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*Langerhans Cell Histiocytosis in childhood*

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1. Introduction

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.

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).

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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, S100 (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 a-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 seborrhoeic 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 seborrhoeic 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, cutaneous 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).
Both anterior and posterior pituitary function can be affected. Anterior pituitary hormone deficiency is usually permanent, presenting with growth failure, amenorrhea, 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 hepatitis. 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 organ systems 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 epiphysseal extension and neurological signs. In these cases, local measures can be used, as surgical resection, intraläsional steroids or low-dose irradiation. Intraläsional 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-chlorodeoxyadenosine 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.

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