

## LANGERHANS CELL HISTIOCYTOSIS

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Langerhans cell histiocytosis is a rare disease in children, its initial presentation is variable, the clinical course, prognosis and survival are mostly unpredictable. LCH is a proliferative disorder where pathologic Langerhans cells accumulate in a variety of organs. Historically, the nomenclature regarding this entity has been confusing because the disease was subcategorized as eosinophilic granuloma, Hand-Schüller-Christian disease and Abt-Letterer-Siwe disease, simply based upon the different clinical manifestations. This nomenclature remains valuable and preserves the important historic perspective of these disorders. Currently, LCH can be divided according to disease extent and localisation of the disease at the time of evaluation. The following clinical categories have been defined: single- or multi-system disease. This article summarizes the classification, history, pathophysiology, diagnostic criteria, different clinical manifestations, treatment, prognosis and long-term sequelae of LCH in children.

**Key words:** Histiocytosis ■ Children ■ Langerhans cell histiocytosis ■ Pediatric oncology

### Introduction

Histiocytic disorders are defined as disorders caused by an abnormal accumulation of cells of the mononuclear phagocytic system (MFS), consisting of dendritic cells and macrophages. They include a wide range of different conditions that affect both children and adults (1). Histiocytic disorders are classified in the group of hematological diseases since dendritic and monocyte/macrophage cells are the main pathological substrate. There is still nosological confusion regarding histiocytic disorders considering the fact that histiocytes have many different

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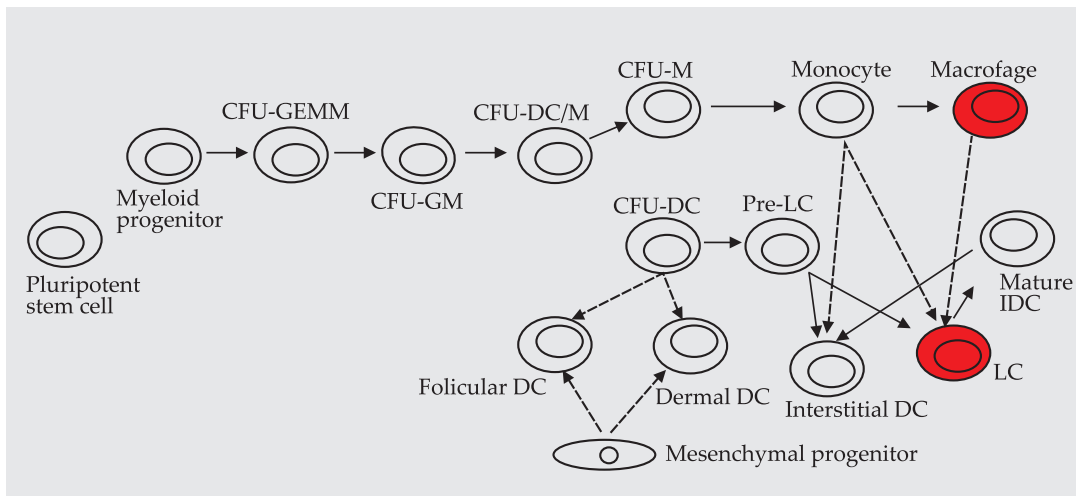
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metabolic potential and line orientations, their ubiquitous nature, their role in the regulation of hematopoiesis, the role of immune and inflammatory response as well as the uncertain ontological origin of dendritic and monocyte/macrophage cells. The same principle was formed as in the classification of lymphoid disorders and the latest classification of histiocyte disorders is based on information about their cellular origin and biological behaviour, based on pathological and immunochemical criteria (2, 3) (Figure 1).

A working group of the International Society for Histiocytosis (HS) and the Committee for Histiocytic/Reticulum Cell Proliferation of the World Health Organization (WHO) continuously monitor new laboratory and clinical findings and accordingly pronounce a classification of histiocytic disorders (1,4). Histiocytic disorders are divided into two main groups: "diseases of different biological behaviour" and "malignant disorders" which are then subclassified to dendritic (antigen presenting cells) or monocyte-macrophage (antigen processing) cells disorders (Table 1).

### History

The history of histiocytosis dates back to 1865, when Dr Thomas Smith published the case of four year old child with impetigo and three large bone defects on the calvary. At the same time Paul Langerhans described non-pigmented dendritic cells of the epidermis, which he considered initially to be nerveous and then corrected himself later. These unique histiocytes are now called Langerhans cells. Alfred Hand in 1893, Artur Schüller in 1915 and Henry Christian in 1919 independently of each other described patients with exophthalmos, polyuria and thirst (5, 6, 7). There is also the eponym, Hand Schüller Christian disease, which is still used to describe a child over two years old with symptoms of exophthalmos, diabetes insipidus (DI) and bone lesions of the skull. Dr Erich Letterer 1924 described a six-month old infant with fulminant nonleukemic reticuloendothelial system disorder (8). Nine years later, the Swedish physician Sture Siwe described similar symptoms in a 1.5 year old child. His



Legend: CFU-GEMM- Colony Forming Unit-Granulocyte, Eritocyte, Megakariocyte, Monocyte, CFU-GM - Colony Forming Unit-Granulocyte, Monocyte, CFU-DC/M - Colony Forming Unit-Denritic cell/Monocyte, CFU-M - Colony Forming Unit-/Monocyte, LC – Langerhans cell, IDC - interdigitating dendritic cell

**Figure 1** Histiocyte development

**Table 1** Classification of Histiocytic Disorders (1)

|  |
|--|
| Disorders of varied biologic behaviour                                   |
| Dendritic cell related   |
| Langerhans cell histiocytosis  |
| Secondary dendritic cell processes                                       |
| Juvenile xanthogranuloma and related disorders                           |
| Solitary histiocytomas of various dendritic cell phenotypes              |
| Macrophage related   |
| Hemophagocytic syndromes   |
| Primary Hemophagocytic lymphohistiocytosis                               |
| Secondary hemophagocytic syndromes                                       |
| Infection-associated   |
| Malignancy-associated  |
| Other  |
| Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) |
| Solitary histiocytoma with macrophage phenotype                          |
| <b>Malignant disorders</b>   |
| Monocyte-related   |
| Leukemias (FAB and revised FAB classifications)                          |
| Monocytic leukemia M5A and B   |
| Acute myelomonocytic leukemia M4   |
| Chronic myelomonocytic leukemia  |
| Dendritic cell– related histiocyte sarcoma (localized or disseminated)   |
| Macrophage-related histiocytic sarcoma (localized or disseminated)       |

work provided an overview of the literature and the disease is defined pathologically as a separate entity. He described the presence of marked splenomegaly, hepatomegaly, lymphadenopathy, localized bone tumours, bleeding tendency, anaemia and secondary generalized hyperplasia of macrophages, which do not contain lipids, in various organs (9). A few years later, Arthur Abt and Deneholz Edward published a paper showing 9 patients and a disease named Letterer Siwe. In 1940 two similar works appeared which described bone lesions. The first paper was written by the doctors, Sadao Otani and Ehrlich Josef, who named the disease as solitary granuloma of the bone. The second paper was written by Louis Lichtenstein and Henry Jaffe who called the disease eosinophilic granuloma (10, 11). In 1953 Luis Liechtenstein

introduced the term histiocytosis X, bringing under the same heading eosinophilic granuloma, Hand-Schüller-Christian and Letterer-Siwe disease, indicating that they are the same clinical entity with a similar pathophysiological mechanism of origin. The next significant discovery was by Birbeck (Clive Stanley Michael Birbeck) in 1961, with a description of characteristic organelles seen under an electron microscope, initially called Langerhans bodies. Today they are called Birbeck granules. Christian Nezelof, a pathologist, finally in 1973 introduced the name Langerhans Cell Histiocytosis - LCH. He also became a founding member and the first president of the International Histiocyte Society (HS) established in 1985 in Philadelphia. This society is actively working on the standardization of nomenclature, clinical

and pathological criteria and provides the basic guidelines and recommendations for the treatment of this disease (12).

### **Etiopathogenesis**

The pathogenesis of LCH is unclear. Still there is debate whether LCH is a neoplasm or a reactive disorder or immune dysfunction. The often spontaneous remission of the disease argues against its malignant nature which occurs even in patients with multiple changes in multiple organs, extensive secretion of numerous cytokines, a so-called cytokine storm, and the generally high survival rates of patients (2, 10, 13, 14). Also a number of genetic studies of DNA ploidy, karyotype, single nucleotide polymorphisms - SNP, characterization of gene expression (array based comparative genomic hybridization) have not shown the existence of significant and consistent abnormalities. These observations support the theory that LCH is a reactive disorder. On the other hand, pathological tissue infiltration of cells with clonal character, the occasionally lethal outcome of the disease and cytostatic therapy, which is primarily used for the treatment of malignant disease, supports the theory that LCH is a neoplasm. Clonality was identified in localized and in the multisystemic form of the disease (15). The identification of clonality does not mean malignancy. Pathologically, Langerhans cells are characterized by functionally immature immunophenotypes that can mature *in vitro* after exposure to CD40 ligand (16). There are data showing that there are certain specific regions of chromosomes that exhibit microsatellite instability and loss of heterozygosity, which is characteristic of cancer cells (17). Significant matches of genetic changes are observed in twins with LCH (18). Furthermore, an aberrant expression of proteins that influence the promotion of or block the cell cycle

was detected in LCH (19). However, the typical genetic disorders found in LCH cells have not been identified in other cells. All these data suggest that LCH is a clonal proliferative disorder of the immature Langerhans cells, with varying clinical behaviour. Recent studies of gene expression of CD207+ (LCH cell marker) LCH lesions and epidermal CD207+ cells have showed a difference in expression over 2000 genes. These differences were found in genes involved in cell cycle regulation, apoptosis, signalling pathways and myeloid differentiation, but not in the expression of proliferative markers, so we can assume that the LCH is a disease of abnormal cell accumulation (20). The extensive variation in gene expression between these cell populations has prompted speculation that LCH cells develop from a population of cells that are different from the LCH cells of the epidermis. The hypothesis is that dendritic cells are recruited to specific anatomical sites where they interact with T cells, and they arise as a consequence of local immune modulation responsible for the characteristic lesions of LCH. Some evidence suggests an important role of immune dysfunction in the pathogenesis of LCH. In fact, immunohistochemical analysis of LCH lesions indicates that immature cells stimulate the expansion of LCH polyclonal regulatory T cells. These regulatory T cells can then inhibit the immune system (the action of interleukin (IL) -10) by preventing the regeneration of LCH lesions (21). The finding of high serum levels of proinflammatory IL 17A cytokine in patients with LCH has encouraged speculation that IL-17A is also involved in the pathogenesis of the disease. Further exploration of this phenomenon has shown that IL-17A causes the fusion of dendritic cells/Langerhans cells in multinuclear giant cells, which then recruit other inflammatory cells and cause local destruction of tissue, creating the characteristic lesions of LCH. However, these findin-

gs have not been confirmed and the role of IL-17A in the pathogenesis of LCH remains still controversial (21, 22). Some studies have shown that the expression of vascular endothelial growth factor - VEGF, Bcl-2 family proteins and FADD, FLICE and FLIP protein in the Fas signalling path may be involved in the pathogenesis of LCH. E-cadherin-beta-katenin-Wnt signalling pathway is also involved in the pathogenesis of LCH. Disturbance of regulation of E-cadherin is related to disease dissemination (23).

### Epidemiology

The prevalence of LCH is approximately 1:50,000, with an incidence of about 5 - 10 cases per year per million children under the age of 15. Male children are affected more often, the relationship of the disease is 2:1 in favour of male children. LCH affects primarily infants and children, while in adults the disease occurs significantly less frequently (3).

### Clinical Manifestations

Symptoms and signs of LCH vary depending on which organs are infiltrated with Langerhans and associated immunoreactive cells. Bone, skin, teeth, gums, ears, endocrine organs, lungs, liver, spleen, lymph nodes, bone marrow, CNS (pituitary/hypothalamic regions) and other organs may be affected by the pathological process and manifest dysfunction as a result of cellular infiltration. With this wide spectrum of clinical manifestations, the division is fairly traditional. Forms such as eosinophilic granuloma, Hand-Schüller-Christian disease and Abt-Letterer-Siwe disease only have historical significance but are still often used in everyday clinical practice.

Multifocal or solitary eosinophilic granuloma is mainly seen in older children and young adults, usually within the first three decades of life. The incidence peaks between

5 and 10 years. This form of LCH is approximately 60% to 80% of LCH.

Hand-Schüller-Christian disease is a multisystemic form of the disease, seen in all age groups, most often described in younger children, aged 2 to 5 years. This form of the disease is found in 15% to 40% of all patients with LCH.

Abt-Letterer-Siwe disease is the rarest (10% of cases) and most severe form of LCH. Typically, patients are younger than 2 years with a rough seborrhoeic and eczematoid skin rash which sometimes is purpuric, involving mostly the head, ear canal, abdominal wall, intertriginated region, face and neck.

Today, patients with LCH, for decisions about treatment, are stratified into one of two groups depending on the number of affected organs: the involvement of an organ/organic system, Single System, SS-LCH or multisystem organ involvement - MS-LCH (Table 5).

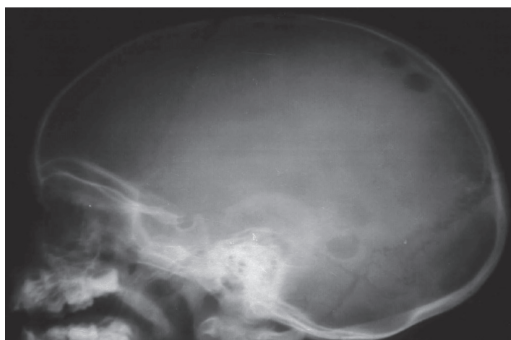
### Bones

Bone lesions are usually manifested by swelling and pain of the affected region during exercise. The most often affected are the flat bones, skull, ribs, pelvis and shoulder blade, while the hand and feet bones are rarely affected. Complications of osteolytic lesions are anatomically defined, for example, chronic middle ear inflammation is caused by mastoid and petrous infiltration of the temporal bone. Inflammation of the external ear canal are also seen (24). Exophthalmos is due to the presence of a tumour in the orbital cavity and infiltration of the roof and lateral wall orbital cavity (skeletal involvement, although not always found). Infiltration of the orbit can cause loss of vision or strabismus. Periorbital infiltration may cause proptosis. The skull can be extensively infiltrated, with many irregular fields that give the appearance of the so-called geographical fields. The long bones and lumbosacral regions of the spinal column are less commonly affected, usu-

ally the front of the vertebral body. The spread of infiltrate into the medullary canal of the long bones can cause destruction of the cortex which stimulates the formation of periosteal reaction and swelling of the soft tissue.

Differential diagnoses include Ewing's sarcoma, bone lymphoma, benign bone tumour and, cysts and infections. Oral involvement is manifested with gum and palatal infiltration. Dental radiography can show characteristic "floating teeth". The erosion of the gingiva causes premature eruption, decay and tooth loss.

Bone involvement is seen in 80-100% of LCH patients. Radiography is the first method of choice for the detection of bone lesions. The lesions are sharply marginated, round or oval, and usually have edges that give the appearance of depth (24) (Figure 2).



**Figure 2** Skull bone lesions

### Skin

The skin is affected in one third of children with LCH (25). The areas most often affected are the scalp and folds (groin, perianal area, neck and axilla). The rash can be maculopapular or nodulopapular. Ulcers can occur, especially in intertriginous regions. Ulcers and other skin damage may be the entry place for the infection which can cause sepsis. Isolated cutaneous forms of LCH have been described in children and adults. They occur

in about 10% of children, mainly in male infants. Spontaneous regression is common in such cases. Rarely, the disease may be manifested only by deep subcutaneous nodules, as previously described Hashimoto-Pritzker syndrome. LCH of the skin is often misdiagnosed as seborrheic dermatitis and delayed diagnosis is common.

### Lymph nodes

The lymph nodes are affected at the presentation of the disease in less than 10% of patients and usually as part of disseminated disease or as part of the local involvement of the skin or bones. The neck lymph nodes are affected most often. Sometimes a massive increase in the lymph nodes is seen. LCH may have a strictly nodal presentation and should not be identified with sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman disease. This form of LCH is characterized by a significant increase in several groups of lymph nodes, with little or no other signs of disease (24).

### Bone marrow

Although pancytopenia is common in patients with a disseminated form of the disease, bone marrow infiltration of Langerhans cells (not normally found in bone marrow) is rarely seen (26).

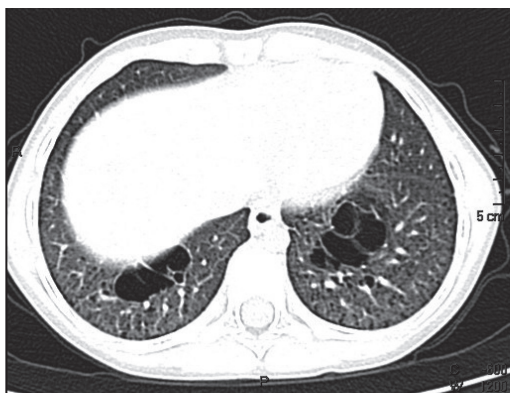
### Liver and spleen

Although enlargement of the liver is common in patients with the disseminated form of the disease, the causes of this increase are not yet fully understood. Systemic inflammatory hyperactivation of the monocyte macrophage system can lead to Kupffer cell hyperplasia. Liver infiltration by Langerhans cells has to be histologically documented because in some cases it is the main cause of liver en-

largement. Liver enlargement can be caused by massive periportal lymphadenomegaly with cholestatic hepatomegaly. Persistent infiltration of the liver initially causes mild cholestasis, portal infiltration, and then cholangitis, which can progress to fibrosis (sclerosing cholangitis) and biliary cirrhosis. This damage can occur regardless of whether the disease is active. Liver transplantation may be indicated in patients with LCH (27). An enlarged spleen is seen in at least 5% of patients at the beginning of the disease.

### Lungs

Pulmonary disease is diagnosed in almost half of children with MS-LCH. Isolated pulmonary LCH is usually seen in young adults in the third or fourth decade of life and occasionally in adolescents. The clinical picture varies. It can be detected on radiography during clinical assessment of patients. Coughing and dyspnea are commonly seen. The disease can have severe, chronic course and is often clinically manifested as pneumothorax. Smoking has a significant impact on the occurrence of primary pulmonary histiocytosis. The course of the disease is usually mild, although fulminant forms are described. The radiograph picture varies, from diffuse infiltration as bilateral interstitial pneumonia, to changes which are described as a "honeycomb lung" (Figure 3).



**Figure 3** Lung LCH

### Gastrointestinal system

Involvement of the gastrointestinal tract is not common and ranges from 2% to 3% (28). Although some children with a systemic form of LCH lose weight, intestinal malabsorption is not always the cause. Vomiting, diarrhoea or enteropathy with protein loss are rare and gastrointestinal LCH has to be confirmed histologically, by bowel biopsy

### Insipid diabetes and endocrine system

Diabetes insipidus (DI) occurs in 5% to 40% of patients with LCH. Most cases of DI occur in children with the systemic form of the disease and bone involvement of the skull and orbit. Polydipsia and polyuria as initial symptoms of LCH are found in less than a third of children. Most children develop DI within four years of diagnosis. DI occurs due to infiltration of the hypothalamus with or without involvement of the pituitary gland. DI can occur at any time during the LCH disease. Patients with LCH should be familiar with the symptoms of DI in order to avoid serious complications due to dehydration and electrolyte imbalance (29). Low growth is seen in up to 40% of children with the systemic form of LCH. The chronic course of the disease and steroid therapy play an important role in the development of this disorder. Short stature may also be due to damage of the anterior pituitary gland and growth hormone deficiency, which can occur in at least half of patients with early signs of pituitary dysfunction. Other endocrine manifestations may occur, such as hypogonadism and hyperprolactinemia. Infiltration of the pancreas and thyroid gland has also been described (30).

### Central nervous system

Involvement of the central nervous system (CNS), without the hypothalamus and pituitary region is among the worst forms of LCH and is seen in less than 1% of children with LCH. Most patients with CNS involvement

also have skull, orbit or mastoid infiltration. Nuclear magnetic resonance imaging is the method of choice for identification of CNS lesions. The hypothalamus-pituitary region is the most common site of lesions in the CNS, followed by the cerebellum, pons and cerebral hemispheres. Lesions of the basal ganglia, spinal cord and optic nerve have also been described. CNS involvement is usually manifest many years after onset. Infiltrative and atrophic lesions of the cerebellum and pons often lead to severe sequelae, which are characterized primarily as neurodegenerative. The aetiology of this neurodegenerative process is unknown but is believed to be an immune-mediated paraneoplastic response that occurs as a consequence of cytokines due to occult cerebellar infiltration of LCH cells (31).

### **Prognosis**

Prognosis depends on the number of affected organs and the degree of dysfunction of involved organs (32). Adolescents or adults with a solitary bone lesions have the best prognosis, while infants with a large number of affected organs have the worst prognosis. Children older than 2 years have a good prognosis, whereas patients younger than two years have less favourable outcome. Age itself is not of prognostic significance but younger children usually have more affected organs, which show some degree of dysfunction. Involvement of less than four organ systems is a relatively good prognostic sign. Dysfunction of the liver, spleen and bone marrow is an extremely important predictor of unfavourable outcome (24). When LCH occurs after 65 years of age, the prognosis is poor regardless of the number and type of affected organs. In assessing the outcome of the disease it is necessary to distinguish organ dysfunction from organ involvement without functional disorder (eg, hypoproteinemia, hyperbilirubinemia vs hepatomegaly), because involvement is not itself always a negative prognostic sign as a dysfunction.

### **Histopathology**

The diagnosis of LCH is based on histological and immunophenotypic examination of biopsymaterial, usually bone, affected by a pathological process. LCH is characterized by a pathological lesion of mixed cellular infiltrate. The main characteristic of the disease is the proliferation and accumulation of immature Langerhans cells, which do not show cellular atypia characteristic of most malignant diseases and variable number of macrophages, T cells, eosinophils and multinucleate giant cells. Langerhans cells are characterized by Birbeck granules, which are seen ultrastructurally as pentalaminar tennis racquet-shaped structures (33). The classic diagnostic criteria, defined in 1987, is the presence of Birbeck granules (BG) on the electron microscope and immunochemical demonstration of CD1+. Today it is easier to prove the presence of BG by immunochemical staining of langerin (CD207). Langerin is a relatively new monoclonal antibody directed to a type II transmembrane C-type lectin. It was shown that Langerin expression confirms the presence of BG and ultrastructural demonstration of these granules is no longer set as the gold standard for definitive diagnosis of LCH. These criteria formally verify HS (34, 35).

The histopathological findings in patients with localized and systemic clinical forms of the disease are the same and attempts to define favourable and unfavourable histologic forms have failed. Lesions in patients with eosinophilic granuloma are similar if not identical, to those in the multisystem disease (24).

### **Differential diagnosis**

Differential diagnosis of LCH depends on the clinical presentation of the disease. It includes immunodeficiency syndromes with graft-versus-host disease (GVHD), viral infections, infiltrative malignancies such as leukaemia, lymphoma or metastasis of solid



tumours, storage disease, congenital infections, benign and malignant bone tumours and cysts, papular xanthoma etc.

### Work up

After the diagnosis, along with medical history and physical examination it is necessary to perform complete, clinical, laboratory and radiological investigations in order to identify all the affected places (Table 2). The medical history must be detailed and particular attention should be paid to pain, swelling, skin changes, otorrhoea, ear, fever, loss of appetite, diarrhoea, changes in activity level, polydipsia, polyuria, fatigue, smoking, changes in behaviour and neurological changes. Physical examination must also be detailed, it is necessary in all patients to determine pubertal status, to perform dental examination, the characterization of changes to the skin, to pay attention to the presence of jaundice, oedema, lymphadenopathy, secretions from the ear, lesions in the genital area and anal

mucosa, tachypnoea, intercostal feeding space, ascites, liver and spleen size. For neurological evaluation (the presence of cranial nerve abnormalities, loss of deep muscle reflexes, visual disturbances and cerebellar dysfunction) it is necessary to do a detailed neurological examination and appropriate specific tests. Laboratory tests include complete blood count, routine biochemical analysis, coagulation treatment, abdominal ultrasound and radiography of the complete skeleton. For a definitive diagnosis of DI, measurement of osmolality and electrolytes in serum and urine before and after a few hours of water deprivation should be performed. The level of vasopressin may be measured in order to document the vasopressin deficiency. Testing of infants and young children should be carefully monitored in hospital conditions to avoid severe dehydration. Finally, desmopressin acetate (DDAVP) is applied in order to achieve an increase in urine concentration. These tests are done in all children with LCH. Other tests, such as dental panoramic

**Table 2** Recommended baseline evaluation upon diagnosis LCH (35)

|   |
|---|
| Full blood count  |
| Haemoglobin, white blood cell and differential count, platelet count                        |
| Blood chemistry:  |
| - Total protein, albumin, bilirubin, ALT(SGPT), AST(SGOT), alkalinephosphatase, $\gamma$ GT |
| - BUN, creatinine, electrolytes   |
| - Ferritin  |
| Coagulation studies   |
| - INR/PT, APTT/PTT, fibrinogen  |
| Early morning urine sample  |
| - Specific gravity and osmolality   |
| Abdominal ultrasound  |
| - Size and structure of liver and spleen  |
| Chest radiograph  |
| - Skeletal radiograph survey*   |

INR= International Normalized Ratio; PT= Prothrombin time; APTT= activated partial thromboplastin time; PTT= partial thromboplastin time.

\*Functional imaging such as bone scan is optional and can be performed in addition to skeletal survey. PET scan has proven to be the most sensitive functional test used in the identification of LCH lesions and in evaluating patient response to therapy. However, PET scan is currently expensive and not widely available (36)

**Table 3** Laboratory investigations, imaging and specialized clinical assessments recommended for specific clinical scenarios

| Indication  | Assessment/Test  |
|---|--|
| - Bicytopenia, pancytopenia or persistent single cytopenia  | - Bone marrow aspirate or trephine biopsy  |
| - Liver dysfunction   | - Liver biopsy only recommended if there is clinically significant liver involvement and the result will alter treatment (i.e. to differentiate between active LCH and sclerosing cholangitis) |
| - Lung involvement (abnormal CXR or symptoms/signs suggestive for lung involvement)   | - Lung high resolution computed tomography (HR-CT) Lung function test (if age appropriate)   |
| - Abnormal lung CT and findings not characteristic for LCH  | - Bronchoalveolar lavage (BAL): >5 % CD1a positive cells in BAL fluid is diagnostic in non-smokers   |
| - Suspected craniofacial bone lesions including maxilla and mandible  | - Lung biopsy (if BAL is not diagnostic)   |
| - Suspected vertebral lesions   | - MRI of head*   |
| - Suspected endocrine abnormality (i.e. short stature, growth failure, polyuria, polydipsia, hypothalamic syndromes, precocious or delayed puberty) | - MRI of spine (to exclude spinal cord compression)  |
| - Aural discharge or suspected hearing impairment/mastoid involvement   | - Endocrine assessment (including water deprivation test and dynamic tests of the anterior pituitary and thyroid)  |
| - Unexplained chronic diarrhoea, failure to thrive, or evidence of malabsorption  | - Formal hearing assessment, MRI of head*, HR-CT of temporal bone  |
|   | - Endoscopy and biopsy   |

\*MRI of head should include the brain, hypothalamus - pituitary axis and all craniofacial bones. The use of intravenous contrast (Gadolinium – DTPA) is mandatory.

X radiography, pulmonary function tests, CT and NMR of the brain and middle ear, and bone marrow examination should be done if there is suspected involvement of certain organs (Table 3).

The criteria for the definition risk organ involvement gave HS (Treatment guidelines 2009) (35).

## Therapy

As our knowledge about the effectiveness of certain therapeutic modalities progressed so the therapy changed. The generally accepted standard for initial treatment of patients with LCH is to use the least toxic therapy. Patients with the diagnosis of potentially life-threat-

ning signs and symptoms or development of serious pathological conditions require the application of aggressive treatment. Such an individual approach to treatment emphasizes the need for implementation of clinical protocols in which the optimal therapy is applied to patients by aligning risk groups based on carefully balanced risk assessment. HS has initiated a randomized clinical trial in which to test the effectiveness of certain drugs, vinblastine and corticosteroids first, and then to classify patients into risk groups to predict the outcome of disease. Based on the results of several clinical studies, a widely accepted system for the disease classifying has been developed and treatment guidelines were published in 2009 (35). (Table 4 and 5).

**Table 4** Definition of risk organ involvement

|   |  |
|---|--|
| Hematopoietic involvement: (with or without bone marrow involvement*) | At least 2 of the following: <ul style="list-style-type: none"> <li>• Anaemia: haemoglobin &lt;10 g/dl, infants &lt;9 g/dl (not due to other causes; e.g. iron deficiency)</li> <li>• Leukocytopenia: leukocytes &lt;4.0</li> <li>• Trombocitopenija: trombociti &lt;100×10<sup>9</sup>/l</li> </ul> |
| Spleen involvement  | • Enlargement >2 cm below costal margin in the midclavicular line  |
| Liver involvement   | • Enlargement >3 cm below costal margin in the midclavicular line and/or liver dysfunction (i.e. hypoproteinemia <55 g/l, hypoalbuminemia <25 g/l not due to other causes) and/or histopathological diagnosis  |
| Lung involvement  | • Typical changes on HR-CT and/or histopathological/cytological diagnosis  |

\*Bone marrow involvement is defined as demonstration of CD1a positive cells on bone marrow smears.

**Table 5** Clinical classification of LCH (35)

|   |
|---|
| Multisystem LCH (MS-LCH)  |
| - Two or more organs/systems involved, with or without involvement of “Risk Organs” |
| Single System LCH (SS-LCH)  |
| - One organ/system involved (unifocal or multifocal)                                |
| - Bone: unifocal (single bone) or multifocal (>1 bone)                              |
| - Skin  |
| - Lymph node (not the draining lymph node of another LCH lesion)                    |
| - Lungs   |
| - Hypothalamic-pituitary/Central nervous system                                     |
| - Other (e.g. thyroid, thymus)  |

**Table 6** Localisations and disease extent categories are considered indications for systemic therapy

|  |
|--|
| SS LCH –with “CNS-risk” lesions                    |
| SS LCH –with multifocal bone lesions (MFB)         |
| SS LCH – with “special site” lesions               |
| MS-LCH - with/without involvement of “risk organs” |

### Initial treatment - the involvement of one organ system (SS-LCH)

There is a very high likelihood of spontaneous resolution and a favourable outcome for patients with SS-LCH disease with skin or bone involvement. Local therapy is sufficient. Further treatment may be necessary only in certain circumstances (Table 6).

Bone lesions heal spontaneously, usually within a few months to years. In most cases of bone lesions, curettage and biopsy leads

to diagnosis and the healing process begins. Surgical resection is usually not necessary and can lead to deformity. The criteria for further treatment are pain, risk of deformity, dysfunction due to infiltration or secondary pathological fractures, prevention of epiphyseal extensions and neurological signs. In these cases local measures might be applied, such as surgical resection, intralesional corticosteroids or low doses of radiation. Intralesional infiltration of corticosteroids is effective in relieving pain and for the process of healing

(37). Today, radiation therapy is reserved for emergencies, to prevent serious damage such as optic nerve or spinal cord compression (38)

**Special sites** - In certain situations, such as cervical vertebra and the second vertebral lesions with intraspinal propagation of soft tissue, abnormal tissue is found on functionally and anatomically critical sites. Local therapy (biopsy and curettage) of the region carries a significant risk of a life-threatening condition and permanent nerve damage. Those lesions are considered as "special places". Application of chemotherapy in isolated involvement of the special sites is indicated. Vertebral lesions, such as vertebra plana (spondylitis in which the vertebral body is reduced to a sclerotic disk) without infiltration of soft tissues do not come into this group.

**CNS risk lesions** - Recent findings indicate that long-term involvement of the skull bones (except the calvary, such as the craniofacial bones, involvement of the eyes, ears and mouth predispose to DI appearance (39). Craniofacial bone involvement includes changes in the orbital, temporal, mastoid, sphenoidal, zygomatic or ethmoidal bones, maxilla and paranasal sinuses, or cranial fossa, with intracranial propagation of soft tissue.

Eye involvement is defined if there are proptosis, exophthalmos or lesions in the orbit, zygomatic or sphenoidal bones. Ear involvement is defined if there is external otitis, otitis media, otorrhoea or changes in the temporal bone, mastoid or petrous bone. Involvement of the oral cavity is defined if there is a lesion on the oral mucosa, gums, palatal bone, maxilla and mandible.

Patients with the MFB (multifocal bone involvement) form of the disease have a favourable prognosis (survival of 100%), but they also have a high propensity for reactivation of disease (30 - 50%) and permanent consequences. The probability that these patients will develop DI, other endocrinopathies

and parenchymal diseases of the brain is 40%. The greatest risk for severe disabilities is parenchymal brain disease in the basal ganglia and cerebellum. The therapy in this group of patients is used for the prevention of reactivation of disease, disability and permanent consequences. Data from nonrandomized prospective DAL-HX 83 and DAL-HX 90 studies show the favourable effect of chemotherapy, vinblastine, prednisone and 6-mercaptopurine in reducing the incidence of reactivation of the disease and frequency of permanent consequences compared to historical controls (40). Based on these data, the HS recommended chemotherapy in these patients

Disease localised in the skin, especially in infants, most often resolves spontaneously so treatment is not necessary. In severe forms, corticosteroids are applied locally. Disseminated and very severe forms of skin refractory to corticosteroids are treated with phototherapy, topical mustin application or even chemotherapy (41).

### **Initial treatment - a multisystem disease**

According to preliminary data of LCH-III clinical trials, a total of 12 months treatment reduces the risk of disease reactivation compared with shorter (six months) treatment. Patients with MS-LCH have a variable disease outcome. Patients with good response to initial therapy and without involvement of risk organs have a good prognosis. A combination of prednisone and vinblastine has been proven effective and minimally toxic therapy and it is recommended as the standard for initial therapy in all patients in whom systemic therapy is necessary. Patients with RO involvement who react poorly to initial therapy, especially if there is a clinical disease progression, have a very poor prognosis (42, 43). For such patients, the use of early intensive therapy is warranted.

The initial therapy of vinblastine and prednisone for 6 weeks is recommended for all patients with MS-LCH, irrespective of whether they are affected by RO. Further therapy depends on the initial response to the applied treatment. Evaluation of the disease after 6 weeks must be performed. Patients with RO involvement who do not have a favourable therapeutic response are candidates for application of various types of intensive care. The same is recommended for patients who develop disease progression during therapy and involvement of RO. For patients without involvement of the RO without improvement on initial therapy and patients with RO involvement at diagnosis, who have a favourable therapeutic response, it is advisable to continue treatment with prednisone and vinblastine. It is also recommended that all patients who have complete resolution of disease after the initial 6 or 12 weeks therapy should continue maintenance therapy. Maintenance therapy consists of vinblastine and prednisone pulses every 3 weeks with continuous application of 6-mercaptopurine (6MP) for a total of 12 months of treatment.

In patients with RO involvement where there is no improvement after 12 weeks of therapy, the recommended therapy is salvage therapy while in patients without the involvement of RO second-line therapy is advised, that is, the use of alternative medicines.

## **Second line treatment**

### **Salvage therapy**

Currently, there are no recommendations for optimal treatment of severe progressive MS-LCH, which does not respond to standard therapy. Promising results with 2-chlorodeoxyadenosine (2-CDA, Cladribine, Leustatin) and cytarabine (Ara-C) combinations have been published and also of bone marrow transplantation after reduced

intensity conditioning (RIC-SCT) (44, 45). These results must be confirmed by prospective clinical studies. Treatment of patients with CNS involvement depends on the type of change, the extensiveness of the changes and prior therapy, and must be conducted on a strictly individual basis.

### **Second line therapy in patients without RO involvement**

The optimal treatment for this group of patients is not yet known. Intralesional use of corticosteroids, the combination of vincristine, cytarabine and prednisone and 2-CDA as monotherapy were effective.

### **Long-term consequences of LCH, permanent sequelae**

Long-term sequelae of LCH and its treatment can severely impair the quality of life of survivors. Consequences according to some statistics are seen in 40 - 65% of survivors. They are more frequent in MS LCH and can become manifest many years after initial diagnosis with a wide spectrum of clinical presentations. DI is the most common complication seen in 35 - 50% of MS LCH. About 25% of patients with bone changes develop mainly orthopaedic complications. Better diagnostics, patient stratification and application of less invasive treatment techniques, without the use of radiotherapy, without the extensive surgical interventions done in the past, will contribute to a fall in the frequency of these complications. Hearing loss, various neurological problems, short stature, dental disorders, deficiency of sex and thyroid hormones are also complications that may be seen in LCH (39, 46, 47). Secondary malignancies are more common than in the general population and are most likely caused by chemotherapy. Long-term monitoring of these patients is necessary in order to prevent reactivation and late complications of the disease (48).

## Conclusion

Nearly a century has passed since histiocytic disorders were recognized and only recently in the last few decades has seen major gains in knowledge regarding the underlying defects, clinical presentation, therapy and outcome of the histiocytic disorders. Still many questions remains unanswered concerning epidemiology, pathophysiology and optimal

treatment. Further experimental investigations and clinical trials will ultimately lead to a better understanding and, subsequently, to a better treatment and improved outcome of patients with Langerhans cell histiocytosis.

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