Review

Haemophagocytic Syndrome

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Haemophagocytic Syndrome(HS)/Haemophagocytic Lymphohistiocytosis (HLH) is a life threatening and relatively uncommon medical condition with excessive immune activation. It is a hyper-inflammatory condition which leads to dysregulated immune activity resulting in malignant inflammation and multi-organ dysfunction syndrome.[1,2] The disease can be classified as either primary or secondary. Primary HLH is the result of inherited genetic mutations whereas secondary HLH can be caused by an inappropriate host response to infection, malignant condition or an autoimmune disease.[3]

Primary Haemophagocytic Syndrome

It presents in early childhood as a result of genetic mutations that leads to dysregulation between NK (Natural killer) cells, $CD8^+$ cytotoxic cells and antigen presenting cells. These can be due to an increase in the production of pro-inflammatory cytokines leading to systemic activation of macrophages and subsequent cellular destruction. The primary HLH can be subdivided into hereditary, syndromic and familial HLH.[4] If not detected and treated on time it is usually fatal, typically within few months. Even with treatment the prognosis is sometimes only for few years, unless a bone marrow transplant can be successfully performed.

Secondary Haemophagocytic Syndrome

It triggers in response to underlying critical illness rather than an underlying genetic mutation. The most common triggers include sepsis, malignant condition and autoimmune disease. In the context of autoimmune disorder it is referred as macrophage activation syndrome (MAS).[5] The secondary HLH, if detected early and treated promptly then the prognosis appears to be better.

Symptoms and signs of HLH

The HLH is not a single disease, but it is rather a hyperinflammatory condition caused by excessive activation of lymphocytes and macrophages which lead to production of high levels of cytokines. Fever and enlargement of the spleen are the most common symptoms of HLH. Apart from these, it clinically manifests as enlargement of the liver, rashes, enlargement of the lymph nodes, yellowish discoloration of skin and eyes.[6] In case of genetic HLH, atypical symptoms in form of chronic diarrhea and sensorineural hearing loss. The clinical condition resembles chronic variable immunedeficiency.[7] Laboratory findings may include elevated triglyceride levels, transaminases, low fibrinogen levels, hyperbilirubinemia, high lactate dehydrogenase (LDH) level and ferritin levels. The neurological manifestations in form of seizures, retinal haemorrhages, ataxia and altered consciousness can also be present.

In general, HLH is a syndrome of pathologic immune activation with clinical manifestation of intense inflammation. HLH can present with an extreme end of the spectrum of the inflammatory reactions and it is characterized by the magnitude of the clinical and laboratory abnormalities. The intense progression of the symptoms and uncontained hyperinflammation, results in high mortality with multi-organ dysfunction syndrome. CNS dysfunction and bacterial and fungal infections due to prolonged neutropenia can also be present.

Diagnosis

There are 2 scoring systems widely used for the diagnosis of HLH. First is HLH2004 criteria and second is Hscore (HLH probability calculator). Mutation testing is not done routinely and is reserved for children who has a strong family history of HLH. Flow cytometry is alternative to mutation testing but has low sensitivity.

HLH2004 criteria:

Molecular diagnosis consistent with HLH Or 5 of the 8 criteria listed below 1. Fever ≥ 38.3°C 2. Splenomegaly 3. Cytopenia (affecting at least two of the three lineages in the peripheral blood) Hemoglobin < 9 g/dL (infants upto 4 weeks: hemoglobin <10 g/dL) Platelets < 1,00,000/µL Neutrophils < 1000/µL 4. Hypertriglyceridemia (≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 150 mg/dL) 5. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver 6. Low or absent NK cell activity 7. Ferritin ≥ 500 ng/mL 8. sCD25(Soluble form of CD25) (sIL2Ra) ≥ 2400 U/mL

H-score

It is an online calculator which takes into consideration immunosuppression, fever, organomegaly, hypertriglyceredmia, ferritin, AST (aspartate aminotransferase)/SGOT (serum glutamic oxaloacetic transaminase), fibrinogen, cytopenias of only 1 or more cell lineages and hemophagocytosis in bone marrow samples. The total score varies from 0 to 337 & optimal cut off for diagnosis is 169, which has a sensitivity of 93% and a specificity of 86%.[9] The sensitivity and specificity of the H-Score are greater in the pediatric group (100% and 80%, respectively) than in adults (90% and 79%, respectively).[10] However there is not much difference between the sensitivity and specificity for HLH2004 and H-score in critically ill adult patients.

Morphologic Diagnosis

The typical microscopic findings include haemophagocytosis seen in lymphocytes and macrophages. Bone marrow is the commonest site but can also be seen at lungs, CSF, meninges, liver, spleen, lymphnodes and even in subcutaneous sites.[11] It is important to note that haemophagocytosis is not specific to diagnose HLH, without other features.

Laboratory Features

Serum Ferritin has a good negative predictive value, while high values are neither sensitive or specific to HLH.[12] Altered renal functions is another prominent finding which has poor outcome with hypofibrnogenemia.

Differential Diagnosis

1. Sepsis[13]
2. Atypical infections like Tuberculosis, Brucella, visceral leishmaniasis, Bartonella, Histoplamosis, Adenovirus and herpes simplex
3. DRESS (Drug reaction with eosinophilia and systemic symptoms)
4. Fulminant hepatic failure in pediatrics
5. Gaucher's and Wolman disease in pediatrics
6. Viral encephalitis or CNS vasculopathy[13]
7. Langerhan cells histiocytosis

Treatment

Being a high mortality disease with survival rate of less than 5% at 1 year, it is best to start treatment early and remain aggressive to control the disease.

HLH94 Protocol

The standard HLH94 treatment protocol which is widely used in most centers includes giving 8-week therapeutic dose of etoposide (150 mg/m^2 twice weekly for
2 weeks and then weekly) plus dexamethasone (initial dose of 10 mg/m^2 slowly tapered over 8 weeks). Those patients who have familial disease or persistent disease should be continued on above treatment till allogenic

stem cell transplant has been done. Pulses of dexamethasone (10 mg/m^2 for 3 days every second week) and etoposide (150 mg/m2 every alternating second week) with daily oral cyclosporine therapy should be given as continuation treatment. Those with neurological findings benefit from intrathecal methotrexate.[14] Adult treatment is almost same as pediatric population but since adults have more comorbidities, the chances of end organ damage due to cytokine surge are very high.

HLH2004 Protocol

It is similar to HLH94 Protocol, but the only difference is that starting of cyclosporine A in the initiation phase itself in the beginning so as to get immunosuppression and oppose the action of Interferon γ. In this protocol haemopoietic stem cell transplant is performed as soon as the donor is available. It is advisable to administer intrathecal prednisolone along with methotrexate for patients with neurologic symptoms.

Salvage therapy for relapsed and refractory cases

Following agents can be used
Cyclophosphamide, Doxorubicin, vincristine, prednisone (CHOP)–like regimens with etoposide anti-CD52 antibody alemtuzumab, cytokine adsorption catridges or plasmapheresis RuxolitinibJAK2 inhibitor (off-label) Emapalumab anti–IFN-γ antibody

Hematopoietic Stem Cell Transplantation

It can cure familial HLH in patients who have a risk of hematologic malignancy. If donors don't match, then unrelated mismatched donors may be used as the disease is fatal. The bone marrow undergoes myeloablative conditioning using busulfan, cyclophosphamide, etoposide with or without antithymocyte globulin, or reduced-intensity conditioning using melphalan/treosulfan, fludarabine, and alemtuzumab with or without antithymocyte globulin. Unrelated umbilical cord blood is also tried.

Macrophage Activation Syndrome treatment

These patients are treated with high dose corticosteroids and don't require cytotoxic treatment. Cyclosporine A may be used in patients not responding to steroids. HLH2004 may be considered for patients not responding to steroids and cyclosporine A. Other alternatives with less efficacy and more side effects include antithymocyte globulin, plasmaphereis, IVIG & cyclophosphamide, biological agents like Anakinra, an IL-1 receptor antagonist has also been recently tried.[15]

Prognosis

Prognosis is poor in pediatric patients with survival of just 1-2 months. Those who survived had severe neurological problems in form of epilepsy, mental retardation and cranial nerve palsies. Other sequelae includes growth stunting, hypertension, deranged kidney functions, deafness and obstructive bronchiolitis.[16]

Conflict of Interest: Not declared

References

1. Al-Samkari H, Berliner N. Hemophagocytic Lymphohistiocytosis. Annu Rev Pathol. 2018 Jan 24;13:27-49.
2. Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: Pathogenesis, diagnosis, and management. Pediatr Int. 2016 ;58:817-25.
3. Schram AM, Comstock P, Campo M, Gorovets D, Mullally A, Bodio K, Arnason J, Berliner N. Haemophagocytic lymphohistiocytosis in adults: a multicentre case series over 7 years. Br J Haematol. 2016 ;172:412-9.
4. Emile JF, Abla O, Fraitag S, Horne A, et al. Histiocyte Society. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016 ;127:2672-81.
5. Allen CE, McClain KL. Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. Hematology Am Soc Hematol Educ Program. 2015;2015:177-82.
6. Esteban YM, de Jong JLO, Tesher MS. An Overview of Hemophagocytic Lymphohistiocytosis. Pediatr Ann. 2017;46:e309-e313.
7. Rohr J, Beutel K, Maul-Pavicic A, et al. Atypical familial hemophagocytic lymphohistiocytosis due to mutations in UNC13D and STXBP2 overlaps with

primary immunodeficiency diseases. Haematologica. 2010;95:2080-7.
8. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr. 2007 ;166:95-109.
9. Fardet L, Galicier L, Lambotte O, et al.. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66:2613-20.
10. Debaugnies F, Mahadeb B, Ferster A, Meuleman N, Rozen L, Demulder A, Corazza F. Performances of the H-Score for Diagnosis of Hemophagocytic Lymphohistiocytosis in Adult and Pediatric Patients. Am J Clin Pathol. 2016;145:862-70.
11. Chen JH, Fleming MD, Pinkus GS, et al. Pathology of the liver in familial hemophagocytic lymphohistiocytosis. Am J Surg Pathol. 2010;34:852–867.
12. Schram AM, Campigotto F, Mullally A, et al.. Marked hyperferritinemia does not predict for HLH in the adult population. Blood. 2015 5;125:1548-52.
13. Machowicz R, Janka G, Wiktor-Jedrzejczak W. Similar but not the same: Differential diagnosis of HLH and sepsis. Crit Rev Oncol Hematol. 2017;114:1-12.
14. Henter JI, Samuelsson-Horne A, Aricò M et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood. 2002 ;100:2367-73.
15. Coca A, Bundy KW, Marston B, Huggins J, Looney RJ. Macrophage activation syndrome: serological markers and treatment with anti-thymocyte globulin. Clin Immunol. 2009;132:10-8.
16. Trottestam H, Horne A, Aricò M, et al. Histiocyte Society. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood. 2011 ;118:4577-84.