Hemophagocytic Lymphohistiocytosis and Infections

An Update

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Key Words: hemophagocytic lymphohistiocytosis; pediatric; infection

Hemophagocytic lymphohistiocytosis (HLH) is not one condition but descriptive of a life-threatening, hyperinflammatory syndrome with multiorgan involvement with a variety of triggers, both genetic and environmental. It is described as primary HLH (familial HLH) and secondary HLH (acquired following malignancy, rheumatologic disorders, primary immune deficiencies or infection alone). Infections commonly precipitate HLH in those with primary HLH, in combination with an underlying disease (malignancy, rheumatologic or primary immune deficiency) or may be the sole trigger.[1] Many people with "secondary" HLH may also have potentially pathogenic polymorphisms in an HLH- associated gene.[2] Rapid diagnosis of HLH and initiation of appropriate treatment is essential to reduce mortality from this condition.

Accepted for publication November 6, 2018.
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The authors have no funding or conflicts of interest to disclose.
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ISSN: 0891-3668/19/3803-0e54
DOI: 10.1097/INF.0000000000002248

PATHOGENESIS

Across the spectrum of HLH, impaired natural killer (NK) and cytotoxic T lymphocytes (CTL) function has been a consistent finding. These cytotoxic deficiencies lead to loss of feedback inhibition on activated macrophages resulting in a "cytokine storm," causing multiorgan tissue damage. The excessive activated macrophages engulf host blood cells (hemophagocytosis), which may be seen in biopsies from the bone marrow, lymph nodes, liver and spleen.[1,3]

Around 25% of all HLH presentations are thought to be autosomal recessive primary HLH and these commonly present in early life, although may develop at any age. Genes identified as causing monogenic HLH include: *PRF1*, *UNC13D*, *STX11*, *STXBP2*. Other genetic causes of HLH include primary immunodeficiency syndromes including Griscelli syndrome (*RAB27A*), Chediak-Higashi syndrome (*LYST*), Hermansky-Pudlak 2 (*Ap3B1*) and X-linked lymphoproliferative disease 1 and 2 (*SH2D1A*, *XIAP*).[2]

Viral infections are a common precipitant in primary HLH, malignancy and in those without known underlying disease. Epstein-Barr virus (EBV) is a well-described trigger and X-linked lymphoproliferative disease is almost exclusively associated with EBV.[4,5] Other common viruses found in association with HLH include cytomegalovirus (CMV), parvovirus, herpes simplex virus (HSV) (particularly neonates), varicella-zoster virus (VZV), measles, human herpes virus (HHV)-6, HHV-8, H1N1 influenza virus, parechovirus, parvovirus, Dengue virus and HIV. Bacteria causing HLH are far less common, but Gram-negative bacterial infections, Brucellosis and *Mycobacterium tuberculosis* associated HLH have been described. HLH has also been described in fungal infections such as *Histoplasma capsulatum* and in parasitic infections such as Leishmania and malaria.[6]

Malignancy is a common cause of HLH, especially lymphoid malignancies with acute B-lymphoblastic leukemia being the commonest. Cytokines produced by malignant cells activate CTLs, NK cells and macrophages. HLH also can occur during hematopoietic stem cell transplantation, especially in the early phase.[6]

Rheumatologic conditions, especially systemic-onset juvenile idiopathic arthritis and less commonly polyarticular juvenile idiopathic arthritis, systemic lupus erythematous and Kawasaki disease can present with HLH at diagnosis, during treatment or any time in response to infection; therapeutic drugs themselves may trigger HLH. In the context of a rheumatologic condition, HLH is referred to as macrophage activating syndrome.[6]

Any of the primary immune deficiency disorders will increase the risk of HLH as a

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result of the immune dysregulation. In combined immune deficiencies, viral infections are commonly associated with HLH, especially EBV and CMV, and in chronic granulomatous disease patients, common infectious precipitants were *Burkholderia cepacia*, Leishmania and fungi. The development of HLH in patients with absence of T and NK cells indicates excess macrophage activation may occur independently of lymphocytes.[7]

CLINICAL PRESENTATION AND INVESTIGATION OF HLH

Regardless of the underlying cause, HLH is a clinical diagnosis with supporting laboratory criteria. Typically, patients are febrile, acutely unwell with multiorgan involvement; therefore, the initial differential diagnosis includes liver disease, encephalitis, malignancy, autoimmune, rheumatologic diseases and general sepsis. A family history of immunodeficiency, consanguinity or autoimmunity may be relevant. Key clinical features identified in the HLH-94 study were hepatosplenomegaly (95%), fever (93%), lymphadenopathy (33%), neurologic symptoms (33%) and rash (31%).[8] Other features include bleeding (epistaxis, hematemesis, rectal bleeding, petechiae and purpura), liver dysfunction and respiratory insufficiency. Specific features (such as albinism) may point towards syndromes predisposing to HLH (eg, Chediak-Higashi syndrome, Griscelli syndrome type 2 and Hermansky-Pudlak syndrome type 2). In the neonate, HLH may present with isolated central nervous system disease or fulminant liver failure.[6]

Figure 1 outlines suggested investigations and management. Early laboratory parameters in a septic child which indicate the development of HLH are a climbing ferritin >500 μg/L (ferritin >10 000 μg/L in children was found to be 90% sensitive and 96% specific for HLH[9] however, diagnosis and treatment should not be delayed until ferritin reaches this threshold); evolving cytopenias which are transfusion dependent, (anemia and thrombocytopenia present in over 80% patients on presentation[9]); and multiple organ involvement (renal, liver, neurologic). High triglycerides and low fibrinogen further support the diagnosis of HLH. A rising C-reactive protein occurs, while erythrocyte sedimentation rate may fall due to reduced fibrinogen from liver consumption.[6] Low immunoglobulins or lymphocyte subsets point towards an underlying immunodeficiency although commonly deranged by severe illness.

Bone marrow biopsy, where possible, is useful to provide evidence of hemophagocytosis and to look for any underlying malignancy. It should also be sent for microscopy, culture and viral and Leishmania polymerase chain reactions (in endemic areas). Hemophagocytosis is not always visualized in the bone marrow during HLH; it may also be present in lymph nodes, liver and spleen and is not specific for HLH. If lymphadenopathy is present, node biopsy should be taken as lymphoma is frequently the underlying condition. Cerebrospinal fluid shows a pleocytosis in 50% of cases and a high protein.

DIAGNOSIS

The HLH-2004 protocol uses the presence of 5/8 criteria to diagnose HLH: (1) fever, (2) splenomegaly, (3) bicytopenia, (4) hypertriglyceridemia and or hypofibrinogenemia, (5) hemophagocytosis, (6) low/absent NK cell activity, (7) hyperferritinemia (>500) and (8) high soluble interleukin-2 receptor levels.[10] However, probable HLH should be considered and treated well before the presence of 5/8 criteria, as several of the tests are only done in reference laboratories and if treatment is delayed for these results, it may be too late to reverse the process. Other common features aiding diagnosis include liver enzyme derangement and neurologic abnormalities.

All cases of HLH should be investigated for primary immunodeficiency syndromes, and underlying genetic causes as clinical presentation cannot distinguish between primary and secondary HLH. Soluble interleukin-2 receptor alpha is a useful marker of disease activity but is not available in most centers. Protein expression studies and genetic panels are helpful in diagnosing primary HLH conditions which will need HSCT for definitive cure.

MANAGEMENT

Patients with HLH commonly require pediatric intensive care support to maximize chances of survival. Replacement blood products are necessary to maintain hemoglobin, platelet levels and normal coagulation. Induction of amenorrhea is advised in menstruating girls. Whilst supportive therapy is given, the priorities for initial management are identifying and treating the trigger, exclusion of malignancy (as this diagnosis is difficult once immunosuppression has been given) and early immune modulation.[11] These patients may deteriorate quickly and should be treated in centers with facilities for bone marrow transplantation and intensive care. Prompt aggressive therapy may be necessary even when infection is present.

It may be possible to tailor therapy according to the severity of the condition and the rapidity of response. In some cases, where early intervention produces a rapid response then induction chemotherapy may be avoided or weaned with close monitoring. However, if the condition does not respond to initial management, then early recourse to more aggressive treatment will be necessary; in primary, persistent or recurring HLH, chemotherapy should be continued to HSCT.[12] Opportunistic infection during therapy may confound the picture and careful surveillance is necessary particularly where symptoms recur after an apparent initial response.

Key markers of response to treatment are resolution of fever, reducing ferritin (although it can be slow to decline and levels fluctuate with blood transfusions), reducing transfusion requirements, improved coagulation parameters and resolving organ dysfunction. Neurologic involvement should be monitored with serial cerebrospinal fluid analysis with each intrathecal therapy and neuroimaging. Weekly monitoring of soluble interleukin-2 receptor alpha or soluble CD163 may be helpful to guide reduction or increase in therapy. Markers of infection should be monitored for response to treatment.[12]

When induction therapy is being planned, HLA tissue typing should be sent to allow for rescue HSCT without delay if this becomes necessary. The HLH-1994 protocol[8] recommends combination chemotherapy [etoposide, ciclosporin A, corticosteroids and intrathecal methotrexate if (central nervous system) involvement] followed by HSCT for persistent, recurring or primary HLH. The HLH-2004 protocol modified this with early cyclosporin, but survival was not significantly improved.[10] An alternate regimen using steroids and anti-thymocyte globulin (ATG) was similarly effective.[13]

Survival is dramatically improved with these protocols compared with survival without treatment with an overall survival at 3 years of 55% (51% in the familial cases) and 3-year probability of survival 3 years after HSCT of 62%.[8]

Trials comparing a combination of the two main regimes (the Hybrid Immunotherapy trial and the European cooperative pilot study for testing Hydbrid ImmunoTherapy for Hemophagocytic LymphoHistiocytosis (EuroHIT-HLH) trial) have finished recruiting, and results are awaited. Other studies of alternate or combination approaches have also been initiated with agents such as alemtuzumab, ruxolitinib and anti-interferon gamma monoclonal antibody. Alemtuzumab (monoclonal antibody to CD52 protein expressed on surface of mature T cells and NK cells) may be a useful salvage agent for refractory HLH enabling survival to HSCT.[12]

CONCLUSIONS

HLH is a life-threatening hyperinflammatory condition that needs to be considered early in any patient with fever, multiorgan failure and cytopenias. Infection plays a key role as a trigger but also causes concern for clinicians when delivering the necessary immunosuppression to terminate the cytokine storm.

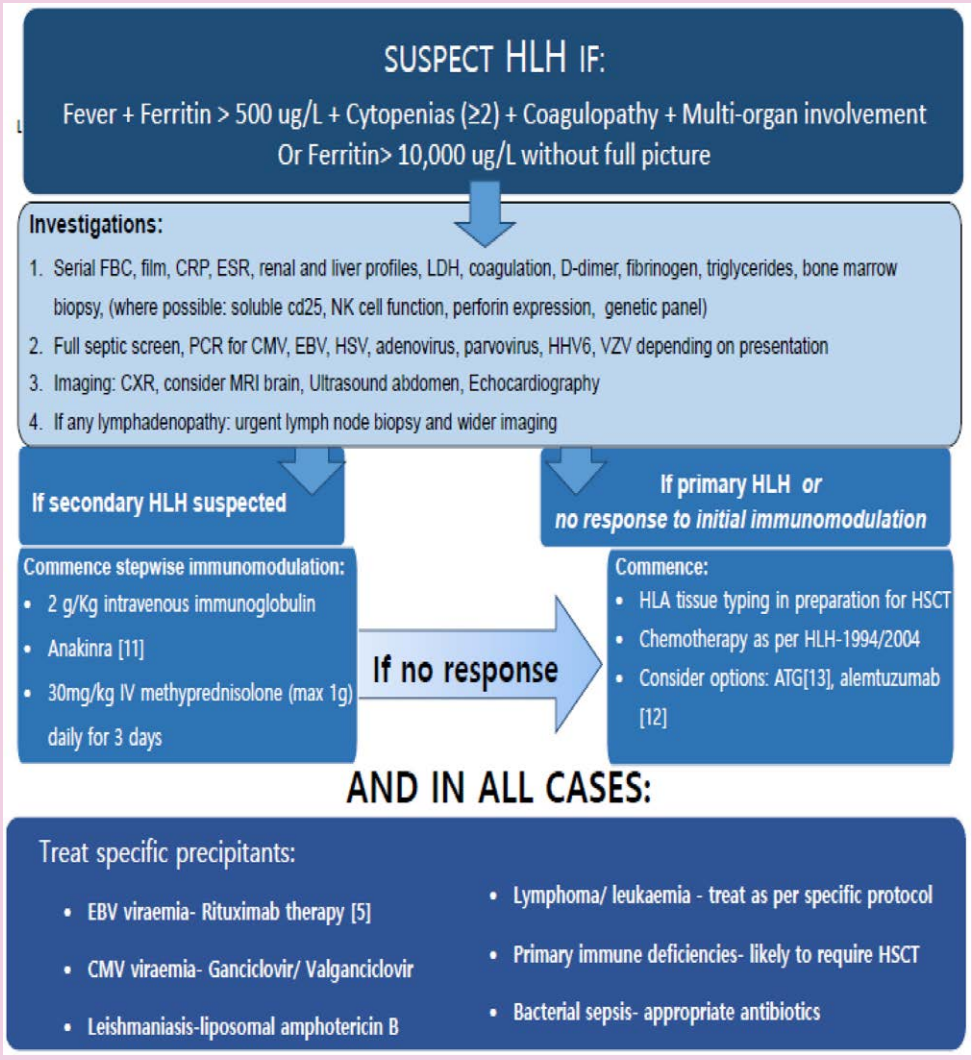

FIGURE 1. Investigation and management of HLH. CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IV, intravenous; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCR, polymerase chain reaction. Full blood count (FBC), Chest radiograph (CXR), haematopoietic stem cell transplant (HSCT).

Immunomodulatory treatment should be started if high clinical suspicion, and not wait for specific immunology and genetic testing. Early recourse to chemotherapy and planning for HSCT if HLH is recurrent or refractory to initial treatment. Survival has improved with this treatment, however, mortality remains very high.

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