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Review Article

Biology and Treatment of Hemophagocytic Lymphohistiocytosis

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ABSTRACT

Hemophagocytic lymphohistocytosis (HLH) is a hyperinflammatory syndrome that occurs at all ages and is characterized by high levels of cytokines, secreted by activated T-lymphocytes and macrophages. All symptoms and laboratory changes can be explained by organ infiltration by these cells and hypercytokinemia. HLH occurs as an inherited form (genetic, primary HLH) with mutations primarily in the cytotoxic vesicle pathway, and an acquired form that, in children, is triggered mostly by infections, but also by autoinflammatory/autoimmune diseases, malignancies and metabolic diseases. The pathogenesis of genetic forms of HLH can be explained by the inability of cytotoxic cells to induce apoptosis in (infected) target cells and to terminate the immune response for which perforin is essential. The pathogenesis of acquired forms is multifactorial, and several factors may have to be present for the development of HLH: e.g. acquired immune defects; stimulation of the innate immune system via toll-like receptors or danger signals; interference of viruses and tumor cells with cytotoxicity and apoptosis; secretion of cytokines by tumor cells; mutations or single nucleotide polymorphisms in genes important for the immune response; heterozygous mutations in HLH-genes; environmental factors. Treatment of HLH is a balancing act between too little and too much therapy; cytokines have to be downregulated without destroying all immune defenses. Once HLH is controlled, therapy can be ended in acquired cases, whereas genetic cases need hematopoietic stem cell transplantation for cure. Therapy with corticosteroids and etoposide, as in the international HLH studies, is still the standard of care. New promising drugs are available; clinical trials have to confirm their efficacy.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an inflammatory syndrome where a deregulated immune response results in uncontrolled activation of lymphocytes and histiocytes (macrophages), resulting in hypercytokinemia, that, untreated, may lead to organ failure and death.[1] Characteristic, although unspecific symptoms and laboratory findings are prolonged fever, hepatosplenomegaly, pancytopenia, elevated ferritin and triglycerides as well as low fibrinogen. Neurological symptoms are frequent. Hemophagocytosis, which has given the disease its name, may be absent initially and is not necessary for diagnosis.

HLH may occur at any age. It was first described in children as a familial disease;[2] with increasing frequency it is being reported in adults as well.[3]

Classification of HLH

HLH can be inherited (primary, familial) or acquired (secondary). So far, mutations in four genes have been identified in familial HLH (fHLH). Mutations in *PFR1* were the first to be linked to fHLH, followed by mutations in *UNC13D, STX11 and STXBP2*. In addition, the immune deficiencies Griscelli syndrome 2 (GS2) and Chédiak-Higashi Syndrome (CHS), which both are characterized by hypopigmentation, and the 2 x-linked lymphoproliferative diseases XLP-1 and XLP-2 are also counted among primary HLH. In babies and young

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children, a genetic basis for HLH predominates. However, considering all pediatric age groups, non-genetic cases prevail.[4] These children have either infectious triggers, or, less frequently, autoimmune/autoinflammatory diseases, metabolic diseases, malignancies, or other rare immune deficiencies. Infectious triggers have also been reported in genetic HLH.[5] Recently, the need for an infectious trigger for primary HLH has been questioned.[6] In adults, malignancies or infectious triggers predominate;[7] a minority of patients harbors mutations in HLH-relevant genes. In a large series in 178 adults, biallelic or monoallelic mutations in HLH genes were found in 6.8%, respectively 7.4% of the patients.[8] The preponderance of hypomorphic mutations in adults correlates with the later-onset of disease.

HLH in the context of autoinflammatory/autoimmune diseases is commonly called macrophage activation syndrome (MAS) or MAS-HLH.

Biology of HLH

Biology of HLH can be divided into the biological mechanisms that lead to the disease (pathogenesis) and the physiological processes, which explain clinical symptoms and laboratory finding (pathophysiology).

Pathogenesis of HLH (Figure 1)

The genes mutated in fHLH play an important role in recruitment, trafficking and contents of cytotoxic vesicles in natural killer (NK) cells and cytotoxic T lymphocytes (CTLs), leading to failure of apoptosis of the target cell.[9] *UNC13D* is important for priming of docked cytotoxic granules for membrane fusion. *STX11* regulates granule membrane fusion and interacts with *STXPB2*. *PRF1* codes perforin which together with serine proteases, secreted into the immunologic synapse by cytotoxic vesicles, leads to apoptosis of the target cell. Perforin is also vital in downregulating the immune response by eliminating activated dendritic cells. Mutations in *LYST* (CHS) cause defective formation and maturation of cytotoxic granules. In GS2 the mutated protein prevents docking at the membrane. The inability of NK cells and CTLs to kill the target cell leads to failed disengagement of killer cell and target cell, prolonging mean synapse time fivefold and greatly amplifying the amount of inflammatory cytokines.[10] In XLP-1, where *SH2D1A* codes SAP, impairment of cytotoxicity does not involve the secretory pathway of cytotoxic granules. The specific susceptibility to Epstein-Barr virus is explained by a selective cytotoxic impairment of SAP-deficient CTLs towards infected B cells.[11] XLP-2 is linked to mutations in *XIAP (BIRC4)* that are not associated with loss of cytotoxic function.[11] XIAP restricts inflammasome activation in mice.[12] Like patients with *NLRC4*-related disorders, also a rare cause for HLH,[13] XLP-2 patients may develop inflammatory

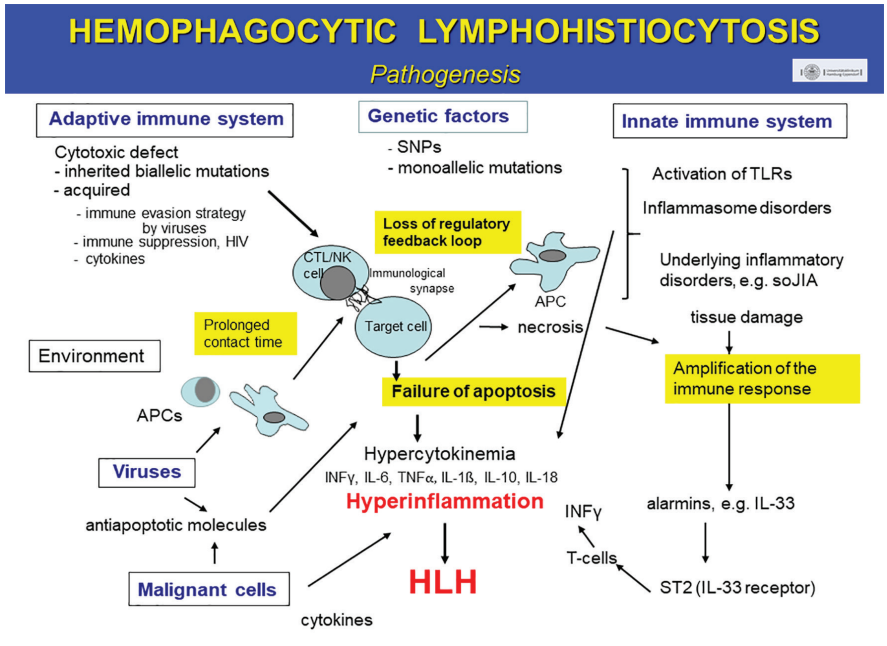

Figure 1: Adaptive immune system: Normally, natural killer cells and cytotoxic T-lymphocytes engage with the antigen-presenting target cell, leading to apoptosis. Failure of apoptosis as consequence of inherited or acquired cytotoxic defects or defective activation or signaling of T-cells, results in a prolonged synapse time with augmentation of cytokine secretion, leading to the clinical picture of HLH. Perforin deficiency as consequence of genetic disorders of the cytotoxic granule pathway, results in the loss of the regulatory feedback loop that eliminates antigen-presenting cells. Failed apoptosis is associated with alternate cell death, which, as does tissue damage, elicits the production of alarmins that can amplify the immune response by signaling through ST2. Genetic factors: Besides biallelic mutations leading to cytotoxic defects, or mutations affecting T cell signaling or activation, single nucleotide polymorphisms in genes important for the immune response, or monoallelic mutations in HLH-relevant genes, can be contributing factors. Innate immune system: activation of toll-like receptors and inflammasome disorders, can also lead to the clinical picture of HLH. Autoinflammatory diseases, such as systemic-onset juvenile idiopathic arthritis, already have a high inflammation levels that can be further augmented by infections. Viruses: Viruses are able to interfere with cytotoxicity, as well as apoptosis. Malignant cells: Malignant cells inhibit the extrinsic and intrinsic pathway of apoptosis and produce cytokines. The role of environmental factors is debated.
Abbreviations: CTL=cytotoxic T-lymphocyte; NK cell=natural killer cell; HIV=human deficiency virus; SNPs=single nucleotide polymorphisms; APC= antigen-presenting cell; TLRs=toll-like receptors; soJIA=systemic-onset juvenile idiopathic arthritis.

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bowel disease and have high levels of IL-18.

Besides defects in cytotoxicity, there can be other mechanisms that lead to the clinical picture of HLH, as proven by patients with a severe combined immune deficiency and lack of T-cells, developing HLH nevertheless.[14] There is evidence from several studies in mice that the innate immune system plays an important role in the development of HLH. Repeated activation of toll-like receptor (TLR) 9 induces HLH in mice,[15] and abrogating the function of the TLR adaptor myd88 prevents HLH in *UNC13D* mice.[16] A recent paper showed that blockade of ST2, the myd88-dependent receptor for interleukin-33, markedly improved survival of LCMV-infected perforin-deficient mice.[17] IL-33, an alarmin, is likely released from damaged tissues and adds to increased interferon-γ production, and thus hyperinflammation.

Pathogenesis of HLH may also involve inhibition of cytotoxic function by viruses and cytokines,[18, 19] interference with apoptosis by viruses and tumor cells 2014,[20, 21] secretion of cytokines from tumor cells,[22] acquired immune defects by drugs or HIV infection, and possibly also an imbalance between viral load and immune effector cells. Genetic factors include mutations or single nucleotide polymorphisms in genes important for the immune response;[23] heterozygous mutations in HLH-genes may also contribute.[24] Finally, environmental factors cannot be excluded.

Pathophysiology of HLH

The clinical symptoms and laboratory findings of HLH can all be explained by hypercytokinemia and organ infiltration by activated lymphocytes and histiocytes. Fever is caused by interleukin (IL)-1 and IL-6. Several factors are involved in pancytopenia besides phagocytosis of mature blood cells. Interferon-γ (INF- γ) and tumor necrosis factor- α (TNF-α) both inhibit hematopoiesis and increase apoptosis.[25, 26] A recent paper presented evidence that hematopoietic stem cells (HSCs) themselves are phagocytosed in HLH patients.[27] Self-recognition to prevent phagocytosis is regulated by interaction of CD47 (expressed in hematopoietic cells) and SIRPA (expressed in macrophages). Inflammatory cytokines downregulate CD47 specifically in HSCs. CD47 was shown to be downregulated in stem cells of HLH patients with active disease. Consequently, the number of HSCs in HLH patients was reduced to 23% of those in healthy adults.[27] Infection of HSCs or supportive stromal cells by several viruses may also play a role in pancytopenia. Increased triglycerides can be explained by decreased lipoprotein lipase [28] and increased synthesis.[29] Several mechanisms exist for the elevated ferritin levels which are found in nearly every patient with HLH: TNF-α and oxidative stress lead to increased synthesis of hemoxygease-1 [30] which cleaves hemoglobin, thus stimulating ferritin synthesis. Passive release of ferritin from damaged liver cells may be another cause.[31] Finally, increased iron absorption could play a role.[32] Various cytokines induce plasminogen activator,[33] leading to cleavage of plasminogen into plasmin, which induces hyperfibrinolysis. The large number of activated lymphocytes can explain the high levels of the α-chain of the soluble interleukin-2 receptor (sCD25).

Treatment of HLH

HLH treatment aims at suppressing hyperinflammation with its dangerous side effects for the host. Another aim is to eliminate the target cells by cytotoxic treatment since apoptosis of the (infected) cell is deficient. It is of vital importance to also treat the underlying trigger to prevent persistent stimulation of the immune cells. If there is an underlying genetic defect, the immune system has to be replaced by hematopoietic stem cell transplantation.

Agents directed at hyperinflammation are immunosuppressive/immunomodulatory or cytotoxic agents. Corticosteroids are included in all HLH treatment protocols. Immunomodulatory agents comprise intravenous immunoglobulins, cyclosporine A, antagonists of single cytokines (IL-1, IL-6, INFγ), the janus kinase 1/2 inhibitor ruxolitinib, and antibodies against the IL-2 receptor (basiliximab). Cytokines can also be removed by plasmapheresis[34] or a cytokine-adsorption column.[35] Corticosteroids and T-cell antibodies are cytotoxic for lymphocytes; cytotoxicity of rituximab is restricted to CD19 positive cells. In 1980, a seminal paper appeared, showing that etoposide had marked efficacy in patients with HLH.[36] In perforin-deficient mice, etoposide selectively ablated activated T-cells.[37]

In 1989 the HLH Study Group of the Histiocyte Society was founded and in 1994 the first international HLH protocol was started. Therapy consisted of dexamethasone, etoposide, and cyclosporine A. In the subsequent protocol HLH-2004, cyclosporine A was moved upfront to increase the initial response rate and to prevent the reactivations that were frequent when dexamethasone was tapered and etoposide doses decreased. Both protocols targeted children with familial disease or infection-triggered disease without known underlying condition such as malignancies or autoimmune diseases. The results of both studies have been published.[38, 39] Most patients entered into the studies had genetic/familial HLH. In both protocols, 14% of patients died within 2 months, nearly all because of nonresponse to treatment. Another 10% (HLH-1994), respectively 6% of patients (HLH-2004) died within 12 months. Mortality after stem cell transplantation was over 30% in both studies. Altogether, probability of 5-year survival was 61% in the 369 patients of study HLH-2004.[39] CNS reactivations with a high potential of late sequelae continue to pose a severe problem.[40]

Since results of HLH-2004 were not significantly different, and there was some concern about neurotoxicity of combined high-dose dexamethasone and cyclosporine A, the recommendation of the HLH Study Group is to use protocol HLH-1994. Just recently, the HLH Steering Committee of the Histiocyte Society has worked out recommendations on the use of protocol HLH-1994.[41]

Therapy of HLH is a two-sided sword: On one hand, it has to suppress hypercytokinemia to prevent its dangerous effects on organ function, but on the other hand, treatment should not destroy all defense mechanisms and may be counterproductive for control of infectious triggers and recovery of the bone marrow.

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Not all patients need the full HLH-1994 protocol. Less severe cases often respond to corticosteroids +/- immunoglobulins or fewer doses of etoposide. However, the dynamics of the disease have to be watched carefully. Patients with MAS-HLH usually respond to high-dose methylprednisolone, with or without cyclosporine A. However, Anakinra is also a very useful agent for this condition.[42]

Patients who do not respond within 2 weeks, are candidates for salvage treatment. Data on salvage treatment are scarce; the most frequent data are on alemtuzumab[43] which is very effective in front-line treatment with a complete response rate of more than 80% (Moshous D., pers. comm.) Emapalumab, an interferon-γ antibody has been tested in in children, most of whom had relapsed or refractory disease.[44] Comprehensive data have not been published yet. A study, using liposomal doxorubicin, etoposide and methylprednisolone in 34 adults refractory to HLH-1994 treatment after 2 weeks (lymphoma patients excluded) showed 12 complete and 14 partial remissions; 8 patients failed to respond.[45] There are anecdotal reports of other agents, including ruxolitinib, which seems to be a promising agent. Ruxolitinib has shown good efficacy in several mouse models.[46, 47]

Patients with genetic HLH can only be cured by hematopoietic stem cell transplantation (HSCT). Myeloablative conditioning was associated with a high transplant mortality both in study HLH-1994 and HLH-2004. Reduced intensity conditioning leads to a better survival rate,[48, 49] but mixed chimerism often necessitates donor lymphocyte infusions or a second stem cell boost.[50] In a recent international survey on patients transplanted for HLH, donor chimerism of 20-30% was found to be protective against late reactivation. Interestingly, several patients did not reactive in spite of a persistently low overall and lineage-specific donor chimerism of ≤10%.[51] Children with acquired HLH are usually no candidates for HSCT. However, the experience with EBV-associated HLH that is very frequent in Asia shows that these patients often have a refractory course, possibly associated with evolution into proliferation of malignant cells, which necessitates HSCT.[52]

Conclusion

HLH is a hyperinflammatory syndrome arising on the basis of many underlying conditions. Treatment has to be adjusted to the severity of the disease and the underlying condition. Etoposide-based treatment protocols have improved survival considerably; however, mortality in the first 2 months is still high. Some newer drugs are in clinical testing and could prove to be valuable alternatives or additions.

Conflict of Interest: None declared.

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