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REVIEW

Familial and acquired hemophagocytic lymphohistiocytosis

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition of severe hyperinflammation caused by the uncontrolled proliferation of activated lymphocytes and histiocytes secreting high amounts of inflammatory cytokines. Cardinal signs and symptoms are prolonged fever, hepatosplenomegaly and pancytopenia. Characteristic biochemical markers include elevated triglycerides, ferritin and low fibrinogen. HLH occurs on the basis of various inherited or acquired immune deficiencies. Impaired function of natural killer (NK) cells and cytotoxic T-cells (CTL) is shared by all forms of HLH. Genetic HLH occurs in familial forms (FHLH) in which HLH is the primary and only manifestation, and in association with the immune deficiencies Chédiak-Higashi syndrome 1 (CHS 1), Griscelli syndrome 2 (GS 2) and x-linked lymphoproliferative syndrome (XLP), in which HLH is a sporadic event. Most patients with acquired HLH have no known underlying immune deficiency. Both acquired and genetic forms are triggered by infections, mostly viral, or other stimuli. HLH also occurs as a complication of rheumatic diseases (macrophage activation syndrome) and of malignancies. Several genetic defects causing FHLH have recently been discovered and have elucidated the pathophysiology of HLH. The immediate aim of therapy in genetic and acquired HLH is suppression of the severe hyperinflammation, which can be achieved with immunosuppressive/immunomodulatary agents and cytostatic drugs. Patients with genetic forms have to undergo stem cell transplantation to exchange the defective immune system with normally functioning immune effector cells.

In conclusion, awareness of the clinical symptoms and of the diagnostic criteria of HLH is crucial in order not to overlook HLH and to start life-saving therapy in time.

Keywords Histiocytosis · Hemophagocytosis · Immune deficiency · Bone marrow transplantation · Review

Abbreviations

CHS 1	Chédiak-Higashi syndrome 1
CSF	cerebrospinal fluid
CNS	central nervous system
CTL	cytotoxic T lymphocyte
EBV	Epstein-Barr virus
FHLH	familial hemophagocytic lymphohistiocytosis
GS 2	Griscelli syndrome 2
HLH	hemophagocytic lymphohistiocytosis
IAHS	infection-associated hemophagocytic syndrome
IL	interleukin
INF-γ	interferon γ
LAHS	lymphoma-associated hemophagocytic syndrome
MIP1-α	macrophage inflammatory protein 1-α
MRT	magnetic resonance tomography
NK cell	natural killer cell
sCD25	α-chain of the soluble interleukin-2 receptor
SCT	stem cell transplantation

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sJRA	systemic-onset juvenile rheumatoid arthritis
TNF-α	tumor necrosis factor α
VAHS	virus-associated hemophagocytic syndrome
XLP	x-linked lymphoproliferative syndrome

Introduction

In 1983, a first comprehensive review about hemophagocytic lymphohistiocytosis (HLH) appeared in this journal [60]. At that time, knowledge about this syndrome was still limited. Only about 100 cases had been published, and the cause and pathophysiology of HLH remained unclear. Twenty-three years later, a lot of new information about HLH has been accumulated. Underlying conditions predisposing to HLH have been identified, gene defects have been discovered in familial cases, allowing insights into its pathophysiology, and, most important of all, successful treatment can now be offered to the majority of patients. This review aims at describing the new knowledge and at drawing the pediatrician's attention to a disease that is still easy to overlook, difficult to diagnose, and life-threatening if untreated.

Underlying conditions and epidemiology

HLH is not a single disease, but a clinical syndrome that can be encountered in association with a variety of underlying conditions leading to the same characteristic hyperinflammatory phenotype (Table 1).

Genetic hemophagocytic lymphohistiocytosis

Genetic (primary) HLH is inherited in an autosomal recessive or X-linked manner and can be divided into two subgroups: familial HLH (FHLH), first described by Farquhar and Claireaux in 1952 [19], and the distinct immune deficiencies Chédiak-Higashi syndrome 1 (CHS-1) (OMIM 214500), Griscelli syndrome 2 (GS 2) (OMIM 607624), and X-linked proliferative syndrome (XLP) (OMIM 308240).

In FHLH, the clinical syndrome of HLH is the primary and only manifestation. In a retrospective study, the incidence was estimated as 0.12/100,000 children per year [42]. There is a slight male preponderance [43, 60]. FHLH has been reported from many different countries. As an autosomal recessive disease, it is found especially in ethnic groups where consanguineous marriages are common. In the German Registry, half of the children with another afflicted sibling came from a consanguineous marriage and a third of the patients with presumed genetic disease because of age below 1 year, disease progression or relapse, had consanguineous parents.

Table 1 Classification of hemophagocytic lymphohistiocytois

Genetic HLH
Familial HLH (Farquhar disease)
Known gene defects
Unknown gene defects
Immune deficiency syndromes
Chédiak-Higashi syndrome 1
Griscelli syndrome 2
X-linked lymphoproliferative syndrome
Acquired HLH
Exogenous agents (infectious organisms, toxins)
Infection-associated hemophagocytic syndrome (IAHS)
Endogenous products (tissue damage, metabolic products)
Rheumatic diseases
Macrophage activation syndrome (MAS)
Malignant diseases

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The onset of disease is below 1 year of age in 70–80% of the cases [4, 60]. A symptom-free interval after birth is typical; only about 10% of the patients become symptomatic within the 1st 4 weeks, and a few may have symptoms already at birth [60, 80]. Several late-onset cases in adolescence and even adulthood have been reported [1, 12]. In the same family, the age of onset is usually similar in the first and second affected child, but a time lag of 1–3 years is possible [4].

CHS 1, GS 2 and XLP are immune deficiencies in which the development of HLH is sporadic, though frequent. HLH is often the presenting symptom, but may also occur later during the course of the disease.

Patients with CHS 1, an autosomal recessive disease, express variable degrees of oculocutaneous albinism, easy bruising and frequent pyogenic infections, due to decreased chemotaxis and bactericidal activity [105]. Their white blood cells exhibit characteristic giant inclusion bodies (lysosomes), which resemble Doehle bodies in granulocytes and are of purple color in lymphocytes and monocytes. These can be easily identified in a blood or bone marrow smear. The clinical picture of HLH in CHS 1, also called the "accelerated phase," cannot be distinguished from other genetic or acquired HLH forms [7].

Patients with GS 2, another autosomal recessive disease with hypopigmentation, have various degrees of neutrophil dysfunction, but lack the giant granules. Episodes of HLH are frequent and life-threatenting [68].

XLP, also called Purtilo syndrome, is transmitted in a X-linked way. HLH triggered by Epstein-Barr virus (EBV) is the cause of death in half of the patients.

Other manifestations are hypogammaglobulinemia, malignant lymphoma or aplastic anemia [92].

Acquired hemophagocytic lymphohistiocytosis

Acquired (secondary) forms of HLH can occur in all age groups. There are no data about the incidence of acquired forms. From numerous case reports and from the author's own experience, however, it appears that acquired cases are more common than genetic cases.

The clinical picture of HLH can be induced by a variety of infectious organisms. The first report was by Risdall et al., who described several patients, mostly adults after organ transplantation, the majority of whom had evidence of a viral infection and presented with clinical signs and symptoms of HLH [99]. The authors designated this as virus-associated hemophagocytic syndrome (VAHS). Subsequently, it became clear that occasionally also other organisms could trigger HLH, such as bacteria, protozoa or fungi [30, 59, 98]. Among these, infection by Leishmania seems to be a frequent trigger [30]. It also accounted for 12% of the acquired cases in the German Registry, and as in the report by Gaignaire, the majority of the patients had not visited a foreign country [30]. The term infection-associated hemophagocytic syndrome (IAHS) is now commonly used instead of VAHS.

Whereas in the first report by Risdall et al. the majority of the patients had an acquired iatrogenic immune deficiency, most patients in subsequent reports had no known genetic or acquired immune defect. Not unlike familial HLH, IAHS proved to be a dangerous disease: a review of the published cases in children diagnosed with IAHS before 1996 reported a mortality of 50% [59]. In this series most patients had only received supportive care. More than half of the patients were from the Far East, and EBV was the triggering organism in 74% of the children in whom an infectious agent could be identified.

The presence of an infection was originally thought to discriminate between familial and acquired forms. However, it is now clear that most episodes in the genetic forms of HLH are also triggered by infections [4, 39]. This cannot be emphasized enough since appropriate therapy should not be withheld when an infectious agent has been found.

Acquired HLH in association with malignant diseases, especially lymphomas (lymphoma-associated hemophagocytic syndrome, LAHS) [18, 56], is for unknown reasons more common in adults than in children. HLH can develop before or during treatment, associated with an infection or without a known triggering factor. From the author's own experience, in children HLH occurs especially in large cell anaplastic lymphomas. Cases formerly diagnosed as histiocytic medullary reticulosis or malignant histiocytosis included patients with LAHS, but also IAHS [18].

Hemophagocytosis and symptoms of HLH have also been described in association with inborn errors of metabolism, such as lysinuric protein intolerance and multiple sulfatase deficiency [16, 50]. In such cases, it is not clear what role metabolic products may play as triggers to the immune system.

Besides the clinical pictures listed above, any other condition with an inherited or acquired immune defect can be associated with HLH such as other rare genetic immune defects, treatment for malignancy with cytostatic drugs, or bone marrow transplantation during the phase of incomplete immune reconstitution. HLH in association with autoimmune disease is a special entity and will be discussed later.

Pathohistology

The diagnosis of (F)HLH is nowadays usually made during the life time, and autopsy reports have become rare. Nevertheless, there are still cases in which only a post-mortem examination led to the correct diagnosis. The main characteristic pathohistological feature of HLH is a diffuse infiltration with T-lymphocytes and histiocytes involving mainly the liver, spleen, lymph nodes, bone marrow, and central nervous system, but practically no organ is spared. The histiocytes show no evicence of cytological malignancy. Phagocytosis in autopsy material is usually present, but it may not be evident in all organs or may be missed. Another characteristic feature is atrophy of the lymphoid tissues even without preceding treatment [33, 60]. The histological picture is indistinguishable in genetic and acquired forms [33]. The histiocytes in HLH were shown to express typical markers for macrophages, but also for antigen-presenting cells such as CD1a and S100 [45]. Liver biopsies, which are still performed in some instances, typically display a chronic hepatitis-like pattern with portal lymphohistiocytic infiltrates dominated by T lymphocytes. Hemophagocytosis is found in only half of the cases [20]. A prominent loss of intrahepatic bile ducts may be present [63].

Clinical features

Clinical signs and symptoms

The cardinal clinical signs and symptoms of HLH are prolonged fever, which is unresponsive to antibiotics, and hepatosplenomegaly. Fever may be accompanied by signs of an upper respiratory or gastrointestinal infection. Less frequent signs are lymphadenopathy, icterus, an uncharacteristic rash, or edema. Neurological signs such as seizures, opisthotonic posture, or cranial nerve palsies are present in up to a third of the patients [36, 80].

Laboratory findings and imaging studies

Anemia and especially thrombocytopenia are early signs. Neutropenia is present initially in only half of the patients. The white blood cells are reduced in one third of the patients and elevated in one fourth of the children [80].

Characteristic laboratory values include high triglycerides, ferritin, transaminases, bilirubin (mostly conjugated) and lactate dehydrogenase and decreased fibrinogen. The bone marrow is usually normocellular to hypercellular; the markedly increased erythropoiesis often shows unspecific dysplastic changes suggesting even a myelodysplastic syndrome at times. Moderate reticulocytosis in the presence of severe anemia is indicative of ineffective erythropoiesis with intramedullary destruction. Hemophagocytosis is absent in the initial bone marrow in the majority of cases [32, 60, 80] as illustrated also by Farqhuar's patients [19]. Repeated bone marrow aspirations to document hemophagocytosis may be helpful.

Changes on chest radiographs include interstitial opacities, pulmonary edema and pleural effusions. Ascites, thickening of the gall bladder wall and enlargement of kidneys were frequent findings on abdominal ultrasound studies [28].

A slightly elevated cell count and/or moderately increased protein content in the CSF is present in more than half of the patients [36, 60, 80]. Not only symptomatic patients, but also about 40% of the children without neurological signs and symptoms have CSF changes [80]. Isolated lymphocytic pleocytosis or an increase in protein content is more common than both together [80]. Increased neopterin concentrations in the CSF were reported to correlate with neurological signs and symptoms [49]; this could be confirmed in six of our patients. Changes on magnetic resonance tomography (MRT) in symptomatic patients consist of parenchymal atrophy, diffuse abnormal signal intensity in the white matter on T2-weighted images, focal hyperintense lesions in both the white and gray matter, delayed myelination, and parenchymal calcification [70].

Figure 1 illustrates that HLH is a progressive disease: the percentage of patients that shows the characteristic signs and symptoms is far smaller at first presentation than at the time when the diagnosis is made. In this retrospective evaluation of 65 patients, the median time to diagnosis was 3.5 months [80].

High levels of cytokines characterize hemophagocytic lymphohistiocytosis

Patients with HLH have high levels of various pro-inflammatory cytokines such as interferon γ (INF-γ), interleukin (IL)—6, IL-8, IL-10, IL-12, IL-18, tumor necrosis factor α (TNF-α) and macrophage inflammatory protein (MIP 1-α) [41, 84, 102, 114, 116]. In our experience, TNF-α and IL-6 are only moderately increased if patients are investigated early in the course of the disease. Remarkably, the inflammatory cytokine IL-1β was not elevated in classical HLH cases [38]. The cell type secreting pro-inflammatory cytokines has not been identified, but activated T lymphocytes, monocytes/macrophages and endothelial cells are the most likely candidates. The selective role of INF-γ, secreted by virus-activated cytotoxic cells and NK effectors, in the manifestation of HLH was demonstrated in a perforin knock-out mouse model [62]. The alpha chain of the soluble IL-2 receptor (sCD25) appears to be a good disease marker because of constantly increased levels during active HLH [52, 71, 102]. In addition, sCD25 is also a marker for CNS disease in HLH. Another soluble receptor found in HLH is CD95-ligand (sCD95-L) [37]. When compared with sCD25, sCD95-L is less discriminative for diagnosis [102]. Another marker of immune activation, β-2 microglobulin, the stabilizing molecule of polymorphic MCH class I molecules, also reflects disease activity in patients with HLH [46].

All clinical and laboratory findings of HLH can be explained by hypercytokinemia and organ infiltration with lymphocytes and histiocytes:

- Fever is caused by high levels of interleukins.
- Pancytopenia can probably be attributed primarily to high concentrations of TNF-α and INF-γ, and hemophagocytosis, which is present initially in only the minority of cases in spite of profound depression of blood counts, seems to play a secondary role.
- High triglycerides result from increased levels of TNF-α, leading to decreased activity of lipoprotein lipase.
- Low fibrinogen can be explained by secretion of high levels of plasminogen activator by macrophages leading to increased concentrations of plasmin, which in turn cleaves fibrinogen. In the experience of the author, cases with normal fibrinogen usually show increased fibrinogen split products.
- Ferritin is secreted by activated macrophages and has become an easily available marker for disease activity.
- High concentrations of the α chain of the soluble IL-2 receptor and of β-2 microglobulin are produced by activated lymphocytes.
- Hepatosplenomegaly, increased transaminases and bilirubin, and neurological signs and symptoms can be explained by organ infiltration with lymphocytes and histiocytes.

While many of the symptoms of HLH are found in immune-competent patients in response to an infectious organism, they are more pronounced in patients with HLH.

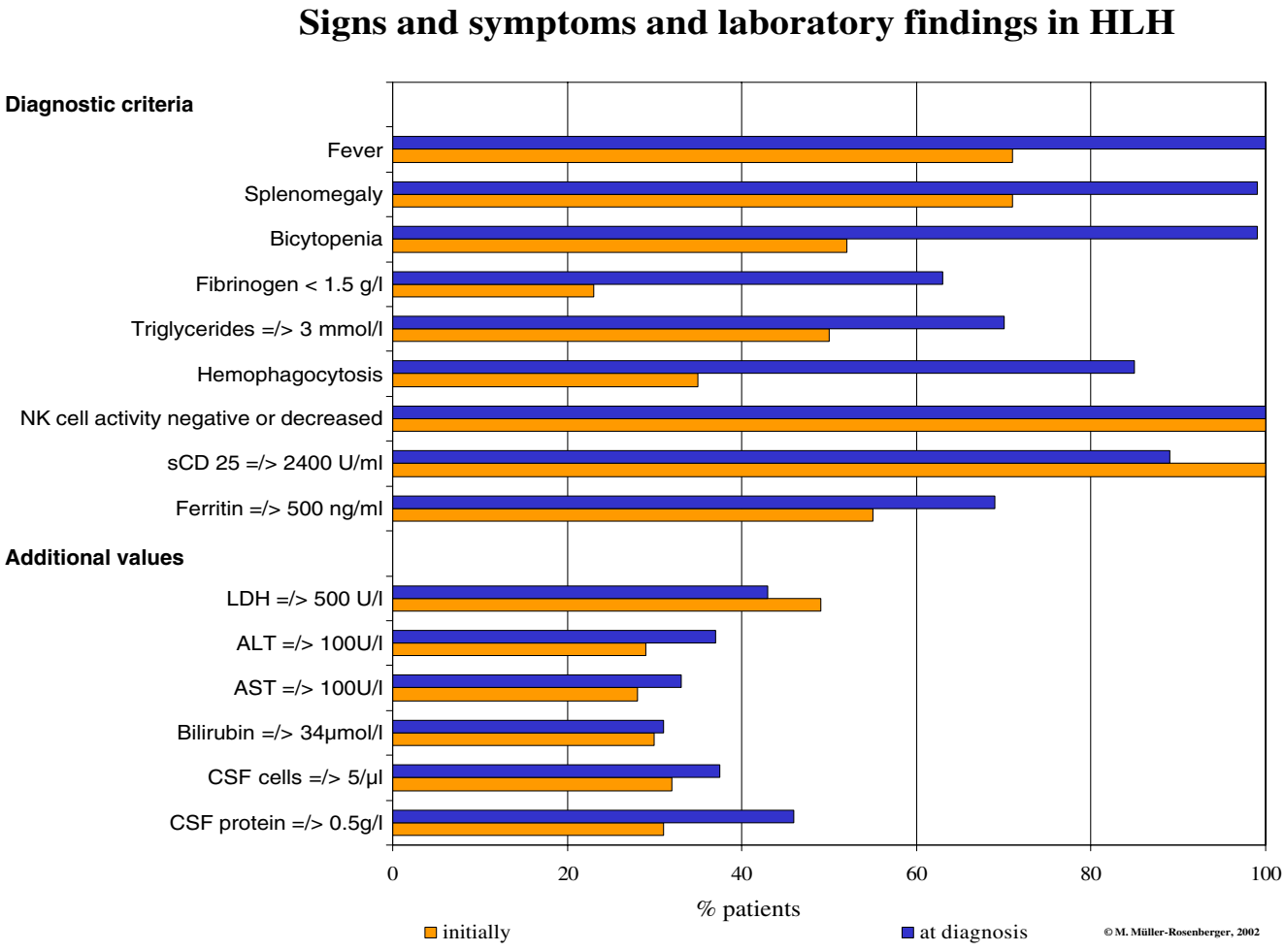

Fig. 1 Clinical symptoms and laboratory parameters in 65 patients with HLH at first presentation and at the time of diagnosis. The light bars represent the percentage of positive patients at first presentation, the dark bars the percentage at diagnosis. Bicytopenia: two cell lines are decreased (see diagnostic criteria)

Most important, the progression of organomegaly, of cytopenias and of conspicuous biochemical parameters such as elevated ferritin, triglycerides, liver enzymes, and bilirubin or low fibrinogen should alert the physician that this could be an unusual response to an infectious agent.

With very few exceptions, FHLH is fatal when untreated [60], although some patients may enjoy prolonged symptom-free intervals, some even without therapy. Death is usually due to bacterial and fungal infections acquired during prolonged neutropenia, to multiorgan failure or to cerebral dysfunction due to inflammatory CNS lesions.

Immunology

A hallmark of HLH, in genetic as well as in acquired cases, is impaired or absent function of natural killer (NK) cells and cytotoxic T lymphocytes (CTL) measured as lysis of K652 cells in a standard 4h chromium release assay [5, 17, 88, 102, 112]. Four distinct types of NK cell deficiency were described in a large group of 65 patients: In type 1-, 2-, and 4-deficient patient cells, negative cytolytic function could be reconstituted by either mitogen, by high-dose IL-2 activation, or by prolonged incubation time, respectively. Most patients belonged to the so-called type 3 group, whose killer-deficient cytotoxic cells could not be reconstituted by any of these experimental variations. Most Turkish patients were in group 3 and four had a perforin mutation [102]. Type 3 deficient NK cell function was associated with a worse prognosis [47, 102].

In patients with FHLH, NK cell numbers are normal and the defect is usually persistent [5, 17, 25]. However, in one of the first publications on NK cell function in HLH, Perez et al. observed normalization in two of six patients in remission and deterioration upon relapse [88]. Recently, recovery of NK cell function was reported in some patients with mutations in *UNC13D* [118], but experimental conditions were not adequate to distinguish NK- from non-NK

effectors. Parents and siblings of patients with FHLH also often demonstrate decreased NK cell function although they are healthy [5, 112]. Granule-independent cellular cytotoxicity has been demonstrated to substitute granule- and calcium-dependent cytotoxcitiy in the relatives of HLH patients [103].

Patients with acquired HLH may have low NK cell numbers [25] and usually have decreased NK cell function with active disease [25, 102]. NK cell function reverts to normal after treatment; however, patients with a defect persisting over years have also been described [57].

Genetics and pathophysiology

Upon triggering of the immune system with an (infectious) agent, histiocytes (macrophages and dendritic cells), NK cells and CTLs are activated and mutually stimulate each other by receptor interaction as well as by secretion of a variety of inflammatory cytokines and chemokines. In immune-competent individuals, this concerted action leads to killing of the infected cell, removal of antigen and termination of the immune response. In conditions with an inherited or acquired defect of NK cells and CTLs, this process is impaired, the infected cell is not killed and persistently high cytokine levels lead to the clinical picture of HLH.

The cytotoxic function of NK cells and CTLs is mediated by the release of cytolytic granules, containing perforin, granzymes and other serine-specific proteases, into the immunological synapse that forms between the effector and the target cell. Cytolytic granules have to traffic to the contact site, dock and fuse with the plasma membrane and release their contents [111]. Several independent genetic loci related to this activity have been implicated in the pathophysiology of genetic HLH (Table 2).

In 1999, mutations in the perforin gene were described in eight patients with HLH [110]. Perforin is required for the introduction of cytolytic effector molecules (e.g., granzyme) into the target cell, thereby triggering the complex steps of apoptosis. A large spectrum of mutations has been described, and some appear to be associated with the geographical origin of the patients [64, 122]. Missense mutations may lead to a protein dosage effect of the mature protein [100]. *UNC13D* was the second gene found to be associated with FHLH [21]. *UNC13D* mutations do no impair docking of cytolytic granules at the plasma membrane, but they impair granule exocytosis with the subsequent release of perforin and granzymes. Recently, mutations in a third FHLH-associated gene, syntaxin 11, were identified [123]. The encoded protein, t-SNARE syntaxin 11, also plays a role in intracellular trafficking, but its precise role is not known. The protein was detectable only in monocytes and not in lymphocytes. Linkage analysis in two families of Pakistani origin revealed a fourth potential locus for familial HLH, but the gene has not yet been identified [83].

Table 2 Genetic defects in hemophagocytic lymphohistiocytosis

Disease	Chromosome location	Associated gene	Gene function
FHLH-1 OMIM %267700	9q21.3–22	Not known	Not known
FHLH-2 OMIM 603553	10q21–22	PRF1	Induction of apoptosis
FHLH-3 OMIM 608898	17q25	UNC13D	Vesicle priming
FHLH-4 OMIM 603552	6q24	STX11	Vesicle transport
GS-2 OMIM 607624	15q21	RAB27A	Vesicle docking
CHS-1 OMIM 214500	1q42.1–q42.2	LYST	Vesicle transport; not further defined
XLP OMIM 308240	Xq25	SH2D1A	Signal transduction and activation of lymphocytes

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Depending on the ethnic origin, 13%–50% of patients with FHLH have mutations in the perforin gene, and 17%–30% in *UNC13D*. So far, mutations of syntaxin11 have only been found in patients of Turkish origin and accounted for 19% of FHLH cases in this population. In 70% of the patients of German ancestry, the genetic defects are still unknown [122].

In patients with Griscelli syndrome tpye 2 (GS-2), immune dysfunction results from mutations in *RAB27A*, encoding a member of the small GTPase family [75] (Table 2). Activated T cells of Rab27a-deficient patients are unable to dock their secretory granules at the plasma membrane [74]. Munc 13-4 and Rab27a interact with each other; the complex seems to be an important regulator of secretory granule fusion with the plasma membrane [82]. The Chédiak-Higashi syndrome 1 is caused by mutations in the *LYST* (lysosomal trafficking regulator) gene [81]. The role of LYST in trafficking of granules, resulting in defective release of melanin or cytolytic enzymes, explains the hypopigmentation as well as the cytotoxic defect. The exact mechanism by which the LYST protein is involved in granule secretion, however, is not known yet [111]. X-linked lymphoproliferative syndrome results from mutations in the

SH2D1A (also known as *SAP*) gene [13] encoding for SAP, which can associate with several surface receptors of the signaling lymphocytic activating molecule (SLAM) family. Recent findings indicate that SAP is required for the function of SLAM, thereby participating in intracellular signaling [10], and for cytotoxicity of NK cells and CTLs by association with the receptors 2B4 and NTB-A of the SLAM familiy [76].

Thus, all known gene defects in HLH are involved in the cytolytic function of immune effector cells (Fig. 2): *LYST* mutations by impairment of granule secretion at a yet unknown stage, *RAB27A* defects by impaired docking of granules at the membrane, *UNC13D* mutations by defective granule priming at the immunological synapse, and *SH2DA1* mutations by impaired receptor engagement. Finally, the lack of perforin leads to impaired triggering of apoptosis. How the syntaxin 11 protein, which was found to be expressed only in monocytes, fits into this picture is presently not known. It may be speculated that the known interaction of dendritic and killer cells [24, 77] may play a role.

HLH cases associated with genetic defects in the granule exocytosis pathway demonstrate a critical role of the granule-dependent cytotoxic activity in T lymphocyte homeostasis [74]. Activated NK cells and CTLs can kill infected cells and antigen-presenting cells, thus reducing the antigen load; however, more complex mechanisms seem to be involved in the down regulation of the immune response.

The mechanisms leading to impairment of NK cells and CTLs in immune competent patients with acquired HLH are less clear. Viruses may interfere with CTL function by specific proteins [23], and high levels of cytokines may have the same effect [90]. In some patients a genetic susceptibility may be present as indicated by several mild episodes of HLH. Follow-up after an acquired episode of HLH is usually not stringent enough to identify this category of patients.

Macrophage activation syndrome

The macrophage activation syndrome (MAS) occurs in children and adults with autoimmune diseases, especially systemic onset juvenile rheumatoid arthritis (sJRA) or adult-onset Still's disease, but also lupus erythematodes or other entities [35, 94, 95, 108, 109]. Hadchouel et al. were the first to imply activated macrophages in its pathogenesis [35], and Stéphan et al. are credited with the first description as macrophage activation syndrome [109].

The clinical picture has all of the characteristic features of HLH, including clinical signs and symptoms, laboratory findings (especially very high ferritin levels), and hemophagocytosis, although initially blood changes may be less pronounced. Severe coagulopathy and cardiac impairment are common [108]. Neurological symptoms may progress to a severe encephalopathy and coma. Patients with MAS exhibit the defective NK cell function common to other patients with HLH [34]. They may also have decreased expression of perforin or SAP, mimicking the defects associated with FHL-2 and XLP, respectively [115, 121]. Interestingly, patients with sJRA could be distinguished

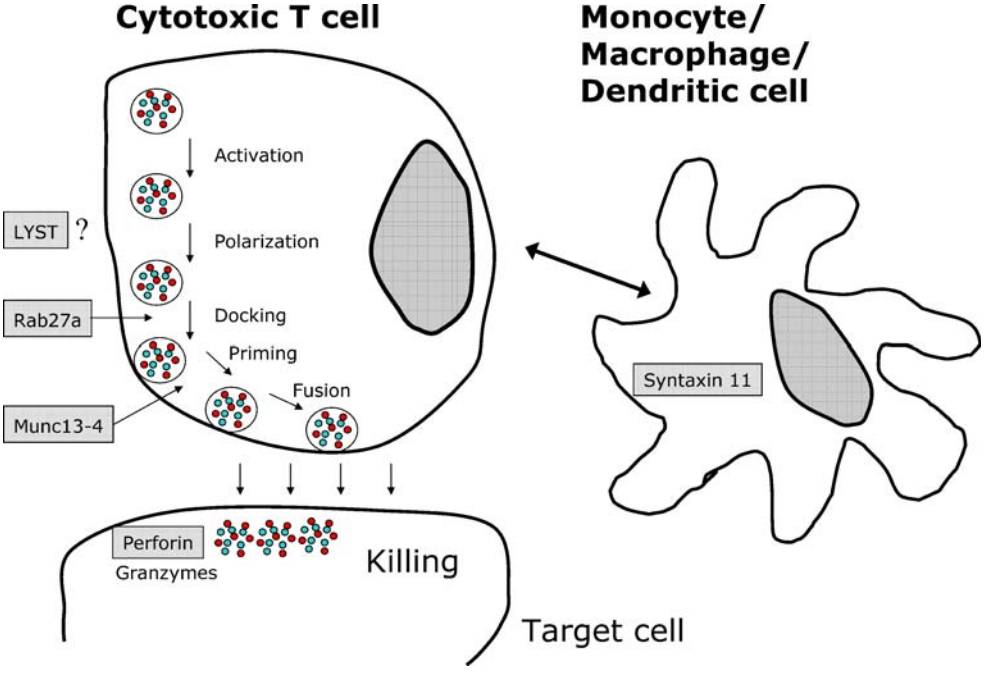

Fig. 2 Molecular mechanisms based on the identification of genetic defects associated with the clinical picture of familial hemophagocytic lymphohistiocytosis. Perforin is secreted via cytotoxic granules and leads to disruption of the target cell. Cytotoxic granule processing occurs by means of a complex that contains at least a Rab27a/Munc13-4 complex and several other unknown proteins. The exact functions of LYST and syntaxin 11 are not known. In case of syntaxin 11, monocytes or macrophages/dendritic cells may interact with cytotoxic cells by an unknown mechanism. Reprinted with permission from American Society of Hematology, Washington

from those with other clinical forms of juvenile rheumatoid arthritis by low NK cell function and perforin expression [119]. As triggering factors for MAS, viruses have been implicated, but also nonsteroidal anti-inflammatory drugs, methotrexate, and gold-salt injections.

The overall incidence of MAS is estimated to occur in up to 7% of patients with sJRA [94]. Mortality of patients with MAS is between 10–20%.

MAS may not be distinguishable from other cases of HLH when arthritis is missing. Several features, however, strongly suggest MAS in the author's own experience: a high C-reactive protein (which is unusual in HLH which is rarely triggered by a bacterial infection), an only moderate bicytopenia or pancytopenia at presentation, and a very high ferritin if EBV has been excluded as the trigger. In contrast to other forms of HLH, the bone marrow in patients with MAS usually is characterized by decreased erythropoiesis and a left shift of granulopoiesis. When the cytokine pattern is compared in patients with HLH and MAS, the pro-inflammatory IL-β is often elevated in MAS and the concentrations for TNFα and IL-6 tend to be higher.

Diagnostic problems and differential diagnosis

How to recognize HLH

In a patient with prolonged unexplained fever unresponsive to antibiotics, HLH as differential diagnosis should be kept in mind. It is typical that at first presentation the children are usually in a good clinical condition in spite of the high fever. Also typical is that the fever often subsides spontaneously, but recurs after days to weeks. A suspicious sign is always hepatosplenomegaly, which should prompt a complete blood count analysis. Indicative of familial HLH is parental consanguinity or unclear deaths during infancy in the family history.

Marked depression of peripheral blood cells in association with organomegaly are suspicious of HLH if leukemia has been excluded. It is important to think of the possibility of HLH in order to arrange for the appropriate laboratory studies. The progression of clinical signs and symptoms and of pathological laboratory values is a strong indication that this patient may have HLH.

Diagnostic requirements

Minimal diagnostic requirements are a complete blood count, transaminases, bilirubin (conjugated and unconjugated), triglycerides, ferritin, and a coagulation profile including fibrinogen. Children suspected of HLH should receive a bone marrow examination and spinal tap at an experienced center. If the bone marrow is not diagnostic and the diagnostic criteria are not yet fulfilled (see below), a repeat examination is indicated. Valuable diagnostic parameters are increased concentrations of sCD25 and decreased NK cell function, which, however, are only available in specialized laboratories. A search for an infectious organism is recommended, preferably by PCR methods since serology is unreliable. The most frequent triggering organisms are EBV, cytomegalovirus or other herpes viruses, Leishmania, and parvovirus B19.

The patients should be screened for an underlying disease like GS 2, XLP, CHS 1, autoimmune diseases or malignancy by detailed clinical history, physical examination and other appropriate studies.

Expression of perforin by flow cytometry can identify patients with perforin defects [69] and is also desirable in patients with MAS or other acquired forms of HLH in which data on perforin expression are still scant. In proven familial cases or in presumed familial cases with persistent or relapsing disease, material for genetic analysis should be obtained.

Diagnostic criteria

In 1991 the HLH Study Group of the Histiocyte Society published the first diagnostic guidelines for HLH. The diagnostic criteria were recently revised [61] and are shown in Table 3. For patients with sJRA who develop MAS, not all criteria may be relevant. For example, pre-existing inflammation is associated with a higher white blood count and platelets as well as fibrinogen. Accordingly, for MAS other preliminary diagnostic guidelines have recently been advocated that take the specific characteristics of these patients into account [96].

Why HLH is still overlooked

The main problem is that initially HLH masquerades as a normal infection and too little attention is paid to unusually marked hepatosplenomegaly or unusually severe blood count changes. Much time then may be lost with extensive work-up for an infectious disease or with prolonged antibiotic treatment. Ferritin, triglycerides, and fibrinogen are not routinely determined in children with fever; HLH has to be kept in mind to order these laboratory studies. Also progression of symptoms may be overlooked or may not be considered unusual. The absence of hemophagocytosis is often the reason why the diagnosis of HLH is ruled out.

Another problem is that the identification of an infectious organism may serve to explain all symptoms, without taking into account that their severity and progression indicate an immune deficiency.

Table 3 Diagnostic criteria for hemophagocytic lymphohistiocytosis*

List of criteria for HLH
1. Familial disease/known genetic defect
2. Clinical and laboratory criteria (5/8 criteria)
Fever
Splenomegaly
Cytopenia =>2 cell lines
Hemoglobin <90 g/l (below 4 weeks <120 g/l)
Platelets $<100\times10^9$/l
Neutrophils $<1\times10^9$/l
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides =>3 mmol/l
Fibrinogen <1.5 g/l
Ferritin =>500 μg/l
sCD 25=>2,400 U/ml§
Decreased or absent NK-cell activity
Hemophagocytosis in bone marrow, CSF, or lymph nodes

Supportive evidence are cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, LDH
*Janka and Schneider, Brit J Hematol 2005
§ For methods see Schneider et al. Blood 2002
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Misleading may be that some patients improve with unspecific methods such as transfusions or immunoglobulins. The fever may subside and laboratory values may transiently even revert to normal. If these children are not closely followed, signs like persisting splenomegaly or anemia may be overlooked.

In babies with huge organomegaly, abnormal liver function, or high triglycerides, diagnostic measures often focus on a metabolic disease before sufficient attention is paid to other symptoms.

Lymph node biopsies may be misinterpreted as lymphoma due to immature-looking activated lymphocytes; liver histology usually is interpreted as chronic hepatitis because phagocytosing histiocytes are not present or are overlooked, and brain biopsy may suggest encephalitis.

Hepatic failure may be the leading symptom hampering the correct diagnosis [86].

Finally, isolated CNS involvement, either preceding systemic symptoms or remaining the only manifestation, may present a formidable diagnostic challenge [22, 40, 66, 106].

Differential diagnosis

The main differential diagnosis is a normal infection in an immune-competent patient. It is the severity of symptoms and the progression that are important for differentiation. The characteristic laboratory values usually deviate markedly from values seen in a normal infection [61]. Triglycerides can be elevated during infections, but, apart from patients with bacterial sepsis, usually do not surpass values of 3 mmol/l in children. Low fibrinogen is a rather specific parameter for HLH as patients with infections (apart from disseminated intravascular coagulation) are expected to have normal or elevated levels. Ferritin may be elevated in children with infections, but values usually remain below 200 μg/l. However, it has to be remembered that children with systemic onset juvenile rheumatoid arthritis without signs of MAS may already have very high ferritin values.

Hepatosplenomegaly, fever and blood count changes are signs of acute leukemia (easily to be excluded by a bone marrow examination), but also of multisystem Langerhans cell histiocytosis (LCH). The characteristic skin rash, bone lesions (which are never found in HLH), lack of meningeal involvement and a distinct pathohistological picture clearly separate LCH from HLH.

Unremitting fever, lymph node enlargement, and organomegaly may be caused by large-cell anaplastic lymphoma (LCAL), formerly called malignant histiocytosis. Especially in the lymphohistiocytic variant, infiltration by benign macrophages may be prominent with only intermingled anaplastic large lymphocytes expressing CD30 and T cell markers [89]. As mentioned previously, LCAL may also be associated with a full-blown clinical picture of HLH.

Treatment and prognosis

Aims of treatment

The immediate aim in the treatment of any patient with HLH is to suppress the severe hyperinflammation that is responsible for the life-threatening symptoms. A second aim is to kill pathogen-infected antigen-presenting cells to remove the stimulus for the ongoing, but ineffective activation of cytotoxic cells. It should be emphasized that it is usually not sufficient to treat an identified organism to control hyperinflammation with the possible exception of leishmania-induced HLH, which in most patients can be treated successfully with liposomol amphotericin only. The third, and ultimate aim in genetic cases of HLH is stem cell transplantation to exchange the defective immune system by normally functioning cells. Treatment should be guided primarily by the severity of signs and symptoms, but also known familiarity of the disease, age of the patient and underlying conditions have to be considered [61].

Hyperinflammation, caused by hypercytokinemia, can be suppressed successfully by corticosteroids, which are cytotoxic for lymphocytes, inhibit the expression of cytokines and chemokines [31], and also interfere with the production of CD95 ligand and differentiation of dendritic cells [120]. Since dexamethasone crosses the blood brain barrier better

than prednisolone, it is preferred for treatment. Cyclosporin A inhibits activation of T-lymphocytes by interfering with the cyclophilin pathway [29]. As a single agent, it proved to be effective for maintaining remission [73] and for children with MAS [78]. Immunoglobulins probably act by cytokine- [101] and pathogen-specific antibodies. Etoposide, which was introduced to the treatment of HLH in 1980 [3], is highly active in monocytic and histiocytic diseases. Antithymocyte globulin in combination with steroids and cyclosporin A was used successfully in France [107].

To treat a febrile and pancytopenic child with corticosteroids, immunosuppressive drugs and cytostatics is a highly unusual experience for a pediatric oncologist and may take a lot of willpower. However, if hyperinflammation is not controlled, the patient will die from multiorgan failure, from bacterial or fungal infection due to prolonged neutropenia, or from cerebral dysfunction.

Choice of treatment

Children below 1 year of age in whom genetic HLH is likely and all patients with severe signs and symptoms such as progressive pancytopenia, coagulation problems, liver dysfunction and cerebral symptoms are candidates for combination therapy with dexamethasone, cyclosporin A, and etoposide. This is irrespective of the identification of an infectious organism with Leismaniasis as the possible exception. Less severe cases, usually in older patients, may do well with corticosteroids and immunoglobulins, but children have to be followed carefully for signs of progression [61]. Since initially mild cases may deteriorate rapidly, it is the author's opinion that the indication for the use of etoposide should be determined liberally. The risk of etoposide, even if given for 8 weeks, is by far exceeded by the risk of losing a patient through inadequate treatment.

For patients with MAS, corticosteroids with or without cyclosporin A are sufficient in most cases to control hyperinflammation; however, there is no clear consensus or evidence to suggest any particular therapeutic strategy [109, 94].

HLH in Chédiak-Higashi syndrome 1, Griscelli syndrome 2 as well as X-linked proliferative syndrome also responds to etoposide-containing regimens [61], but as in FHLH, the cure can only be achieved with stem cell transplantation.

Treatment of HLH associated with malignant lymphoma, with chemotherapy for malignancy, or with bone marrow transplantation during the period of inadequate immune function, has to be decided on an individual basis.

Immunochemotherapy is an effective treatment for HLH

FHLH used to be a rapidly fatal disease, if untreated. In the early 1980s, the median survival was less than 2 months [60]. The introduction of etoposide into treatment regimens and, most important, the possibility of stem cell transplantation (SCT) [27] were the basis for successful treatment.

The FHL Study Group of the Histiocyte Society was formed in 1989, and a treatment protocol for HLH was opened in 1994 (HLH-94). Patients with familial or non-familial HLH from 21 countries were recruited. The treatment included an initial 8-week period with dexamethasone and etoposide, followed by maintenance with cyclosporin A and alternating pulses of etoposide and dexamethasone for patients with known familial disease or presumed familial disease because of incomplete response or relapses. Maintenance was continued until stem cell transplantation. In patients with resolved, non-familial disease, treatment was to be discontinued after 8 weeks. Relapses after cessation of therapy qualified the patient for renewed treatment and stem cell transplantation.

The outcome of children treated for HLH on protocol HLH-94 was recently published [43]. At a median follow-up of 3.1 years, the estimated 3-year probability of survival was 55% for all 113 children and 51% for verified familial cases. Twenty-five patients (22%) died prior to SCT. Forty patients underwent SCT, and no familial case survived without a transplant. There were 23 patients alive (20 off therapy) who had not undergone SCT. All except one were above 1 year of age; the mean age at diagnosis was 47 months compared to 13 months for familial cases. Presumably, these patients in retrospect had acquired HLH, but were sufficiently ill to require HLH therapy.

The new follow-up protocol HLH-2004 is a modest modification of HLH-94; cyclosporin A is moved up front since previously many patients had experienced a relapse when dexamethasone was tapered after 2 weeks.

Treatment of CNS disease and of reactivations

In the HLH protocols, systemic treatment including dexamethasone, which penetrates the blood-brain barrier well, is the suggested first line therapy also for patients with CNS disease at diagnosis. Intrathecal therapy is recommended in patients with a persistently pathological CSF on a repeat lumbar puncture after 2 weeks. Nevertheless, several patients received intrathecal methotrexate up front. Of the 35 patients with CNS symptoms at diagnosis, an equal percentage had normalization of symptoms with or without intrathecal therapy [43].

Reactivations are a frequent problem, and many occur in the CNS. In a study of 65 children experiencing 93 reactivations, 30 were associated with neurological signs and symptoms [80]. Reactivations usually respond to an intensification with the drugs used for initial therapy. In the case of CNS reactivations, use of dexamethasone is

recommended as well as intrathecal therapy with methotrexate and prednisolone [58]. CNS involvement is a serious diagnosis since long-term survivors may have neurological sequelae.

Salvage treatment

About 25% of children with HLH do not reach bone marrow transplantation due to progressive disease. For patients not responding within the first 4 weeks to the three-drug combination, alternative therapies are missing. Antithymocyte globulin, which was shown to be effective as the front-line treatment [107], was reported to be also helpful in a non-responder [87], but from the author's own experience, it was ineffective as a rescue therapy in several patients. Treatment protocols for non-Hodgkin lymphomas or Hodgkin's disease induced a response in some refractory EBV-associated HLH cases [53, 58]. There are some case reports on treatment with drugs directed at TNF-α [44, 91], with the anti-CD25 antibody daclizumab [117], and with the anti-CD52 antibody alemtuzumab [A. Filipovich, personal communication]. In a child resistant to etposide, steroids and antithymocyte globulin, fludarabine was shown to be effective, allowing subsequent bone marrow transplantation [104]. Since therapeutic successes rather than failures tend to be reported, the value of these drug remains to be proven in larger numbers of patients. As yet, there is no established salvage treatment.

EBV-associated HLH

Among the herpes viruses, EBV is the leading triggering agent in HLH and deserves some special comments. EBV-associated HLH is a frequent and serious problem in Asia [51]. Genetic and environmental factors may play a role. Male patients with EBV-related HLH may harbor mutations in *SH2D1A* [113], and mutation analysis is recommended. Although mutations in *SH2D1A* were not found in seven Taiwanese children with EBV-associated HLH, a common pathway may be shared since the viral protein LMP1 was found to inhibit the expression of *SH2D1A* [11].

Fatal cases of EBV-related HLH have also been reported in Western countries [79]. Twenty-nine of the 180 HLH cases in the German registry, including also some proven familial cases, were caused by EBV and 9 were fatal [8]. Serology is of limited value to ascertain EBV infection in patients with HLH. In 94 cases from Japan, two thirds had a serological pattern compatible with previous exposure and only one third showed a pattern typical of either first exposure or reactivation [51]. In contrast to infectious mononucleosis where B cells are infected, EBV-associated HLH is characterized by oligoclonal or monoclonal proliferation of EBV-infected T or NK cells [65]. EBV-infected T/NK cells also appear to play a major role in the development of lymphoma-associated HLH [93].

Recently, it was shown that the prognosis for EBV-related HLH in children and young adults has improved considerably with immunochemotherapy including etoposide and corticosteroids. Twenty-one patients were first treated with corticosteroids alone, intravenous immunogloulins alone, cyclosporin A alone, or a combination of these drugs (conventional regimens) without etoposide, and 26 received an etoposide-based regimen initially. In a multivariate analysis, early introduction of etoposide-based regimens was the only significant variable for survival with a relative risk of death 14 times higher for patients not receiving etoposide or receiving it later than 4 weeks after diagnosis [54]. Interestingly, it was shown that etoposide interferes with EBV-induced lymphocyte transformation by the inhibition of not only DNA synthesis, but also synthesis of EBV nuclear antigen (EBNA) [67]. Although not all patients with EBV-associated HLH need etoposide, it is the author's opinion that the indication for its use should be handled generously since initially mild cases may progress very rapidly.

Stem cell transplantation

In 1986, the first report of successful bone marrow transplantation in HLH from an HLA-identical sibling was published [27]. Subsequently, several single cases and larger series with transplants from either related or unrelated donors confirmed that permanent control of the disease was possible [6, 9, 15, 48, 85]. Results of SCT in 86 children treated with protocol HLH-94 [48] show that matched unrelated donor transplants offer the same chance of long-term disease-free survival (approximately 70% at 3 years) compared to transplants from matched siblings. In contrast, results with family haploidentical donor transplants or mismatched unrelated donor transplants were less favorable with a probability of survival around 50%. Also cord blood transplants were successful in some patients. Patients that responded well to initial pretransplant induction therapy fared best. The rate of graft failure was 10%. Acute graft versus host disease (GvHD) grade II-IV was reported in 32% of the patients and chronic GvHD in 9%. Transplant-related mortality was high (26/86 patients), with many deaths attributable to pulmonary and liver problems [48].

Patients with HLH may have severe inflammatory reactions in the posttransplant period, especially around the time of early engraftment, often mimicking HLH [26]. Host T cell expansion (triggered by a viral infection) despite evidence of donor cell engraftment was found in two such patients [2]. The clinical picture of HLH in the first 4 weeks following bone marrow transplantation for a malignant disease has also been described in several reports [55, 72, 97].

Half of the children who receive SCT for HLH develop a mixed chimerism [85]. A sustained remission was achieved with a donor chimerism =>20% of leukocytes.

Recently reduced intensity conditioning with subsequent SCT, mostly from unrelated matched or mismatched donors, was reported for 12 children with HLH, 9 of whom survive [14]. The authors recommend this approach in patients with preexisting severe organ toxicity, but also caution against the increased risk of rejection.

Concluding remarks

HLH is a life-threatening disease characterized by uncontrolled hyperinflammation on the basis of various inherited or acquired immune defects. Awareness of HLH has been increasing over the past decades, but HLH is still often overlooked, especially in older children who have been perfectly healthy previously. Guidelines have been developed that are helpful to establish the diagnosis; however, it still remains difficult to diagnose HLH in its early stages. Genetic defects can now be identified in about half of the patients and have shed some light into the pathophysiology of HLH. Most gratifying, therapy with immunosuppressive and cytostatic drugs, followed by stem cell transplantation in genetic cases, has changed the prognosis from uniformly fatal to a cure rate of more than 50%. Detection of new gene defects, a better understanding of the complex pathophysiology, more effective salvage regimens, and a decrease of the high transplant-related mortality after stem cell transplantation are goals for the future.

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