

Hemophagocytic Lymphohistiocytosis (HLH)

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Hemophagocytic Lymphohistiocytosis (HLH) is clinically characterized by prolonged fever, hepatosplenomegaly and cytopenia (most commonly thrombocytopenia and anemia). Neurological symptoms may complicate, and sometimes dominate, the clinical course. Laboratory investigation may also reveal liver, coagulation and/or lipid abnormalities. The diagnosis may be difficult and, unfortunately, the hallmark (hemophagocytosis) is commonly not found in an initial bone marrow examination.

The primary form, familial hemophagocytic lymphohistiocytosis (FHL), typically seen during infancy and early childhood, is invariably fatal, with a median survival without therapy of two months after onset. Importantly, the inheritance is recessive and the disease is almost never known to the family when their first child is affected.

A secondary form, sometimes termed virus-associated hemophagocytic syndrome (VAHS), can affect all ages and is also associated with a high mortality. Both conditions are under diagnosed. It is important to be aware of these diseases, since effective and potentially life-saving therapy now is available.

Introduction and classification

The term Histiocytosis identifies a group of disorders that have in common the proliferation and accumulation of macrophages and dendritic cells. Based on this biology, the classification of the histiocytoses includes three major groups: macrophage-related disorders, dendritic cell-related disorders (of which Langerhans cell histiocytosis LCH, previously Histiocytosis X, is by far the most common), and truly malignant disorders.

Hemophagocytic lymphohistiocytosis (HLH) includes the majority of the patients with macrophage-related disorders. It comprises two different conditions, which may be difficult to distinguish from each other:

1) Primary HLH: Familial Hemophagocytic Lymphohistiocytosis (FHL, FHLH or FEL).

This is an autosomal recessive disorder and at onset the family history is often negative. The onset as well as bouts of the disease may be triggered by infections.

2) Secondary HLH: Infection-Associated Hemophagocytic Syndrome (IAHS or VAHS) and Malignancy-Associated Hemophagocytic Syndrome (MAHS).

A lymphohistiocytic proliferation with hemophagocytosis may develop also as a result of, and secondary to, strong immunological activation, such as a severe infection. The condition has been described in immunocompromised hosts in association with viral infections.

Although the term virus-associated hemophagocytic syndrome (VAHS) is frequently used, bacteria and parasites may induce secondary HLH as well. The syndrome may also develop subsequent to other types of immunological stress and activation, such as in association with malignancies (malignancy-associated hemophagocytic syndrome, MAHS).

The major aims of this presentation are to describe clinical and laboratory features of these disorders and to provide diagnostic and therapeutic guidelines, with focus on Familial Hemophagocytic Lymphohistiocytosis (FLH).

A brief overview on the biology, immunology and pathophysiology is also provided. The presentation is based on a recent review in the *Hematology Oncology Clinics of North America*, volume 12: pp 417-433, 1998.

Incidence and Epidemiology

In a (Swedish) retrospective study the incidence of primary HLH in children was estimated to be 0.12 per 100,000 children per year, i.e. one per 50.000 live-born. These figures have to be considered as the minimal incidence and most probably there are still patients who are not diagnosed. The male to female ratio is 1:1.

The disease has been reported from many ethnic groups. Since FHL is an autosomal recessive disease, an increased incidence has been reported in ethnic groups with consanguinity as a part of the cultural tradition.

Age at onset

Most patients develop the disease very early in life with around 70 per cent less than one year of age at onset but familial forms have been reported up to the age of eight years. The disease may also present at birth or even at prenatal investigations.

Symptoms and signs

The symptoms may vary widely. The most common early findings are fever, hepatomegaly and splenomegaly. Other early symptoms include a skin rash, lymph node enlargement and neurological abnormalities. The fever is frequently undulant and protracted but may decline spontaneously. In a few children it may develop late during the course of the disease. The splenomegaly and hepatomegaly are usually pronounced and progressive. The rash is uncharacteristic, transient and often associated with high fever. Lymph node enlargement develops in only half of the patients but may occasionally be marked.

Although the signs of CNS involvement may be pronounced already early, it is more common that they develop later during the course of the disease. The picture may include irritability, bulging fontanel, neck stiffness, hypotonia, hypertonia and convulsions. Cranial nerve (sixth or seventh) palsy, ataxia, hemiplegia/tetraplegia, blindness, and unconsciousness may also develop as well as unspecific signs of increased intracranial pressure.

The natural course of the disease is most typically characterized by intermittent or constant fever, pronounced hepatosplenomegaly and cytopenia, in many patients accompanied by progressive cerebromeningeal symptoms. The median survival time without treatment is around two months after onset.

Laboratory findings

Cytopenia, in particular thrombocytopenia but also anemia and to a lesser degree neutropenia, is common already at onset of the disease. Hypertriglyceridemia is a common finding in systemic disease with fever. Hepatic abnormalities including elevated serum transaminases or hyperbilirubinemia, both of which may be markedly elevated (>900 U/L and >300 micromol/L,

respectively), appear to be related to the degree of liver involvement. Elevated ferritin, hyponatremia and low protein/albumin are other common findings, which are associated with the general inflammatory condition. Coagulation abnormalities are common during active disease, in particular hypofibrinogenemia. In the spinal fluid, a moderate pleocytosis with mainly lymphocytes may be found (5-50x10⁶/L) as well as elevated protein levels. Note that caution with lumbar puncture must be taken with regard to a possibly increased intracranial pressure. In the brain, abnormalities may be shown by MR or CT, in particular later in the course of prolonged disease. The alterations may represent areas of past or ongoing inflammatory activity, or demyelination areas. Bleedings, atrophy and brain edema may be found. Hyperdense areas on CT may be interpreted as calcifications.

Pathology

The major histological finding is a nonmalignant mixed lymphohistiocytic accumulation in the reticuloendothelial system. Cytologically, the histiocytes appear activated and hemophagocytosis is an essential, but not specific, finding. The

Hemophagocytosis mostly affects erythrocytes but occasionally also platelets and leukocytes. The organs most frequently involved are the spleen, the liver, the lymph nodes, the bone marrow, and the CNS.

There are no histological and/or cytological findings, which are specific for HLH, and the diagnosis must thus be based on additional clinical and laboratory investigations. An examination revealing no evidence of hemophagocytosis does not rule out the possibility of HLH.

Pathophysiology and immunology

Immune system derangement with defective T-cell function, T-cell and monocyte hyper activation, hypercytokinemia, and a selective deficiency of cellular cytotoxicity has been reported.

A striking finding in FHL patients is the low or absent natural killer (NK)-cell activity, as well as T-cell cytotoxicity, which is restored subsequent to BMT. If and how these findings are related to the basic deficiency and the inappropriate mononuclear inflammatory reaction remains to be clarified.

Hypercytokinemia is one of the most important factors with regard to FHL pathophysiology. The following elements of the cytokine network have been reported to be commonly elevated in FHL: interleukin (IL)-1 receptor antagonist, soluble IL-2 receptor (sIL-2r), IL-6, interferon- γ (IFN- γ), tumor necrosis factor- α (TNF), and neopterin. There is a striking resemblance between biological changes induced by inflammatory cytokines and the clinical and laboratory findings in FHL. It can be speculated that a dysregulation in T-lymphocyte downregulation is the main cause of FHL.

Diagnosis

To establish the diagnosis of FHL may indeed be very difficult and the disease is markedly under diagnosed. Two of the key factors with regard to the diagnostic difficulties are, first, that the disease is uncommon and many physicians are thus not aware of it and, second, that the clinical picture varies markedly. There are less known presentations such as one with encephalitis or other neurological symptoms, a chronic persistent hepatitis, or a neonatal onset.

An important diagnostic problem is the lack of a specific laboratory test. Thus, to facilitate the diagnosis, diagnostic guidelines have been developed. According to these guidelines, the diagnosis HLH requires that five criteria be fulfilled: fever, cytopenia (two of three lineages), splenomegaly, Hypertriglyceridemia and/or hypofibrinogemia, and hemophagocytosis.

In addition, the diagnosis FHL (familial HLH) is justified by a positive familial history, and parental consanguinity is suggestive.

It is of utmost importance to be aware that at least in some cases the disease may not strictly adhere to the guidelines proposed and that atypical presentations are to be expected. Referral to experienced centers for diagnosis and therapy is highly recommended.

Therapeutic recommendations

Without treatment, FHL is usually rapidly fatal with a median survival of about two months. The Histiocyte Society in 1994 developed a common treatment protocol (HLH-94) primarily designed for the primary, inherited disease FHL.

In the HLH-94 protocol, immunotherapy with cyclosporine A therapy is combined with the well-established therapy with steroids and VP-16. Intrathecal methotrexate is added in selected patients. The aim is first to achieve a clinically stable resolution and ultimately to cure by BMT. The protocol has been widely accepted internationally and is used in more than 20 countries and on all continents.

Prognosis

The overall prognosis with regard to survival has improved dramatically during the last decade. One major problem is that many children are still diagnosed late, at a stage when they may have severe and irreversible brain damage or even at the post mortem examination. Preliminary data indicate a high remission rate on the HLH-94 treatment protocol, during which time a suitable BMT donor usually can be identified. With regard to long-term survival, the prognosis will be dependent upon the results of BMT, which also are increasingly rewarding.

This presentation is based on a recent review by the author in the Hematology/Oncology Clinics of North America, volume 12: pp 417-433, 1998.

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