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Review of haemophagocytic lymphohistiocytosis

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) describes a clinical syndrome of hyperinflammation resulting in an uncontrolled and ineffective immune response. It may develop subsequent to a number of recognised genetic mutations or in association with infection, malignancy, autoinflammatory or metabolic conditions. Even with the published diagnostic criteria it can be difficult to make the diagnosis of HLH. Patients presenting acutely to the general paediatrician or paediatric intensivist with a clinical picture of likely sepsis, ie fever, laboratory evidence of inflammatory response, coagulopathy and thrombocytopaenia should be appropriately investigated and managed for sepsis, but the possible diagnosis of HLH should be borne in mind, particularly in the child who deteriorates despite maximal therapy. This review discusses current knowledge on the classification, diagnosis and management of primary and secondary HLH, and suggests a pathway of investigation for the paediatrician faced with a potential case.

INTRODUCTION

In 1952 Farquhar and Claireaux reported two cases of 'familial haemophagocytic reticulosis' which they described as "a rare and invariably fatal condition".[1] The characteristic features appeared to be overgrowth of histiocytes with subsequent histiocytic phagocytosis of blood cells in lymph nodes, marrow, liver and spleen. This probably represents the first description of what is now termed haemophagocytic lymphohistiocytosis (HLH), a multisystem disorder characterised by dysregulation of the immune system with hypercytokinaemia and hyperinflammation.

HLH is not a single disease entity but rather a clinical syndrome of hyperinflammation resulting in an uncontrolled and ineffective immune response. It may develop subsequent to a number of recognised genetic mutations or in association with infection, malignancy, autoinflammatory or metabolic conditions. It is classified as primary (genetic) or secondary (acquired) (see table 1). Regardless of whether the precipitant immune defect is inherited or acquired, the outcome is unbalanced expansion and activation of histiocytes and lymphocytes resulting in hypercytokinaemia, haemophagocytosis and the ensuing clinical signs.

CLASSIFICATION

Primary

Primary HLH was previously diagnosed in infants or patients with a clear family history of multiple infant deaths following a similar illness. However, with increasing understanding of immunology and improved molecular diagnostics, a number of genetic mutations affecting immune effector function have been recognised. This group is now better defined as 'genetic'—encompassing both the familial haemophagocytic lymphohistiocytosis (FHL) cases and also HLH occurring in association with a number of immune deficiencies, namely Chediak–Higashi syndrome, Griscelli syndrome type 2 and X linked lymphoproliferative disorder (XLP) (see table 1). In this group of patients all the genetic mutations recognised to date affect granule-dependent cytotoxicity interfering with the function of both natural killer (NK) cells and cytotoxic lymphocytes (CTLS). HLH has also been reported in a patient with Hermansky Pudlak Syndrome type 2, although an addition Rab27a heterozygous mutation may have contributed to the risk of HLH.[2]

FHL is inherited in an autosomal recessive manner. It has been estimated to occur with an annual incidence of 0.12 cases per 100 000 children per year, although incidence may be higher in areas where parental consanguinity is more common.[3] Up to 80% of familial cases may present before 1 year of age,[4] but only about 10% are symptomatic in the neonatal period.[5] Five mutations leading to FHL have now been identified and the underlying genetic defect described for four of these. FHL1 is a locus described in 1999 following linkage analysis for two Pakistani families although the gene remains unknown.[6] FHL2 encodes for mutations in the Perforin (PFR1) gene.[4] Mutations in the UNC13D gene (FHL3) interfere with the role of the encoded protein Munc 13-4 in cytolytic granule exocytosis[7] and FHL4 affects the STX11 gene and production of syntaxin 11 which also has a role in cytotoxic granule release.[8 9] Recently, mutations in STXB2 encoding syntaxin binding protein2 (Munc 18-2) leading to impaired protein expression and impaired NK cell cytotoxic granule exocytosis have also been described (FHL5).[10]

The sporadic occurrence of HLH, often as a presenting feature, in immune deficiency syndromes such as Chediak–Higashi syndrome, Griscelli syndrome type 2 and XLP, all conditions with defects in cell mediated cytotoxicity, has directed further investigation of the mechanisms of HLH towards the granzyme cytotoxic pathways.

The consistent finding of defects in the cytotoxic pathway in these conditions has enhanced our understanding of the pathophysiology of HLH. Under normal circumstances, infection or antigens which activate the immune system will activate macrophages, dendritic cells, NK cells and CTLS. Through production of cytokines, chemokines and direct cell-to-cell interaction, an inflammatory cascade is initiated designed to remove the antigen/organism and infected cells;

Table 1 Classification of haemophagocytic lymphohistiocytosis

Primary/genetic	Gene	Chromosome location	Associated features
Familial			
Known defects			
FHL1	Unknown	9q21.3 22	
FHL2	PFR1	10q21–22	
FHL3	UNC13D	17q25	
FHL4	STX11	6q24	
FHL5	STXBP2	1913.2-3	
Unknown defects			
Sporadic onset associated with immune deficiencies			
Chediak Higashi syndrome	LYST	1q42.1-q42.2	Oculocutaneous albinism, bruising, frequent pyogenic infections
Griscelli syndrome type 2	Rab27A	15q21	hypopigmentation
X linked lymphoproliferative disorder 1	SH2D1A	Xq25	hypogammaglobulinaemia
X linked lymphoproliferative disorder 2	XIAP		
Secondary/acquired			
Infectious			
Autoinflammatory/macrophage activation syndrome			
Malignancy			
Immunosuppression			
Metabolic			

FHL, familial haemophagocytic lymphohistiocytosis

and, importantly, terminate the inflammatory response. Defects in the cytotoxic granzyme pathway may prevent efficient removal of the antigen or antigen presenting cell resulting in ongoing stimulation of the immune response leading to hypercytokinaemia and continued expansion of populations of histiocytes and activated CTLS. High levels of IFNγ have been found in the serum of HLH patients[11] and mouse models have suggested a prominent role for this cytokine in the persistent inflammation of HLH.[12]

Secondary

The mechanism behind secondary or acquired HLH is less understood. It can present at any age, and while the clinical picture may be identical to primary HLH, there is more variability in severity and outcome. It is seen in the context of infection, underlying autoimmune disorders (when it is often termed macrophage activation syndrome (MAS)), some metabolic disorders[13] and malignancy. With improved molecular diagnostics it is recognised that cases of adult onset HLH that had previously been considered secondary may in fact represent a primary HLH with underlying mutation in the PFR1 gene.[14] It remains to be elucidated whether all cases of secondary HLH may have an underlying genetic predisposition to develop disease dependent on environmental triggers.

Infection/ Epstein Barr virus

HLH has been described in association with a wide variety of infections, including bacterial, viral, protozoal and fungal.[15 16] While the presence of infection was once thought to aid discrimination between primary and secondary HLH, it is now recognised that many clinical episodes of primary HLH are also triggered by an acute infection.[17] Herpes viruses, and in particular Epstein Barr virus (EBV), are among the most common infections associated with HLH in children and young adults. The majority of EBV-HLH occurs in immunocompetent, previously healthy children, although it is also seen in association with XLP.[18] EBV infects B cells, T cells and NK cells, leading to monoclonal or oligoclonal proliferation of these cells.[19 20] The majority of patients with EBV-HLH have a prolonged atypical infectious mononucleosis-like course but some will develop an aggressive rapidly fatal primary EBV infection.[21]

Autoimmune disease associated HLH (MAS)

HLH is also seen in association with a number of rheumatic diseases including systemic onset juvenile idiopathic arthritis (SoJIA), SLE and Kawasaki Disease.[22–24] In the context of an autoinflammatory/rheumatic disease it is generally classed as MAS. MAS may occur in up to 13% of SoJIA patients with a reported mortality of 8–22%.[24–26] The clinical features are often similar to primary HLH but laboratory features may be blurred by the preceding high levels of inflammatory markers associated with the underlying diagnosis. Clinical findings can be explained by underlying hyperactivation of T lymphocytes and macrophages leading to hypercytokinaemia. Tumour necrosis factor (TNF) may be of particular importance in MAS, and while there have been a number of reports of successful treatment with anti-TNF agents,[27–29] use of anti-TNF biologic therapy has also been associated with the development of MAS.[30 31]

Malignancy

HLH may occur in association with malignant diseases, but is less common in children than in adults. It may occur before or during treatment for leukaemias or lymphomas, and, particularly in adult patients, the development of HLH without an infective or autoinflammatory trigger should prompt investigation for underlying malignancy.

Immunosuppression

HLH has also been described in association with iatrogenic or acquired immunodeficiency, specifically in the context of chemotherapy, following organ or bone marrow transplant and in HIV. It is unclear whether the cause of HLH is decreased immune surveillance or secondary to acquired infections. In HIV, HLH has been described in association with a wide variety of infections, but also in the context of HIV in isolation, both in patients with normal CD4 counts and in severely immunocompromised individuals.[32]

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CLINICAL FEATURES

Diagnostic criteria

The clinical presentation of HLH in children can be varied and mimic the clinical features of many other conditions including sepsis, malignancy and autoinflammatory disorders. In order to improve diagnosis of HLH, the Histiocyte Society published diagnostic guidelines in 1991, which were expanded in 2004.[33] The revised criteria are shown in box 1. Five of the eight criteria are required to fulfil a clinical diagnosis of HLH, although patients with a molecular diagnosis, that is, one of the known FHL mutations, do not necessarily need to fulfil the diagnostic criteria.[34]

Paediatric presentations

Fever, hepatosplenomegaly and cytopaenias are cardinal features of HLH and should prompt the clinician to consider HLH in their list of differentials. Failure of fever to respond to first line therapy or continued deterioration despite maximal supportive care is indicative of this potential diagnosis. Children may present with acute fulminant disease or a more gradual insidious course. Other features include rash, lymphadenopathy, jaundice and oedema. Laboratory studies may reveal coagulopathy with hypofibrinogenaemia, hypertriglyceridaemia, hyperferritinaemia and raised transaminases. Cerebrospinal fluid may show moderate pleocytosis and raised protein. It should be noted that fever may be absent in the neonatal period.[35]

Most of these presenting features can be explained by the underlying uncontrolled immune activation and hypercytokinaemia. Fever is caused by the high levels of IL-1, IL-6 and TNF.[36] Ferritin production is upregulated secondary to upregulation of heme-oxygenase, a heat shock protein expressed in response to inflammatory cytokines and endotoxin.[37] Fibrinogen levels decrease following activation of macrophages and secretion of plasminogen activator. Hypertriglyceridaemia may be caused by inhibition of lipoprotein lipase and down regulation of mitochondrial proteins related to lipid metabolism by inflammatory cytokines.

Cases that may present to the general paediatrician include the acutely sick neonate with coagulopathy, cytopaenia and hepatomegaly. Thirty per cent of neonatal HLH in Japan was found in association with herpes simplex virus infection, therefore a positive viral screen should not detract from further investigation for HLH.[35] Hypertriglyceridaemia was only present in 14% of neonates, which the authors suggested might reflect differences in lipid metabolism in this age group. Fever is less common in preterm infants and therefore is not essential for the diagnosis of HLH.

In addition to the diagnostic features of fever, hepatosplenomegaly and cytopaenia, neurological symptoms and signs are seen at presentation in up to 30% of cases.[15] These range from ataxia, irritability and cranial nerve palsies to seizures and encephalopathy. A condition of cerebromeningeal HLH has been described where neurologic signs precede the systemic symptoms.[38] HLH cases presenting with acute neurological deterioration and subdural haemorrhage on CT scans have also been described.[39] These cases were initially thought to represent non-accidental injury (NAI), before subsequent diagnosis of HLH. The authors suggested HLH could masquerade as non-accidental injury and should be considered as a differential in all such cases. However, this remains an isolated report, and the suggestion of HLH should not detract from the usual pathways for management of suspected NAI.[40 41]

Box 1 Revised Diagnostic Guidelines for haemophagocytic lymphohistiocytosis (HLH) (adapted from Henter *et al*[33])

The diagnosis of HLH can be established if either 1 or 2 below are fulfilled
- A molecular diagnosis consistent with HLH
- Diagnostic criteria for HLH fulfilled (5/8 criteria below)

Diagnostic criteria to be evaluated in all patients with HLH
- Fever
- Splenomegaly
- Cytopaenias (affecting ≥2 of 3 lineages in peripheral blood):
  - Haemoglobin <9 g/dl (in infants <4 weeks: Hb <10 g/dl)
  - Platelets $<100\times10^9$/l
  - Neutrophils $<1.0\times10^9$/l
- Hypertriglyceridaemia and/or hypofibrinogenaemia:
  - Fasting triglycerides ≥3.0 mmol/l
  - Fibrinogen ≤1.5 g/l
- Haemophagocytosis in bone marrow or spleen or lymph nodes
  - No evidence of malignancy
- Low or absent natural killer cell activity
- Ferritin ≥500μg/l
- Soluble CD25 (ie, soluble IL-2 receptor) ≥2400 U/ml

Diagnostic difficulties

Even with the published diagnostic criteria (listed in box 1); it can be difficult to make the diagnosis of HLH. Patients of all ages presenting with HLH will often have features consistent with a diagnosis of sepsis. Indeed, many of the criteria listed in the revised diagnostic guidelines for HLH can be found in patients with sepsis or systemic inflammatory response syndrome (SIRS). Furthermore, many HLH patients will progress to develop multi-organ dysfunction (MODS), which is also seen in patients with severe sepsis. Patients presenting acutely to the general paediatrician or paediatric intensivist with a clinical picture of likely sepsis, that is, fever, laboratory evidence of inflammatory response, coagulopathy and thrombocytopaenia should be appropriately investigated and managed for sepsis, but the possible diagnosis of HLH should be borne in mind, particularly in the child who deteriorates despites maximal therapy. There has been criticism of the HLH diagnostic criteria as being too non-specific and encompassing many patients on the paediatric intensive care unit with SIRS/MODS.[42] There are two ways of approaching this—perhaps revision of the criteria will improve specificity or perhaps we need to reconsider the accepted dogma that these are separate disease entities and consider them as variations on a theme. An interesting concept, particularly with increasing evidence of subtle immune defects in older patients presenting with secondary HLH, is whether in fact the conditions of sepsis/SIRS/MODS/HLH form a continuum of immune dysregulation in the presence of a trigger.[42] Patients with a gene defect ablating function may present with a primary HLH but more subtle defects may only affect function at times of increased physiological stress, with the potential for complete recovery with supportive care. This is an important area for investigation as current approaches to treatment of patients with SIRS and HLH are quite different.

Three criteria that were newly included in the 2004 diagnostic guidelines—NK cell activity, serum ferritin and soluble CD25 (soluble IL-2-receptor) have the potential to aid discrimination, however, only ferritin is routinely available through most hospital laboratory services. NK cell activity, as measured by the 51-Cr release assay is reduced or absent in HLH.[43] More detailed analysis of NK function using an extended assay or surface CD107a expression has allowed determination of type of NK dysfunction, indicating whether this may be reversible, with potential for aiding decisions on therapy and prognostication.[44 45] Soluble CD25 is a marker of lymphocyte activation which can be measured by enzyme-linked immunosorbent assay and has been shown to be useful in the diagnosis of MAS in SoJIA.[46] However, both sCD25 and NK function are tests that may require the services of external laboratories and there are likely to be delays in obtaining results and therefore may delay definitive treatment.

Ferritin: a useful diagnostic tool for the paediatrician

Ferritin is often available within 24 h and offers a useful screen of suspected cases of HLH. A criticism of the current diagnostic criterion of serum ferritin >500 µg/l is that ferritin is an acute phase reactant and will also be elevated in SIRS/MODS patients. However, a review of ferritin levels in paediatric patients found a cut off of 10 000µg/l to be 90% sensitive and 96% specific for the diagnosis of HLH.[47] Therefore, for the paediatrician caring for a critically ill child with features consistent with both sepsis and HLH, requesting serum ferritin levels may help to direct further investigation and management of suspected cases (see figure 1).

Treatment

Without treatment, familial HLH is often rapidly fatal, and the reported mortality for secondary HLH exceeds 50%.[48 49] The aim of therapy, whether for primary or secondary disease is to interrupt the amplification cascades of cytokines and suppress the hyperinflammation, with a secondary aim of killing antigen presenting cells to remove ongoing stimulus for inflammatory responses. Treatment options include a pro-apoptotic chemotherapy based regimen as per the HLH protocols of the Histiocyte Society or a more targeted immunotherapy approach as advocated by individual centres.

The HLH-94 and HLH-2004 trial protocols of the Histiocyte society are both based on use of corticosteroids, etoposide and cyclosporine A. Corticosteroids are used to suppress the hypercytokinaemia with dexamethasone offering the advantage of passage across the blood brain barrier thereby suppressing central nervous system inflammation. Etoposide interrupts cell division, thereby preventing the cellular proliferative response. Ciclosporin A inhibits T cell activation and cytokine production. Both HLH-94 and HLH-2004 follow an initial 8-week induction protocol using dexamethasone and etoposide (with the earlier addition of cyclosporine from induction in HLH-2004), regardless of diagnosis of primary or secondary disease (figure 2).[33] Patients with evidence of continued or progressive central nervous system involvement after 2 weeks of systemic therapy require intrathecal therapy with methotrexate (combined with corticosteroid in the HLH-2004 protocol). Continuation therapy is recommended in all symptomatic or familial cases pending donor availability for haemopoietic stem cell transplant (HSCT). In primary cases, due to the underlying immune defect, disease is likely to recur unless the defective immune system is replaced through HSCT. Use of HSCT with both matched related and matched unrelated donors in the context of HLH-94 improved 3-year survival to 55% for all cases and 51% for confirmed familial cases.[50 51] While HLH-2004 continues to recruit patients on a trial basis, the results of the international multi-centre HLH-94 trial have been published and its protocols widely accepted.[50 51]

An alternative approach, employed by a single centre, has been to use immunotherapy with the aim of removing the hyperactivated T lymphocytes thought to be central to the pathophysiology of HLH. Combination therapy with anti-thymocyte globulin (ATG), methylprednisolone and cyclosporine A has been used prior to HSCT in FHL. This has been suggested to reduce the risks of long term toxicity associated with

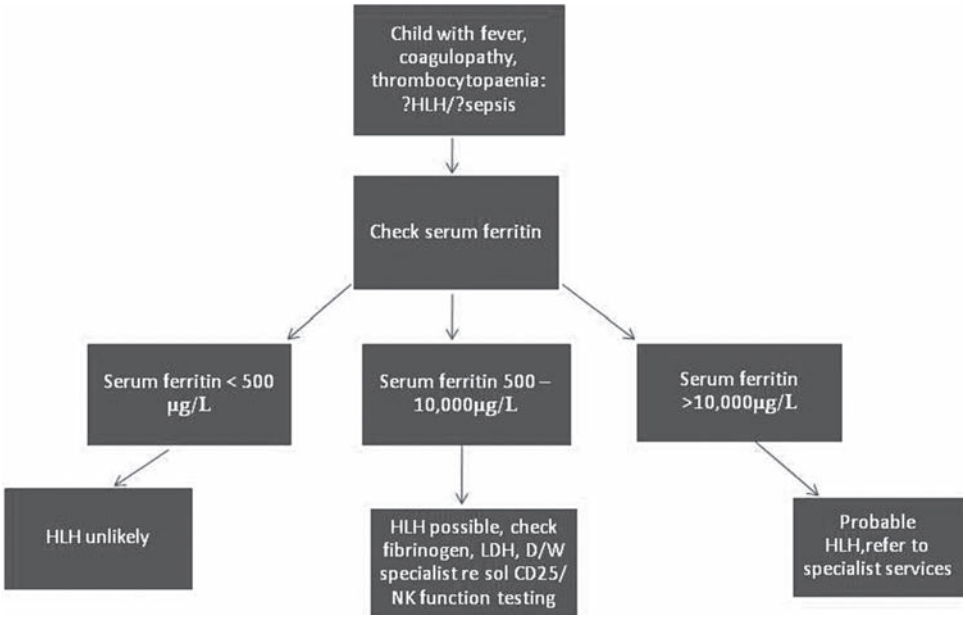

Figure 1 Suggested algorithm for use of serum ferritin for investigation of suspected haemophagocytic lymphohistiocytosis (HLH).

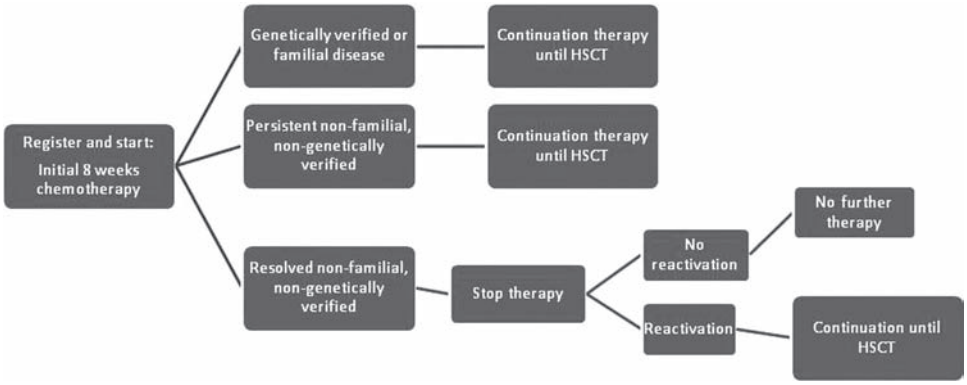

Figure 2 Flow chart of treatment options for children with haemophagocytic lymphohistiocytosis (HLH) according to HLH-2004. Adapted from Henter *et al*.[33]

etoposide use, but may have reduced efficacy in patients with overt neurological disease.[52] A potential future role for targeted immunotherapy has been suggested through the use of mouse models of FHL, with improved recovery and survival noted in mice treated with anti-IFNγ monoclonal antibodies.[53]

A number of studies have reported successful HSCT leading to cure of HLH.[51 54–57] Survival rates for HLA matched donors are consistently better than for mismatched or haploidentical donors, but the poor outcome for FHL without transplant mandates the use of mismatched donors when there are no other options.[33 51] Active disease at the time of transplant appears to be a poor prognostic indicator, indicating the need to optimise induction therapy whether through use of chemotherapeutic and/or immunotherapy regimens.[51 55] The HLH protocols advise choice of conditioning regimen rests with the local HSCT unit, but suggest use of a busulphan/cytoxan/etoposide ± ATG regimen.[33] Transplant related mortality has been high in studies using a myeloablative conditioning regimen—up to 30% in the 100-days post-transplant.[58] While the causes of death have been multifactorial, veno-occlusive disease (VOD) and pneumonitis have been prominent in the deaths reported.[51] It has been suggested that occult tissue damage from HLH and the persistence of activated hepatic Kupffer cells may predispose to the development of VOD.[58] A reduced intensity conditioning regimen consisting of a Campath/fludarabine/melphalan based regimen has been successfully used, reporting a low transplant related mortality and no episodes of VOD in a series of 24 HLH patients.[54] Further work is needed to evaluate the role of a reduced intensity conditioning regimen.

While the HLH treatment guidelines fail to distinguish between primary and secondary disease, reported management of both infection associated HLH and MAS has differed. For cases associated with acute infection, directed treatment of the infecting organism is recommended but may not be sufficient in isolation to resolve the condition. EBV-HLH has been managed successfully with corticosteroid or intravenous immunoglobulin but studies on Japanese adults with EBV-HLH have shown survival is significantly higher if etoposide is started within 4 weeks of diagnosis; therefore it is recommended to follow the HLH-94/2004 protocols.[59] Antiviral therapy may be used to decrease the viral trigger. Rituximab (anti-CD20 antibody) and ATG may be used to deplete the infected B cells or T cells respectively.[60 61] Isolated corticosteroid therapy and intravenous immunoglobulin therapy have both been used in MAS. A suggested management approach to MAS has been to divide patients into low or high risk groups according to clinical features and manage with corticosteroids or HLH-94/2004 protocol respectively.[62]

CONCLUSION

With little published data on the true incidence of secondary HLH, further insights into this fascinating condition can only be obtained with increased awareness, investigation and reporting. The presenting features are so indistinct that unless definitive criteria are actively sought, many cases may go unrecognised or be recorded as sepsis. Further knowledge of underlying immune defects predisposing to disease or biomarkers in autoinflammatory conditions may help to identify children at risk allowing early recognition and treatment or even prevention in years to come.

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