LCH: The Symptoms, Diagnosis and Treatment

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Overview of LCH epidemiology, pathology, symptoms, diagnosis and treatment

Langerhans cell histiocytosis (LCH) is a challenging disease and may be manifested in a variety of ways, ranging from a spontaneously regressing solitary lesion of bone to a multisystem, life-threatening disorder. Some forms require little if any treatment, and others need aggressive therapy.

Major advances have been made in defining the clinical and pathological criteria needed for diagnosis and treatment. Standardization of nomenclature and speaking one histiocytic language have made it possible to accumulate and record coherent data and have initiated cooperative international studies of the natural evolution of LCH and its response to treatment.

Incidence

LCH may occur at any age, although 50 percent of the cases are probably diagnosed in children. There is no significant sex bias. Some forms of LCH, however, are age dependent. Isolated bone lesions are often seen in children between 5 and 15 years old, and systemic LCH is more common in children under 2 years of age.

Pathology and Etiology

The diagnosis of LCH is based on hematologic and histologic criteria established by the international Histiocyte Society in 1987. The lesions of LCH are polymorphous, usually vary little from site to site and patient to patient, and feature a monoclonal population of CD1a+ histiocytes with a phenotype akin to that of cells of the antigen-presenting Langerhans cells family.
T-cells, macrophages, and eosinophils are variably present. CD1a positivity and/or Birbeck granules by electron microscopy are required for definitive diagnosis of LCH. In contrast to normal Langerhans cells, LCH cells are actively proliferating, have a round rather than dendritic shape, and express several contrasting antigenic markers. Investigative research has provided new insights into the disease.

Although clonality of the CD1a+ cell has been found in all LCH lesions studied and reported to date, its significance remains to be clarified. Clonality, however, argues for LCH as a neoplastic disorder with varied biological behavior and does not necessarily indicate a malignant process, as clonal cells have been detected in several nonmalignant disorders.

Until now, clonality has not improved our knowledge and has not led to any therapeutic implications. Cytokines, soluble secondary products of lymphocytes and monocytes, regulate cell growth and differentiation of immunocompetent and hematopoietic stem cells by binding to specific receptors on target cells. Activators can cause these cells to release some cytokines or to cease secreting others, which leads to cell transformation, proliferation, phagocytosis, and other functions.

Langerhans cells are subject to be regulated by cytokines. The morphology of LCH lesions and the clinical signs and symptoms of disease suggest that cytokines may be important in the pathogenesis of the disorder. Recently work of our own indeed demonstrated high expression of a large panel of cytokines in LCH lesions. T-cells and LCH cells proved to be the predominant sources of this "cytokine storm." Actually, most of the studied cytokines were of T-cell origin, suggesting a prominent role for this cell in the disease.
Several of the cytokines produced in LCH lesions directly contribute to pathological sequelae of LCH, including fibrosis, bone resorption, and necrosis.

**Clinical Manifestations**

Symptoms may vary. Besides normal symptoms such as fever, weight loss and fatigue, the following symptoms might develop, isolated or in combination.

The involvement of each organ will be described separately, but in extensive forms of LCH, multiple organs may be affected.

**Skin**

Cutaneous lesions are often the first signs of LCH and frequently become manifest as scaly, erythematous, seborrhea-like brown to red papules, especially pronounced in intertriginous zones (behind the ears and in the axillary, inguinal and perineal areas). Superficial ulceration is a secondary process; weeping lesions similar to eczema are then seen.

When the skin is the only organ involved, the patient is usually a male infant less than 1 year of age, and spontaneous regression occurs frequently. Skin lesions may be the sole manifestation of LCH, but careful assessment is needed to ensure that they are not part of more extensive disease.

**Bone Lesions**

Painful swelling is the most common initial sign, the skull being the bone affected most often, followed in frequency by the long bones of the upper extremity and then flat bones (ribs, pelvis and vertebrae). Adjacent soft tissue swelling may occur. Proptosis from lesions of the orbital wall may also be present.

When the mastoid process is involved, the findings can mimic mastoiditis. Extensive lesions of the middle ear cause destruction of the ossicles and deafness. LCH of the jaw is also associated with contiguous soft tissue swelling (floating teeth, gingival swelling, fractures or pain). In the spine, the lytic process can result in compression and collapse of the vertebral body, causing vertebra plana.

**Lymph Nodes**

Lymph node involvement in LCH may be seen as a reaction to bone or skin lesions. However, it may also be present as a solitary lesion or part of the more extensive type.

**Bone Marrow**
Langerhans cells do not appear to be a normal constituent of the bone marrow, although other dendritic cells can be seen. Pancytopenia caused by bone marrow dysfunction is usually associated with gross hepatosplenomegaly and a poor prognosis.

**Liver and Spleen**

Hepatosplenomegaly in a patient with LCH requires further evaluation. It may be primary involvement, as well as a secondary result, for example, due to enlarged lymph nodes in the porta hepatis. Ascites caused by hypoalbuminemia is a clinical sign of liver dysfunction, which may also be manifested by jaundice and a prolonged prothrombin time.

The 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.

**Lungs**

Tachypnea with rib retractions is often the first and only clinical sign. With time, increasing numbers of cysts form "honeycomb lungs," and in later stages, large bullae. A spontaneous pneumothorax can result from rupture of underlying bullae. Emphysematous changes, along with increasing amounts of interstitial fibrosis, may occur in the final phase of pulmonary LCH.

**Gastrointestinal Tract**

The most common sign is "failure to thrive," which is caused by malabsorption. Other symptoms include vomiting, diarrhea (with or without blood) and protein-losing enteropathy.

**Endocrine Glands**

Diabetes insipidus, the most common endocrinopathy, can occur before, concurrently with, or subsequent to the development of lesions in extracranial sites. In a low number of patients, growth retardation resulting from anterior pituitary involvement and growth hormone deficiency is seen.

**Central Nervous System**

Until recently, an acute sign of central nervous system involvement, such as intracranial hypertension or seizures, was thought to be rare. However, lately it was shown that 10 percent of patients could develop central nervous system involvement or central nervous system impairment as late sequelae.

The symptoms may vary from progressive ataxia to dysarthria, nystagmus, hyperflexia, dysdiadochokinesia, dysphagia, blurred vision, or cranial nerve symptoms.
Staging and Prognostic Factors

Although the diagnosis of LCH might be considered for clinical reasons only, a pathological confirmation is needed. Because of the importance of the number of organs involved for prognosis and morbidity, one can divide the patients into two different categories: patients with an isolated lesion (of skin, lymph node, or bone) and patients with a disseminated form of LCH in which two or more organ systems are involved.

In order to decide which organs are involved and to what extent, the Histiocyte Society developed a standardized evaluation for every patient with LCH. Criteria have been designed for laboratory and radiographic examinations at the time of diagnosis, as well as at the time of followup. The age of the patient at diagnosis of LCH is a prognostic factor: The younger the patient, the worse the prognosis. Besides very young age and the number of organs involved, organ dysfunction is also a bad prognostic factor. The hematopoietic system, liver and lungs are the crucial organs in this disease.

Laboratory and Radiographic Interventions

When LCH is suspected, extensive laboratory evaluation is needed. Besides white blood count, liver function and coagulation studies are requested. Because of the possibility of diabetes insipidus, urine osmolality measurement after an overnight water deprivation is needed. Radiographic evaluations include a chest radiograph, as well as a skeletal radiographic survey. With specific indications of LCH, the following laboratory investigations should be carried out:

Skin

Besides the typical signs and symptoms of skin involvement (if this is the only organ involved), a skin biopsy is required to make definite diagnosis.

Bone

A plain radiograph typically reveals single or multiple irregular, marginated, lytic lesions of bone. At diagnosis, a skeletal radiograph survey is needed, and in followup, one can make a specific radiograph of the bone involved. For oral involvement, a panoramic dental radiograph of mandible and maxilla is necessary. Furthermore, consultation regarding oral surgery is needed.

For aural discharge or deafness, an otolaryngology consultation and audiogram are required. If positive, a followup test is needed every six months.

Lymph Node
If a lymph node is the only organ involved, again a lymph node biopsy is needed to make the diagnosis. In followup, a physical examination with specific x-ray is needed. A chest x-ray may diagnose additional lymph node involvement.

**Bone Marrow**

Anemia, leukopenia, or thrombocytopenia requires a bone marrow aspirate and trephine biopsy. If positive, this needs followup after six months.

**Liver/Spleen**

In case of liver dysfunction, including hypoproteinemia not caused by protein-losing enteropathy, a liver biopsy is required. This might be needed to differentiate between active LCH and cirrhosis. A followup test is only needed when all other diseases have resolved but liver dysfunction persists. Radiographic followup of the visceral organs in the abdomen by ultrasound might be required.

**Lung**

The diagnosis of pulmonary LCH suggested by a diffuse micronodular pattern on chest films can easily be confirmed by electron microscopy of the alveolar fluid obtained by bronchoalveolar lavage. With time, increasing numbers of cysts form "honeycomb lungs" and in later stages, large bullae.

In the case of an abnormal chest x-ray or by tachypnea and intercostal retractions, pulmonary function tests might be required. The diagnosis of pulmonary involvement can be made by the detection of Langerhans cells in bronchoalveolar lavage. If not, a lung biopsy might be needed.

**Gastrointestinal Tract**

Unexplained chronic diarrhea or failure to thrive may lead to small bowel biopsies.

**Endocrine**

Short stature, growth failure, diabetes insipidus, hypothalamic syndromes, galactorrhea, and precocious or delayed puberty are all indications for an extensive endocrine evaluation. Confirmation of diabetes insipidus by an appropriate water-deprivation test and by measurement of urinary arginine vasopressin is essential, as partial defects may occur and may spontaneously remit.

Gadolinium-enhanced magnetic resonance imaging has proved to be revealing. Thickening of the hypothalamic pituitary stalk region and absence of the posterior pituitary "bright" signal are commonly seen.

**Central Nervous System**
Also here, the MRI has added immeasurably to our understanding of the process. The indications for an MRI scan of the brain/hypothalamic-pituitary axis are hormonal, visual or neurologic abnormalities.

**Treatment**

Treatment of patients with LCH depends on the extent of disease. The number of organs involved and the implications of that involvement are of governing importance. Patients with apparently restricted LCH need careful staging of their disease to ensure that the lesions are not part of a more extensive process. The clinical course is generally benign, and spontaneous remissions are common. Initially, treatment of patients with LCH apparently localized to the skin may be unnecessary, because in many cases, mainly in infants, the lesions regress spontaneously. The first step in treatment is the application of topical steroids.

A single bone lesion tends to resolve spontaneously during a period of months to years. Biopsy of the lesion, necessary to confirm the diagnosis, may initiate healing with or without curettage. Criteria for additional treatment include intense pain and the threat of unacceptable deformity or disability. Intraleisonal infiltration of corticosteroids is effective and convenient.

The approaches to the treatment of extensive LCH, with or without organ dysfunction, have been almost as varied as the clinical manifestations of the disease. Most patients have been treated with systemic chemotherapeutic agents due to the progressive nature of generalized LCH. Studies have demonstrated the efficacy of a variety of chemotherapeutic agents, either as monotherapy or in combination. Physicians are urged to participate and to enroll patients in the international randomized clinical studies, organized through the auspices of the Histiocyte Society.

**Conclusion**

Establishing standardized nomenclature, clinical and pathologic criteria and treatment approaches through the Histiocyte Society has made it possible to fine-tune treatment options and focus on followup. The endeavors of physicians and other investigators over the last 10 to 15 years to collaborate and share information and to participate in international studies have clearly borne rich fruit in the fields of the histiocytoses.
References


