Review article

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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Hemophagocytic lymphohistiocytosis (HLH) is a rare disease with severe acute course leading to fatal outcome without adequate treatment. Due to its rapidly developing symptoms requiring timely treatment, it is very important that all pediatricians are well-educated about the clinical findings and diagnostic criteria of HLH. Its clinical presentation is characterized by fever, hepatosplenomegaly, less frequently rash and/or adenopathy. Laboratory analysis frequently shows bi- / pancytopenia, hyperferritinemia, hypertriglyceridemia and hypofibrinogenemia. Hemophagocytosis, one of the defining phenomena of the disease, is displayed by activated macrophages. The disease is caused by multisystem inflammation initiated by prolonged and intensive activation of antigen presenting cells and CD8+ T lymphocytes, as well as incompetence of cytotoxic T cells and natural killer cells to eliminate the pathogens. So far, a large number of gene defects leading to primary HLH have been elucidated. However, a great many patients have no obvious genetic cause and the disease may also develop as a secondary complication of infection, autoimmunity or malignancy. Adequate treatment should be started as soon as diagnostic criteria are fulfilled, without waiting for genetic diagnosis, since the secondary HLH carries a high mortality risk even in adults and in older children too. Intensive immunosuppressive treatment leads to clinical amelioration, however allogeneic hematopoietic stem cell transplantation is the only curative treatment for primary HLH. Therapy should be provided by an experienced medical team with skills for diagnosis and treatment of HLH.

Key words: Hemophagocytic lymphohistiocytosis ▪ Child

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a disorder of histiocytes characterized by excessively stimulated, but inefficient immune response to antigen(s), giving rise to the so-called 'cytokine storm' and consequent uncontrolled hyperinflammatory reaction. In the absence of appropriate treatment, the disease progresses to certain death within 2 to 6 months. First reports of HLH were published in the 1950s (1, 2). About three decades passed before the first review article featuring a comprehensive description of the disorder appeared in the medical literature (3). The Histiocyte Society issued its guidelines for the diagnosis of HLH for the first time in 1991, based on the most common clinical, laboratory and histopathological findings (4). As the disease may have an atypical form in some patients, where one or more of the diagnostic criteria are fulfilled late in its course, in 2004 the Histiocyte Society published a set of revised criteria required for the diagnosis of HLH (5) (Table 1).

Etiology and Pathogenesis

According to the underlying disorder, HLH may be classified into congenital (primary) and acquired (secondary) HLH (Table 2). Congenital HLH can be either familial HLH (FHLH) – a separate entity first described by Farquhar and Claireaux (1) – or arising within some other primary immunodeficiencies: Chédiak-Higashi syndrome, Griscelli syndrome and X-linked immunoproliferative syndrome. The incidence of FHLH is estimated at 1 per 50,000 live births, with 70% manifesting the disease in the first year of life (6). Secondary HLH may accompany various groups of disorders, such as infections, lymphoproliferative disorders and autoimmune disorders (7). Patients with acquired HLH do not have any known immunodeficiency. The most common triggering factors of HLH are pathogenic microorganisms: Ebstein-Barr virus (EBV), cytomegalovirus (CMV) and Leischmania (8, 9, 10, 11). Macrophage activation syndrome (MAS) is a phenomenon related to HLH encountered in the settings of auto-

Table 1 Diagnostic criteria for hemophagocytic lymphohistiocytosis (4)

1. Familial HLH – known gene defect
2. Clinical and laboratory criteria (5 out of 8 necessary for diagnosis)
    1. Fever
    2. Splenomegaly
    3. Bi- or pancytopenia
        - Platelets <100´
        - Platelets <100´
        - Neutrophil count <1´
    4. Hypertriglyceridemia and/or hypofibrinogenemia
        - Fasting serum triglyceride level >3 mmol/l
        - Fibrinogen <1,5 g/l
    5. Ferritin >500 μg/l
    6. sIL-2R*(CD25) >2400 U/ml
    7. Low or absent NK cell activity
    8. Hemophagocytosis in bone marrow, lymph nodes or CSF**

*sIL-2R= Soluble interleukin-2 receptor; **CSF = Cerebrospinal fluid
The diagnosis is additionally supported by central nervous system (CNS) symptoms, CSF pleocytosis and/or hyperproteinorrachia, elevated transaminases, bilirubin or LDH

Table 2 Classification of hemophagocytic lymphohistiocytosis

Primary HLH
Familial HLH (Farquhar's disease)
Known gene defects (perforin, munc 13-4, syntaxin 11)
Unknown gene defects
Immunodeficiency syndromes
Chédiak-Higashi syndrome
Griscelli syndrom
X-linked lymphoproliferative syndrome
Acquired HLH
Exogenous agents (microorganisms, toxins)
Infection-associated hemophagocytic syndrome (IAHS)
Endogenous agents (tissue damage, metabolic products)
Rheumatic diseases
Macrophage activation syndrome (MAS)
Malignancies

immune disease (12, 13). Viral infections may trigger MAS (as with other forms of secondary HLH). However, cases of MAS have also been documented after taking non-steroidal anti-inflammatory agents, methotrexate and gold salts (14). A common trigger for primary and secondary HLH is infection.

Clinical manifestations of HLH are predominantly caused by chronic inflammation resulting from hypersecretion of pro-inflammatory cytokines, such as interferon (IFN)γ, tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6; production of IL-10 and macrophage-colony stimulation factor (M-CSF) is also increased. Pro-inflammatory cytokines are released by activated T cells and macrophages found in many tissues and organs, leading to tissue necrosis and disturbances of organ function. These cytokines are mostly responsible for the clinical feature and laboratory findings: IL-1 and IL-6 induce fever and other signs of inflammation; high levels of TNF and IFNγ impair hematopoiesis, resulting in pancytopenia; TNF inhibits lipoprotein lipase, leading to hypertriglyceridemia; activated macrophages secrete ferritin, as well as plasminogen activator that causes fibrinolysis and hypofibrinogenemia; great quantities of the alpha-chain of soluble IL-2 receptor originate from the activated lymphocytes (15).

A key factor in HLH pathogenesis is a functional defect of cytotoxic T lymphocytes and NK cells (16). This conclusion is based on data obtained in research conducted on a murine model (17) and the known functions of genes mutated in primary HLH (Table 3). Gene defects found in FHLH may affect perforin, one of the main effector proteins of cellular cytotoxicity, found in the secretory granules of cytotoxic T lymphocytes and NK cells, with the principal function of apoptosis induction in the target cell. Another gene that may be mutated in FHLH is Munc13-4, a molecule important in the exocytosis of cytolytic granules. The third known molecule associated with FHLH is t-SNARE syntaxin 11, that plays an – as yet – poorly defined role in vesicular transport. In Griscelli syndrome, mutation of RAB27A prevents the fusion of secretory granules with the cytoplasmic membrane of activated T cells. Chédiak-Higashi syndrome is characterized by the mutation of LYST, a gene with a product known to be necessary for completing the final phase of granule secretion. In X-linked lymp-

hoproliferative syndrome (XLP), SH2D1A mutation impairs signal transduction through the lymphocyte signaling activation molecule (SLAM), required for the activation of cytolytic T lymphocytes and NK cells. The pathogenesis of defects in cellular cytotoxicity in secondary HLH is less clear. However, it has been shown that some viruses can, by acting through specific proteins, interfere with the functions of cytotoxic lymphocytes. It is also known that high levels of some cytokines may lead to similar consequences for the function of NK cells (19). A common element in the pathogenesis of all forms of HLH is the chronic stimulation of inflammatory response due to the inability of cytotoxic T cells and NK cells to clear the pathogen, resulting in chronic production of pro-inflammatory and other cytokines and chronic macrophage activation which is the main cause of the manifestations of the disorder. Functional testing of NK cells is one of the most useful laboratory examination, since this is impaired in about 90% of patients, while mere enumeration of NK cells has little or no diagnostic value. Another very important immunological test is measurement of the concentration of soluble IL-2 receptor in the plasma, usually by enzyme-linked immunosorbent assay (ELISA) (20).

Clinical Features

The clinical features of HLH are the same in primary as in secondary HLH. It was once considered that FHLH always manifested in early childhood. However, genetic analyses have shown that in patients of any age, and even in utero (21), mutations characteristic for the familial form of HLH are detected. Even though it is true that in most patients the disease manifests itself before the age of 18 months, age was not included in the diagnostic criteria for FHLH. On the other hand, regardless of the positive family history, about 50% of children with FHLH do not have known characteristic mutations. In no more than 20-30% of children with FHLH, mostly in those of Turkish origin, mutations in the perforin gene are detected, while other mutations characteristic for FHLH are less prevalent.

It is also important to note that the criteria for diagnosis appear gradually, imposing the need to follow carefully the children suspected of having HLH. Furthermore, hemophagocytosis is not necessarily present at the initial examination (Figure 1). Repeated bone marrow aspirations are indicated when hemophagocytosis is not found and some other diagnostic criteria are satisfied (22).

The main symptoms and signs of HLH are long-standing fever, hepatosplenomegaly and bicytopenia or pancytopenia. Less often encountered are: lymphadenopathy, icterus, non-specific rash and edema. Fever may be of continuous or intermittent type, typically lasting for more than seven days and usually not responsive to antibiotic therapy.

Table 3 Genetic causes of hemophagocytic lymphohistiocytosis

Disease	Gene locus	Gene	Gene function
FHLH-1	9q21.3-22	Unknown	Unknown
FHLH-2	10q21-22	PRF1	Induction of apoptosis
FHLH-3	17q25	UNC13D	Vesicle priming
FHLH-4	6q24	STX11	Vesicle transport; t-SNARE
GS-2	15q21	RAB27A	Vesicle transport; small GTPase
CHS-1	1q42.1-q42.2	LYST	Vesicle transport
XLP	Xq25	SH2D1A	Signal transduction and lymphocyte activation

Hepatosplenomegaly, elevated transaminases and elevated serum bilirubin levels result from inflammation caused by the activation of lymphocytes and histiocytes in the liver and spleen. Bi- or pancytopenia are caused by high concentrations of proinflammatory cytokines (TNF and IFNγ) and hemophagocytosis. The latter is not found in all patients, particularly in the early stage of the disease. Splenic sequestration is infrequently present. Non-specific rash most frequently consists of maculo-papular lesions, erythroderma or macular purpura. Neurological symptoms are present in about one third of the affected children. They may be manifested as cranial nerve palsies, hemiparesis, ataxia, seizures or behavioral changes dominated by irritability. Mild or moderate amounts of protein in the CSF are found in roughly 50% of patients. Lymphocyte pleocytosis and CSF protein elevation are more often isolated than associated. CSF macrophages may also exhibit hemophagocytosis. In children with CNS symptoms, MR imaging may show parenchymal atrophy or calcifications, diffuse changes in the white matter, focal hyperdense lesions in the white as well as grey matter and/or signs of demyelination.

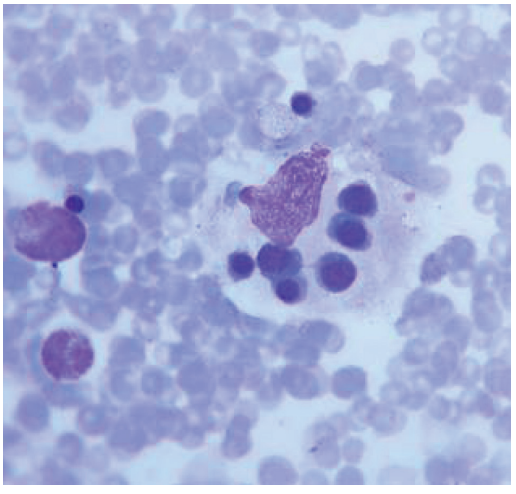


Figure 1 *A histiocyte exhibiting hemophagocytosis*

Diagnosis

In patients with long-standing fever of unknown origin that does not respond to antibiotic treatment, HLH should be considered as a differential diagnostic possibility. Fever may spontaneously subside in the beginning of the disease, only to recur a few days or weeks later. When hepatosplenomegaly and/or bi- or pancytopenia are present, leukemia should be ruled out, leaving HLH as the next most likely diagnosis. It is important to conduct the appropriate laboratory investigations to confirm the diagnosis. On initial examination, the child is usually in good general condition. The progression of clinical signs and symptoms, as well as pathological laboratory findings, will confirm the presence of HLH. FHLH should also be suspected when there is reason to believe that the child's parents may be consanguineous or an unexplained early death of a child in the family has been reported.

Current guidelines for the diagnosis of HLH require the fulfillment of 5 out of the 8 diagnostic criteria cited in Table 1. For patients with MAS, all criteria are not always relevant for the establishment of diagnosis. Thus, for example, in systemic juvenile arthritis, the already present inflammation may lead to leukocytosis, thrombocytosis and elevated fibrinogen levels (23). Universally accepted criteria for the diagnosis of MAS do not yet exist, while the most comprehensive were proposed by Ravelli et al. (24).

Although there are guidelines and criteria for diagnosis, HLH is often left undiagnosed or the diagnosis is established only after a considerable delay (25, 26). Two principal reasons for this are the rarity of the disease (making it easy to overlook) and the frequently atypical clinical presentation. The isolation of an infectious organism may mislead the physician to interpret the signs and symptoms of HLH as those of infection itself, unaware of the fact that the gravity of the clinical condition and the progressive course

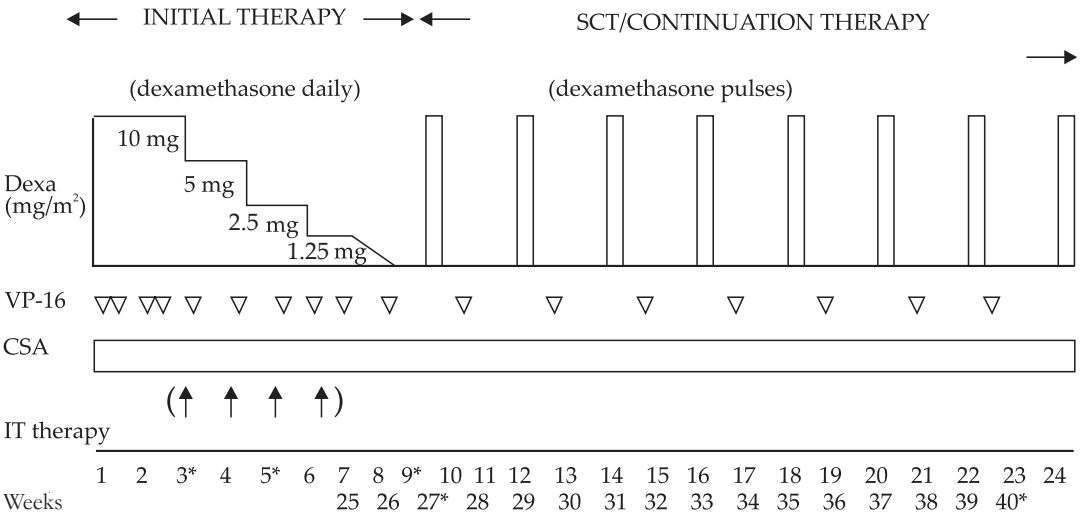
of the disease are consequent to an immune system disorder. At times, non-specific therapy, such as transfusion or intravenous immunoglobulin infusions, may temporarily improve the clinical condition. Infants with marked hepatosplenomegaly and impaired liver function or elevated triglyceride levels are often erroneously investigated for metabolopathies. If liver failure is the most striking finding, the disease may wrongly be thought to be a primary liver disorder. Lymph node biopsy results may be misinterpreted as signs of lymphoma, since the morphology of activated lymphocytes may misleadingly suggest their immaturity. Liver biopsy specimen may also be seen as suggestive of chronic hepatitis, if the phagocytosis by liver histiocytes is scarce or absent. Isolated CNS disease is a particular diagnostic challenge.

Treatment

The specific pathophysiology of HLH forms a basis for specific therapy. Unless therapy is carried out, patients die, mostly of multisystemic failure, bacterial or fungal infections arising on the grounds of neutropenia, or CNS complications. The intense inflammatory response in HLH may be attenuated by the administration of glucocorticoids that cause lymphocyte apoptosis, decrease cytokine secretion and block dendritic cell differentiation. Dexamethasone should be preferred, since this agent is able to cross the blood-brain barrier. Cyclosporin A (CSA) suppresses the activation of T lymphocytes and the functions of macrophages, and thus it may be useful in maintaining remission in primary HLH (27). Etoposide is also effective in the treatment of HLH and its presumed mechanism of action includes the elimination of infected antigen-presenting cells that chronically stimulate the inefficient response of cytotoxic T lymphocytes and excessive cytokine production. French authors use antithymocyte globulin combined with cyclosporin A and glucocorticoids, while immunoglobulins are mostly used in the treatment of adult patients with HLH. In primary HLH, hematopoietic stem cell transplantation (HSCT) is the only curative therapy (28). The small total number of HLH patients, with great inter-individual variation and frequent individual specificities, renders the establishment and evaluation of standardized therapeutic regimens in this disorder difficult.

In addition to diagnostics, the Histiocyte Society has issued recommendations for the treatment of HLH in the most frequently used HLH-2004 protocol (29). The protocol is designed for all patients, with or without confirmation of the familial or genetic form of HLH and regardless of the presence of viral infection (30) (Figure 2). Initial treatment of 8 weeks' duration is based on dexamethasone, etoposide and CSA. In children that still exhibit clinical or laboratory signs of CNS involvement after 2 weeks of systemic treatment, a 4-week course of intrathecal treatment should be initiated.

For patients without family history who achieve a complete remission after the 8-week course of treatment, further application of treatment is discontinued. It is considered that these patients may suffer from secondary HLH. All patients with familial disease, those with confirmed presence of a genetic cause or without any of the former two criteria, but with persistent or recurrent disease, should continue to be treated according to the maintenance protocol. The maintenance protocol includes etoposide, dexamethasone and CSA. HSCT should be performed as soon as possible, pending the finding of an appropriate donor (29, 32). Together with immunosuppressive treatment instituted by the protocol, supportive therapy, constituting of cotrimoxazole (in order to prevent P. jiroveci pneumonia), antiviral therapy (in case of a documented viral infection), gastroprotective agents and substitution therapy by intravenous administration of immunoglo-



Legend:
* = evaluation

Dexa = Dexamethasone daily 10 mg/m² for 2 weeks, 5 mg/m² for 2 weeks, 2.5 mg/m² for 2 weeks, 1.25 mg/m² for 1 week; and taper then discontinue during 8th week. Pulses every second week with 10 mg/m² for 3 days during the continuation therapy.

VP-16 = Etoposide 150 mg/m2 i.v. twice weekly for the first two weeks, then weekly during the initial therapy. Every second week during the continuation therapy. Only in certain conditions, such as if ANC < 0.5´

CSA = Cyclosporin A aiming at levels around 200 microg/l. Start with 6 mg/kg daily orally (divide in 2 daily doses), if normal kidney function.

IT = intrathecal therapy:
Methotrexate, doses by age <1 yr 6 mg, 1-2 yr 8 mg, 2-3 yr 10 mg, >3 yr 12 mg
Prednisolon doses by age <1 yr 4 mg, 1-2 yr 6 mg, 2-3 yr 8 mg, >3 yr 10 mg

SCT = stem cell transplantation

Figure 2 *Treatment protocol for hemophagocytic lymphohistiocytosis (HLH-2004)*

bulins at 4-week intervals should all be given. In case of disease reactivation during the maintenance therapy, treatment intensification, as in the second week of initial treatment, is recommended, but treatment duration is allowed to be less than 8 weeks. In case of reactivation of the disease in the CNS, intrathecal therapy should be given.

Conclusion

HLH is a rare and severe disease characterized by uncontrolled hyperinflammation brought about by various innate and acquired immune defects. Although the recognition and establishment of diagnosis of HLH has been improved in recent years, a great number of children still fail to be diagnosed. The Histiocyte Society has issued the current guidelines for the diagnosis and treatment of HLH. A diagnostic problem is posed by the often atypical clinical features in the early stages of the disease; another problem is that the known characteristic genetic alterations are present in less than half of all children affected by the familial type of the disease. Survival is significantly improved after the elucidation of biological mechanisms invol-

ved in the pathogenesis of HLH. Immunosuppressive treatment and HSCT in children for the genetically caused disease have changed its course from that leading to a swift and certain death, usually ensuing within a few months after the first symptoms, to a cure in more than 50% of children. The likelihood of being cured is far greater in children with the secondary type of HLH, but the timely initiation of treatment is of crucial importance. Best treatment results are achieved in centers with the greatest experience, and thus every child suspected or proven to suffer from HLH should be directed to a tertiary level pediatric institution.

Conflict of Interest: The author declares that she has no conflict of interest. This article was not sponsored by any external organisation.

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