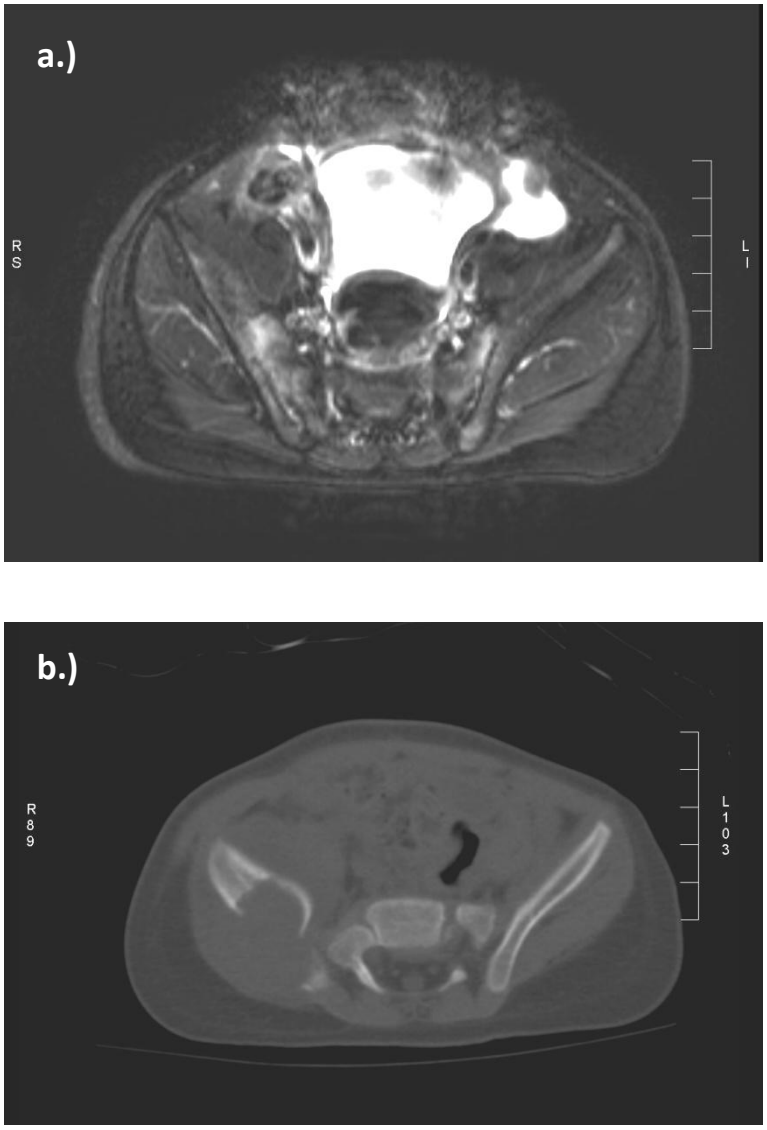

Figure 4. LCH involving the right hip area of a 10 months old boy /a.) pelvic CT b.) T2-weighted MRI axial image/

Both anterior and posterior pituitary function can be affected. Anterior pituitary hormone deficiency is usually permanent, presenting with growth failure, amenorrrhea, precocious or delayed puberty, hypothyroidism, hypocortisolism. Growth hormone deficiency is the most frequent anterior pituitary hormone deficiency and is commonly associated with DI. Growth hormone therapy did not appear to increase the frequency of LCH disease events (50). Infiltration of various areas of the brain gives rise to corresponding signs and symptoms, including cerebellar dysfunction, loss of coordination seizures and those related to increased intracranial pressure (51). CNS degeneration is recognized as a rare but major complication of LCH. Patients who develop endocrine LCH disorders are at a high risk of neurodegenerative LCH and require long-term follow-up (52). CNS involvement deserves special mention because it is a major cause of morbidity and presents a challenge for both diagnosis and treatment (53, 54).

The ***thymus gland*** is commonly involved in LCH, especially in MS disease. Radiologically the gland is enlarged, may contain multiple cysts and has a heterogeneous contrast media enhancement pattern (55, 56).

There are no systematic studies on ***bone marrow*** involvement in LCH. LCs are not normal constituents of the bone marrow, but the presence of excessive numbers of Langerhans cells in the marrow aspirate is not by itself

considered evidence of dysfunction. Although cytopenia is a well established sign of severe LCH, there are no widely accepted criteria and a definition of bone marrow involvement in LCH. Minkov et al propose the combination of conventional aspirate cytology with CD1a staining, as the most reliable tool for bone marrow assessment in LCH (57, 58).

The ***liver*** can be involved directly, by infiltration, and indirectly, by remote effects (59). Liver and spleen involvement is common in MS LCH and usually first manifests by organomegaly. Hepatosplenomegaly in the patient with LCH requires erudite probing. It may herald the presence of organ involvement by LCH, or it may indicate obstructive disease caused by enlarged nodes in the porta hepatis. Both can lead to biliary cirrhosis (41). Liver infiltration may result in tissue damage and increased enzyme levels, jaundice, coagulation disorders, hypoalbuminemia and, rarely, sclerosing cholangitis (60). Gamma glutamyl transpeptidase is a sensitive indicator of liver infiltration. Enlargement of the ***spleen*** may be an additional factor responsible for the depression of one or more of the circulating cellular elements of the blood.

Involvement of the ***gastrointestinal tract*** is probably more common than is clinically recognized, because gastrointestinal involvement by LCH seldom produces prominent clinical manifestations. Lesions in the stomach, small bowel, colon, and rectum have been reported (61-65).

7. Reactivation of the disease

Reactivations occur at a rate of 3–12% for unifocal bone, 11–25% for MF bone and 50–70% for bone as part of MS LCH (66). Unifocal lesions at any site may progress into MS disease in about 10% of patients (67). Reactivation is a frequent and early event in MS-LCH. In most cases, reactivation is an early event, occurring within 2 years after diagnosis. Involvement of risk organs at reactivation is rare and mortality is minimal. The greater the reactivation rate, the higher the incidence of DI and other late complications (49, 68).

8. Treatment

The treatment of patients with LCH has varied over the past century according to the concept of the pathogenesis of the disorder, as well as what potentially therapeutic options were available. For example, when LCH was believed to be secondary to infectious agents, antibiotics were used. The belief that LCH was primarily an immune dysregulatory disorder led to the use of immunosuppressive treatments such as steroids, antithymocyte globulin and cyclosporine. A third approach has been based on the evidence that LCH is a primarily proliferative disorder of dendritic cells and should be treated more like cancer with antineoplastic drugs and radiation therapy. The formation of the International Histiocyte Society in the late 1980s provided the opportunity to accrue sufficient numbers of patients with LCH to begin to establish uniform diagnostic and response criteria to therapy (69).

Treatment of SS disease

There is very high chance of spontaneous resolution and favourable outcome for SS disease involving the skin or bone. In many cases, no therapy or only local therapy is enough, although further treatment may be needed in certain circumstances.

A single ***bone*** lesion tends to resolve spontaneously during a period of months to years. In most single bone lesions, curettage of the centre of it gives diagnostic tissue and usually starts the healing process. Surgical resection is not always necessary and may lead to long-term deformity. Criteria for additional treatment in single lesions include pain, the threat of unacceptable deformity, dysfunction due to the disease itself or secondary to pathological fractures, prevent epiphyseal extension and neurological signs. In these cases, local measures can be used, as surgical resection, intralesional steroids or low-dose irradiation. Intralesional infiltration of corticosteroids is effective in symptomatic localised disease to relieve pain, promote healing, and perhaps prevent complications (70). The use of radiotherapy has decreased considerably, but in case, that the consequences of the disease threaten the function of a critical organ (eg. optic nerve, spinal cord), immediate intervention with low dose radiotherapy should be employed (71, 72). For single or MF lesions, indomethacin, a potent prostaglandin E2 inhibitor has been found top be efficacious (73). A lesion in bones of the anterior and middle cranial fossa or facial bones with a significant risk to intracranial extension or proptosis, is designed “special site” disease (74). As long local therapy is often difficult, these patients should be treated with systemic chemotherapy. If these special site lesions are not adequately treated with prolonged systemic therapy, the chances of developing DI are increased (49, 75). In children with MF bone involvement the use of chemotherapy significantly decreases recurrences (76).

Localised disease of the ***skin***, especially in infants, can spontaneously regress, so in many cases treatment is unnecessary. If treatment is required, application of topical corticosteroids can be tried. Topical mustine is a reasonable treatment option when skin disease is severe or refractory to local steroid or even to systemic treatment (77, 78). Disseminated skin lesions may also be controlled

by phototherapy using ultraviolet A (79, 80). However, these latter two approaches carry risk of being carcinogenic. For extensive skin disease which is causing significant problems, such as chronic superinfection, cosmetic disfigurement or pruritis, systemic therapy may be required. In this situation, pulse steroids or vinblastine are usually effective; etoposide has also been used in this setting (81).

Treatment of MS disease

Patients with MS disease currently systemic therapy is the treatment of choice. The goal of treatment is to relieve clinical symptoms, to increase survival and prevent complications. Therapeutic agents have generally paralleled those used for the treatment of cancers. Two cooperative trials in the 1980s attempted to 'risk group stratify' the intensity of therapy (82, 83). The first systematic large scale study of the treatment of MS LCH was by the DAL group (Deutsche- Arbeitsgemeinschaft für Leukemieforschung und –therapie in Kindersalter). The DAL-HX 83/90 studies were non-randomized clinical trials testing the effectiveness of multi-drug chemotherapy (vinblastine (VBL) and etoposide (VP-16) in conjunction with prednisone (PRED) on MS disease. Patients were classified into three risk groups (MF bone disease, soft tissue involvement without organ dysfunction, and patients with organ dysfunction). The rate of initial complete resolution of disease was high (67-89% in the three groups of patients). Importantly, resolution was rapid, independent of extent of disease, and accompanied by a relatively low rate of recurrence after initial resolution. The incidence of permanent consequences was also lower in these patients (76, 84). These encouraging results have led the Histiocyte Society to establish randomized clinical trials in LCH. The first trial, LCH-I, compared a 6-month course of treatment with either VP-16 or VBL in patients with MS LCH (85, 86). In both groups there was a pulse of high-dose PRED at the beginning of the therapy. Major outcome results showed: 1. VBL and VP-16 for 24 weeks were equally effective in treating disseminated disease, 2. the most predictive prognostic factor for overall survival was the response of patients after 6 weeks of therapy, 3. an incredibly good risk group of patients was identified, characterized by being 2 years of age or older with no pulmonary, hepatosplenic or hematopoietic involvement (their response rate was about 90%, and they had a 100% survival rate at an approximately 6-year follow-up). This trial demonstrates an approximately 65% response rate for all patients. Because overall, thus is a lower rate than obtained using multiagent chemotherapy in the DAL-HX 83/90 studies, the next study (LCH-II) was more intensive (87). LCH-II compared 24 weeks of treatment with VBL/PRED to VP-16/PRED for treatment of MS LCH. There was no difference in survival, number of reactivations, or toxicity between the two regimens. Analysis of data has shown some "special site" lesions of the skull (mastoid, orbit, temporal bones) that are associated with much higher frequency of DI and parenchymal brain lesions. Outcome analysis had established the validity of "risk" organs (liver, spleen, bone marrow, lung), which helped restructure the treatment algorithm for future clinical trials. The above mentioned DAL-HX 83/90 trials, which extended therapy to 1 year and were more intense (additional maintenance therapy with 6-mercaptopurine (6-MP) plus oral methotrexate (MTX) in addition to VBL/PRED pulses) and resulted only a 32% recurrence rate. The ongoing LCH-III study is designed to determine whether prolongation of therapy can reduce reactivations in low and high-risk MS LCH patients (88). It compares 6 and 12 months of therapy with VBL/PRED alone for low-risk patients and treating all high-risk patients for 1 year. The randomization for high-risk patients is between VBL/PRED (Arm A) vs. VBL/PRED/iv. MTX (Arm B) in the first 6 weeks followed by maintenance with VBL/PRED pulses every 3 weeks plus daily oral 6-MP for 1 year with oral MTX weekly for patients in Arm B.

These clinical trials demonstrate that while some patients require very minimal therapeutic interventions, other patients benefit from more aggressive systemic treatment. Another important consequence of these studies is that effective chemotherapeutic treatments have decreased the role of radiation therapy.

Treatment of refractory or recurrent disease

Patients with recurrent disease often respond to the same drugs to which they initially responded. There is no standardized therapy for chronic relapsing, acute refractory and progressive disease. Some alternative approaches have been tested for these patients: cyclosporine-A (89, 90), allogenic hematopoietic stem cell transplantation (91-96), alpha-interferon (97, 98), 2-chlorodeoyadenosine w/o cytosine arabinoside (99-103), cytosine arabinoside w/o vincristine (104), bisphosphonates (105-107), anti-CD1a (108), thalidomide (109-111), interleukin-2 (112), etanercept (113), anti-CD52 (114), imatinib mesylate (115, 116) or zaledronic acid (117). Experience with the use of these agents are ambiguous -not all patients respond, long-term effects in young children are not well-established, so further prospective clinical trials would be necessary to establish the potential therapeutic value of them.

9. Prognosis

The prognosis of LCH is related directly to the number of the organs involved and the presence of organ dysfunction. Prognosis is excellent for SS disease, almost 100%, and for MS disease survival is around 80% (30, 84, 118, 119). MS disease may demonstrate especially aggressive

behaviour in very young children, with the outcome depending largely on the stage of disease and the degree of related organ dysfunction at the time of diagnosis. Young age (less than 2 years) is not an independent risk factor for mortality without involvement of risk organs. Based upon the results of large multi-centre therapeutic trials, it has been shown that the single best prognostic indicator is a patient's response to chemotherapy during the 6-week induction phase. Patients who had not improved by the sixth week (approximately 20%) had only a 17% chance of survival in contrast to the 88% survival of those who had a good initial response (87). Non-responders should be identified early, so that more aggressive therapy may be employed (76, 120-122). Letterer-Siwe disease has poor prognosis: even with aggressive chemotherapy, the 5-year survival is only 50%.

10. Long-term sequelae, long term problems

Permanent consequences (PC) in LCH are irreversible late sequelae related to the disease that may severely impair the quality of life of survivors. PCs are reported in 40-65% of survivors, are more frequent in MS LCH and may become manifest even many years after the initial diagnosis with a wide range of clinical presentations. DI is the most common PC in MS LCH, affecting 35-50% of MS patients. Around 25% patients with SS bone disease developed PC, the majority of which are orthopedic complications directly related to the LCH bone lesion. In addition, other PCs than DI and orthopedic abnormalities are found: hearing loss, different neurological problems (49, 67, 83, 123-130). Lau et al studied the quality of life of children with skeletal LCH and demonstrated that it did not adversely affect the quality of life of survivors, including those with PC who appeared to adapt to their disabilities and medical problems (66). In patients with LCH, malignant neoplasms occur at a frequency greater that could be expected by chance alone, majority of them seem to be therapy-induced (124, 131, 132). Even those patients diagnosed with congenital self-healing LCH may have late relapse or progression to systemic involvement. Consequently, all patients with LCH require long-term follow-up to identify disease recurrence or late-stage complications (133).

11. Conclusion

This article reviews the classification, patho-physiological features, different types of clinical presentation and treatment modalities of LCH in children. It remains a rare, challenging collection of clinical syndromes. Early diagnosis, exact staging, adequate treatment, and close follow-up are critical. Childhood LCH is a well treatable disease and the survival rate is high. There is an improved outcome for most of the patients, but they should not be over-treated. For patients with refractory or relapsed diseases multiagent chemotherapy and prolonged therapy appear to be effective, but alternative therapies are clearly needed. Carefully planned, multidisciplinary follow-up is essential to ensure early recognition of severe late complications

Acknowledgement. The author thanks Dr Z. Karádi and Dr. G. Rudas for the radiological, and for Dr. J. Csomor for the pathological illustrations.

REFERENCES

1. Lichtenstein L. Histiocytosis X; integration of eosinophilic granuloma of bone, Letterer-Siwe disease, and Schuller-Christian disease as related manifestations of a single nosologic entity. AMA Arch Pathol 1953;56:84-102
2. Langerhans P. Über die Nerven der menschlichen Haut. Arch Abl B Pathol 1868;44:325-337
3. Histiocytosis syndromes in children. Writing Group of the Histiocyte Society. Lancet 1987;1:208-209
4. Favara BE, Feller AC, Pauli M, et al. Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol 1997;29:157-166
5. Chu T, Jaffe R. The normal Langerhans cell and the LCH cell. Br J Cancer Suppl 1994;23:S4-10
6. Schmitz L, Favara BE. Nosology and pathology of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:221-246
7. Egeler RM, Favara BE, van Meurs M, Laman JD, Claassen E. Differential In situ cytokine profiles of Langerhans-like cells and T cells in Langerhans cell histiocytosis: abundant expression of cytokines relevant to disease and treatment. Blood 1999;94:4195-4201
8. Laman JD, Leenen PJ, Annels NE, Hogendoorn PC, Egeler RM. Langerhans-cell histiocytosis 'insight into DC biology'. Trends Immunol 2003;24:190-196
9. Kannourakis G, Abbas A. The role of cytokines in the pathogenesis of Langerhans cell histiocytosis. Br J Cancer Suppl 1994;23:S37-40
10. Harrist TJ, Bhan AK, Murphy GF, et al. Histiocytosis-X: in situ characterization of cutaneous infiltrates with monoclonal antibodies. Am J Clin Pathol 1983;79:294-300
11. Rowden G, Connelly EM, Winkelmann RK. Cutaneous histiocytosis X. The presence of S-100 protein and its use in diagnosis. Arch Dermatol 1983;119:553-559

12. Jaffe ES. Malignant histiocytosis and true histiocytic lymphomas. In: Jaffe ES, ed. Surgical pathology of lymph nodes and related organs 2nd ed Philadelphia: WB Saunders; 1995:560
13. McMillan EM, Humphrey GB, Stoneking L, et al. Analysis of histiocytosis X infiltrates with monoclonal antibodies directed against cells of histiocytic, lymphoid, and myeloid lineage. Clin Immunol Immunopathol 1986;38:295-301
14. Geissmann F, Lepelletier Y, Fraitag S, et al. Differentiation of Langerhans cells in Langerhans cell histiocytosis. Blood 2001;97:1241-1248
15. Windebank KP, Spinetta JJ. Do as I say or die: compliance in adolescents with cancer. Pediatr Blood Cancer 2008;50:1099-1100
16. Chen CJ, Ho TY, Lu JJ, et al. Identical twin brothers concordant for Langerhans' cell histiocytosis and discordant for Epstein-Barr virus-associated haemophagocytic syndrome. Eur J Pediatr 2004;163:536-539
17. Zelger B. Langerhans cell histiocytosis: a reactive or neoplastic disorder? Med Pediatr Oncol 2001;37:543-544
18. Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X)--a clonal proliferative disease. N Engl J Med 1994;331:154-160
19. de Graaf JH, Egeler RM. New insights into the pathogenesis of Langerhans cell histiocytosis. Curr Opin Pediatr 1997;9:46-50
20. Corbeel L. Langerhans histiocytosis, haemophagocytic syndrome and Epstein-Barr virus infection. Eur J Pediatr 2004;163:570-571
21. Yu RC, Chu AC. Lack of T-cell receptor gene rearrangements in cells involved in Langerhans cell histiocytosis. Cancer 1995;75:1162-1166
22. Leahy MA, Krejci SM, Friednash M, et al. Human herpesvirus 6 is present in lesions of Langerhans cell histiocytosis. J Invest Dermatol 1993;101:642-645
23. Egeler RM, Annels NE, Hogendoorn PC. Langerhans cell histiocytosis: a pathologic combination of oncogenesis and immune dysregulation. Pediatr Blood Cancer 2004;42:401-403
24. Arico M, Haupt R, Russotto VS, Bossi G, Scappaticci S, Danesino C. Langerhans cell histiocytosis in two generations: a new family and review of the literature. Med Pediatr Oncol 2001;36:314-316
25. Arico M, Nichols K, Whitlock JA, et al. Familial clustering of Langerhans cell histiocytosis. Br J Haematol 1999;107:883-888
26. Baliko Z, Schreiner M, Kishindy KK, Hegedus G, Kosztolanyi G. Different manifestations of langerhans cell histiocytosis affecting two members of a family. Respiration 2000;67:583-585
27. Nezelof C, Basset F. An hypothesis Langerhans cell histiocytosis: the failure of the immune system to switch from an innate to an adaptive mode. Pediatr Blood Cancer 2004;42:398-400
28. Kallen B, Finnstrom O, Nygren KG, Otterblad Olausson P, Wennerholm UB. In vitro fertilisation in Sweden: obstetric characteristics, maternal morbidity and mortality. Bjog 2005;112:1529-1535
29. Salotti JA, Nanduri V, Pearce MS, Parker L, Lynn R, Windebank KP. Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland. Arch Dis Child 2009;94:376-380
30. Broadbent V, Gadner H, Komp DM, Ladisch S. Histiocytosis syndromes in children: II. Approach to the clinical and laboratory evaluation of children with Langerhans cell histiocytosis. Clinical Writing Group of the Histiocyte Society. Med Pediatr Oncol 1989;17:492-495
31. Donadieu J, Piguet C, Bernard F, et al. A new clinical score for disease activity in Langerhans cell histiocytosis. Pediatr Blood Cancer 2004;43:770-776
32. Arceci RJ, Longley BJ, Emanuel PD. Atypical cellular disorders. Hematology Am Soc Hematol Educ Program 2002:297-314
33. Lichtenstein L, Jeffe HL. Eosinophilic granuloma of bone: With report of a case. Am J Pathol 1940;16:595-604
34. Kilborn TN, Teh J, Goodman TR. Paediatric manifestations of Langerhans cell histiocytosis: a review of the clinical and radiological findings. Clin Radiol 2003;58:269-278
35. David R, Oria RA, Kumar R, et al. Radiologic features of eosinophilic granuloma of bone. AJR Am J Roentgenol 1989;153:1021-1026
36. Kamimura M, Kinoshita T, Itoh H, Yuzawa Y, Takahashi J, Ohtsuka K. Eosinophilic granuloma of the spine: early spontaneous disappearance of tumor detected on magnetic resonance imaging. Case report. J Neurosurg 2000;93:312-316
37. Turgut M, Gurcay O. Multi-focal histiocytosis X of bone in two adjacent vertebrae causing paraplegia. Aust N Z J Surg 1992;62:241-244
38. Hand A. Defects of membranous bones, exophthalmos and polyuria in childhood. Am J Med Sci 1921;162:509-515
39. Munn S, Chu AC. Langerhans cell histiocytosis of the skin. Hematol Oncol Clin North Am 1998;12:269-286
40. Hashimoto K, Pritzker MS. Electron microscopic study of reticulohistiocytoma. An unusual case of

congenital, self-healing reticulohistiocytosis. Arch Dermatol 1973;107:263-270
41. Egeler RM, D'Angio GJ. Langerhans cell histiocytosis. J Pediatr 1995;127:1-11
42. Edelweiss M, Medeiros LJ, Suster S, Moran CA. Lymph node involvement by Langerhans cell histiocytosis: a clinicopathologic and immunohistochemical study of 20 cases. Hum Pathol 2007;38:1463-1469
43. Weitzman S, Egeler RM. Langerhans cell histiocytosis: update for the pediatrician. Curr Opin Pediatr 2008;20:23-29
44. Kusumakumary P, James FV, Chellam VG, Ratheesan K, Nair MK. Disseminated Langerhans cell histocytosis in children: treatment outcome. Am J Clin Oncol 1999;22:180-183
45. Abt AF, Denenholz EJ. Letterer-Siwe disease: splenohepatomegaly associated with widespread hyperplasia of nonlipid-storing macrophages: discussion of the so-called reticulo-endothelioses. Amer J Dis Child 1936;51:499-522
46. Ha SY, Helms P, Fletcher M, Broadbent V, Pritchard J. Lung involvement in Langerhans' cell histiocytosis: prevalence, clinical features, and outcome. Pediatrics 1992;89:466-469
47. Smets A, Mortele K, de Praeter G, Francois O, Benoit Y, Kunnen M. Pulmonary and mediastinal lesions in children with Langerhans cell histiocytosis. Pediatr Radiol 1997;27:873-876
48. Schmidt S, Eich G, Geoffray A, et al. Extraosseous langerhans cell histiocytosis in children. Radiographics 2008;28:707-726
49. Grois N, Potschger U, Prosch H, et al. Risk factors for diabetes insipidus in langerhans cell histiocytosis. Pediatr Blood Cancer 2006;46:228-233
50. Donadieu J, Rolon MA, Pion I, et al. Incidence of growth hormone deficiency in pediatric-onset Langerhans cell histiocytosis: efficacy and safety of growth hormone treatment. J Clin Endocrinol Metab 2004;89:604-609
51. Rosenfield NS, Abrahams J, Komp D. Brain MR in patients with Langerhans cell histiocytosis: findings and enhancement with Gd-DTPA. Pediatr Radiol 1990;20:433-436
52. Donadieu J, Rolon MA, Thomas C, et al. Endocrine involvement in pediatric-onset Langerhans' cell histiocytosis: a population-based study. J Pediatr 2004;144:344-350
53. Grois N, Prayer D, Prosch H, Lassmann H. Neuropathology of CNS disease in Langerhans cell histiocytosis. Brain 2005;128:829-838
54. Grois N, Tsunematsu Y, Barkovich AJ, Favara BE. Central nervous system disease in Langerhans cell histiocytosis. Br J Cancer Suppl 1994;23:S24-28
55. Junewick JJ, Fitzgerald NE. The thymus in Langerhans' cell histiocytosis. Pediatr Radiol 1999;29:904-907
56. Sumner TE, Auringer ST, Preston AA. Thymic calcifications in histiocytosis X. Pediatr Radiol 1993;23:204-205
57. Minkov M, Potschger U, Grois N, Gadner H, Dworzak MN. Bone marrow assessment in Langerhans cell histiocytosis. Pediatr Blood Cancer 2007;49:694-698
58. McClain K, Ramsay NK, Robison L, Sundberg RD, Nesbit M, Jr. Bone marrow involvement in histiocytosis X. Med Pediatr Oncol 1983;11:167-171
59. Jaffe R. Liver involvement in the histiocytic disorders of childhood. Pediatr Dev Pathol 2004;7:214-225
60. Kaplan KJ, Goodman ZD, Ishak KG. Liver involvement in Langerhans' cell histiocytosis: a study of nine cases. Mod Pathol 1999;12:370-378
61. Nanduri VR, Kelly K, Malone M, Milla P, Pritchard J. Colon involvement in Langerhans' cell histiocytosis. J Pediatr Gastroenterol Nutr 1999;29:462-466
62. Sabri M, Davie J, Orlando S, Di Lorenzo C, Ranganathan S. Gastrointestinal presentation of Langerhans cell histiocytosis in a child with perianal skin tags: a case report. J Pediatr Gastroenterol Nutr 2004;39:564-566
63. Iwafuchi M, Watanabe H, Shiratsuka M. Primary benign histiocytosis X of the stomach. A report of a case showing spontaneous remission after 5 1/2 years. Am J Surg Pathol 1990;14:489-496
64. Hait E, Liang M, Degar B, Glickman J, Fox VL. Gastrointestinal tract involvement in Langerhans cell histiocytosis: case report and literature review. Pediatrics 2006;118:1593-1599
65. Shima H, Takahashi T, Shimada H. Protein-Losing Enteropathy Caused by Gastrointestinal Tract-Involved Langerhans Cell Histiocytosis. Pediatrics 2010;125:e426-e432
66. Lau LM, Stuurman K, Weitzman S. Skeletal Langerhans cell histiocytosis in children: permanent consequences and health-related quality of life in long-term survivors. Pediatr Blood Cancer 2008;50:607-612.
67. Willis B, Ablin A, Weinberg V, Zoger S, Wara WM, Matthay KK. Disease course and late sequelae of Langerhans' cell histiocytosis: 25-year experience at the University of California, San Francisco. J Clin Oncol 1996;14:2073-2082
68. Minkov M, Steiner M, Potschger U, et al. Reactivations in multisystem Langerhans cell

histiocytosis: data of the international LCH registry. J Pediatr 2008;153:700-705
69. Arceci RJ. The histiocytoses: the fall of the Tower of Babel. Eur J Cancer 1999;35:747-767
70. Egeler RM, Thompson RC, Jr., Voute PA, Nesbit ME, Jr. Intralesional infiltration of corticosteroids in localized Langerhans' cell histiocytosis. J Pediatr Orthop 1992;12:811-814
71. Gramatovici R, D'Angio GJ. Radiation therapy in soft-tissue lesions in histiocytosis X (Langerhans' cell histiocytosis). Med Pediatr Oncol 1988;16:259-262
72. Ugarriza FL, Cabezudo JM, Porras LF, Lorenzana LM. Solitary eosinophilic granuloma of the cervicothoracic junction causing neurological deficit. Br J Neurosurg 2003;17:178-181
73. Munn SE, Olliver L, Broadbent V, Pritchard J. Use of indomethacin in Langerhans cell histiocytosis. Med Pediatr Oncol 1999;32:247-249.
74. Woo KI, Harris GJ. Eosinophilic granuloma of the orbit: understanding the paradox of aggressive destruction responsive to minimal intervention. Ophthal Plast Reconstr Surg 2003;19:429-439
75. Abla O, Weitzman S, Minkov M, et al. Diabetes insipidus in Langerhans cell histiocytosis: When is treatment indicated? Pediatr Blood Cancer 2009;52:555-556
76. Gadner H, Heitger A, Grois N, Gatterer-Menz I, Ladisch S. Treatment strategy for disseminated Langerhans cell histiocytosis. DAL HX-83 Study Group. Med Pediatr Oncol 1994;23:72-80
77. Hoeger PH, Nanduri VR, Harper JI, Atherton DA, Pritchard J. Long term follow up of topical mustine treatment for cutaneous langerhans cell histiocytosis. Arch Dis Child 2000;82:483-487
78. Sheehan MP, Atherton DJ, Broadbent V, Pritchard J. Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. J Pediatr 1991;119:317-321
79. Sakai H, Ibe M, Takahashi H, et al. Satisfactory remission achieved by PUVA therapy in Langerhans cell hisiocytosis in an elderly patient. J Dermatol 1996;23:42-46
80. Neumann C, Kolde G, Bonsmann G. Histiocytosis X in an elderly patient. Ultrastructure and immunocytochemistry after PUVA photochemotherapy. Br J Dermatol 1988;119:385-391
81. Arceci RJ. Treatment options--commentary. Br J Cancer Suppl 1994;23:S58-60
82. Lahey ME. Prognostic factors in histiocytosis X. Am J Pediatr Hematol Oncol 1981;3:57-60
83. Ceci A, de Terlizzi M, Colella R, et al. Langerhans cell histiocytosis in childhood: results from the Italian Cooperative AIEOP-CNR-H.X '83 study. Med Pediatr Oncol 1993;21:259-264
84. Minkov M, Grois N, Heitger A, Potschger U, Westermeier T, Gadner H. Treatment of multisystem Langerhans cell histiocytosis. Results of the DAL-HX 83 and DAL-HX 90 studies. DAL-HX Study Group. Klin Padiatr 2000;212:139-144
85. Ladisch S, Gadner H, Arico M, et al. LCH-I: a randomized trial of etoposide vs. vinblastine in disseminated Langerhans cell histiocytosis. The Histiocyte Society. Med Pediatr Oncol 1994;23:107-110.
86. Gadner H, Grois N, Arico M, et al. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 2001;138:728-734
87. Gadner H, Grois N, Potschger U, et al. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood 2008;111:2556-2562
88. LCH Study Group of the Histiocyte Society. LCH III - Treatment Protocol of the Third International Study for Langerhans Cell Histiocytosis. Protocol 2001
89. Zeller B, Storm-Mathisen I, Smevik B, Lie SO. Multisystem Langerhans-cell histiocytosis with life-threatening pulmonary involvement--good response to cyclosporine A. Med Pediatr Oncol 2000;35:438-442
90. Minkov M, Grois N, Braier J, et al. Immunosuppressive treatment for chemotherapy-resistant multisystem Langerhans cell histiocytosis. Med Pediatr Oncol 2003;40:253-256
91. Nagarajan R, Neglia J, Ramsay N, Baker KS. Successful treatment of refractory Langerhans cell histiocytosis with unrelated cord blood transplantation. J Pediatr Hematol Oncol 2001;23:629-632
92. Suminoe A, Matsuzaki A, Hattori H, Ishii S, Hara T. Unrelated cord blood transplantation for an infant with chemotherapy-resistant progressive Langerhans cell histiocytosis. J Pediatr Hematol Oncol 2001;23:633-636
93. Conter V, Reciputo A, Arrigo C, Bozzato N, Sala A, Arico M. Bone marrow transplantation for refractory Langerhans' cell histiocytosis. Haematologica 1996;81:468-471
94. Cooper N, Rao K, Goulden N, Webb D, Amrolia P, Veys P. The use of reduced-intensity stem cell transplantation in haemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis. Bone Marrow Transplant 2008;42 Suppl 2:S47-50

95. Akkari V, Donadieu J, Piguet C, et al. Hematopoietic stem cell transplantation in patients with severe Langerhans cell histiocytosis and hematological dysfunction: experience of the French Langerhans Cell Study Group. Bone Marrow Transplant 2003;31:1097-1103
96. Kudo K, Ohga S, Morimoto A, et al. Improved outcome of refractory Langerhans cell histiocytosis in children with hematopoietic stem cell transplantation in Japan. Bone Marrow Transplant 2009;doi: 10.1038/bmt.2009.245
97. Jakobson AM, Kreuger A, Hagberg H, Sundstrom C. Treatment of Langerhans cell histiocytosis with alpha-interferon. Lancet 1987;2:1520-1521
98. Bellmunt J, Albanell J, Salud A, Espanol T, Morales S, Sole-Calvo LA. Interferon and disseminated Langerhans cell histiocytosis. Med Pediatr Oncol 1992;20:336-337
99. Morimoto A, Ikushima S, Kinugawa N, et al. Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis: Results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. Cancer 2006;107:613-619
100. Bernard F, Thomas C, Bertrand Y, et al. Multi-centre pilot study of 2-chlorodeoxyadenosine and cytosine arabinoside combined chemotherapy in refractory Langerhans cell histiocytosis with haematological dysfunction. Eur J Cancer 2005;41:2682-2689
101. Stine KC, Saylors RL, Williams LL, Becton DL. 2-Chlorodeoxyadenosine (2-CDA) for the treatment of refractory or recurrent Langerhans cell histiocytosis (LCH) in pediatric patients. Med Pediatr Oncol 1997;29:288-292
102. Rodriguez-Galindo C, Jeng M, Khuu P, McCarville MB, Jeha S. Clofarabine in refractory Langerhans cell histiocytosis. Pediatr Blood Cancer 2008;51:703-706
103. Weitzman S, Braier J, Donadieu J, et al. 2'-Chlorodeoxyadenosine (2-CdA) as salvage therapy for Langerhans cell histiocytosis (LCH). results of the LCH-S-98 protocol of the Histiocyte Society. Pediatr Blood Cancer 2009;53:1271-1276.
104. Allen CE, Flores R, Rauch R, et al. Neurodegenerative central nervous system Langerhans cell histiocytosis and coincident hydrocephalus treated with vincristine/cytosine arabinoside. Pediatr Blood Cancer;54:416-423
105. Brown RE. Bisphosphonates as antialveolar macrophage therapy in pulmonary langerhans cell histiocytosis? Med Pediatr Oncol 2001;36:641-643
106. Farran RP, Zaretski E, Egeler RM. Treatment of Langerhans cell histiocytosis with pamidronate. J Pediatr Hematol Oncol 2001;23:54-56
107. Kamizono J, Okada Y, Shirahata A, Tanaka Y. Bisphosphonate induces remission of refractory osteolysis in langerhans cell histiocytosis. J Bone Miner Res 2002;17:1926-1928
108. Kelly KM, Pritchard J. Monoclonal antibody therapy in Langerhans cell histiocytosis--feasible and reasonable? Br J Cancer Suppl 1994;23:S54-55
109. Thomas L, Ducros B, Secchi T, Balme B, Moulin G. Successful treatment of adult's Langerhans cell histiocytosis with thalidomide. Report of two cases and literature review. Arch Dermatol 1993;129:1261-1264
110. Misery L, Larbre B, Lyonnet S, Faure M, Thivolet J. Remission of Langerhans cell histiocytosis with thalidomide treatment. Clin Exp Dermatol 1993;18:487
111. McClain KL, Kozinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. Pediatr Blood Cancer 2007;48:44-49
112. Hirose M, Saito S, Yoshimoto T, Kuroda Y. Interleukin-2 therapy of Langerhans cell histiocytosis. Acta Paediatr 1995;84:1204-1206
113. Henter JI, Karlen J, Calming U, Bernstrand C, Andersson U, Fadeel B. Successful treatment of Langerhans'-cell histiocytosis with etanercept. N Engl J Med 2001;345:1577-1578
114. Jordan MB, McClain KL, Yan X, Hicks J, Jaffe R. Anti-CD52 antibody, alemtuzumab, binds to Langerhans cells in Langerhans cell histiocytosis. Pediatr Blood Cancer 2005;44:251-254
115. Montella L, Insabato L, Palmieri G. Imatinib mesylate for cerebral Langerhans'-cell histiocytosis. N Engl J Med 2004;351:1034-1035
116. Wagner C, Mohme H, Kromer-Olbrisch T, Stadler R, Goerdt S, Kurzen H. Langerhans cell histiocytosis: treatment failure with imatinib. Arch Dermatol 2009;145:949-950
117. Montella L, Merola C, Merola G, Petillo L, Palmieri G. Zoledronic acid in treatment of bone lesions by Langerhans cell histiocytosis. J Bone Miner Metab 2009;27:110-113
118. Muller J, Garami M, Hauser P, et al. Hungarian experience with Langerhans cell histiocytosis in childhood. Pediatr Hematol Oncol 2006;23:135-142
119. Morimoto A, Ishida Y, Suzuki N, et al. Nationwide survey of single-system single site Langerhans cell histiocytosis in Japan. Pediatr Blood Cancer 2010;54:98-102
120. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between

1983 and 1993. The French Langerhans' Cell Histiocytosis Study Group. Arch Dis Child 1996;75:17-24
121. Minkov M, Grois N, Heitger A, Potschger U, Westermeier T, Gadner H. Response to initial treatment of multisystem Langerhans cell histiocytosis: an important prognostic indicator. Med Pediatr Oncol 2002;39:581-585
122. Esterly NB, Maurer HS, Gonzalez-Crussi F. Histiocytosis X: a seven-year experience at a children's hospital. J Am Acad Dermatol 1985;13:481-496
123. Bernstrand C, Sandstedt B, Ahstrom L, Henter JI. Long-term follow-up of Langerhans cell histiocytosis: 39 years' experience at a single centre. Acta Paediatr 2005;94:1073-1084
124. Haupt R, Nanduri V, Calevo MG, et al. Permanent consequences in Langerhans cell histiocytosis patients: a pilot study from the Histiocyte Society-Late Effects Study Group. Pediatr Blood Cancer 2004;42:438-444.
125. Mittheisz E, Seidl R, Prayer D, et al. Central nervous system-related permanent consequences in patients with Langerhans cell histiocytosis. Pediatr Blood Cancer 2007;48:50-56
126. Nanduri VR, Pritchard J, Levitt G, Glaser AW. Long term morbidity and health related quality of life after multi-system Langerhans cell histiocytosis. Eur J Cancer 2006;42:2563-2569. Epub 2006 Sep 2567.
127. Nanduri VR, Bareille P, Pritchard J, Stanhope R. Growth and endocrine disorders in multisystem Langerhans' cell histiocytosis. Clin Endocrinol (Oxf) 2000;53:509-515
128. Grois NG, Favara BE, Mostbeck GH, Prayer D. Central nervous system disease in Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:287-305
129. Nanduri VR, Lillywhite L, Chapman C, Parry L, Pritchard J, Vargha-Khadem F. Cognitive outcome of long-term survivors of multisystem langerhans cell histiocytosis: a single-institution, cross-sectional study. J Clin Oncol 2003;21:2961-2967
130. Nanduri V, Tatevossian R, Sirimanna T. High incidence of hearing loss in long-term survivors of multisystem Langerhans cell histiocytosis. Pediatr Blood Cancer 2010;54:449-453
131. Egeler RM, Neglia JP, Arico M, et al. The relation of Langerhans cell histiocytosis to acute leukemia, lymphomas, and other solid tumors. The LCH-Malignancy Study Group of the Histiocyte Society. Hematol Oncol Clin North Am 1998;12:369-378
132. Haupt R, Fears TR, Heise A, et al. Risk of secondary leukemia after treatment with etoposide (VP-16) for Langerhans' cell histiocytosis in Italian and Austrian-German populations. Int J Cancer 1997;71:9-13
133. Longaker MA, Frieden IJ, LeBoit PE, Sherertz EF. Congenital "self-healing" Langerhans cell histiocytosis: the need for long-term follow-up. J Am Acad Dermatol 1994;31:910-916.