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Rheumatology: Current Research

Mini Review

A Brief Review Highlighting the Broad Spectrum of Haemophagocytic Lymphohistiocytosis

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ABSTRACT

HLH is a rare, life-threatening condition characterized by an ineffective hyper stimulation of the immune system which leads to a pathologic rise in cytokine levels and to a hyper inflammatory state. Many conditions like Macrophage Activation Syndrome (MAS), sepsis, malignancies and even multi-inflammatory response syndrome after COVID 19 infection share overlapping clinical presentation and laboratory findings with HLH. Our review aims to provide updated clinical-practical generalities of HLH in terms of epidemiology, pathophysiology, clinical features, and management particularly in light of COVID19. The etiology of HLH can be classified as familial or secondary/ sporadic. The differentiation of primary and secondary HLH is very important because primary HLH may require different treatment modalities like hematopoietic stem cell transplantation. Since the emergence of the SARS-CoV2 pandemic, the number of reported cases of HLH in patients with COVID19 has progressively increased. A brief overview of the etiology, genetics, and immunology of HLH is also provided. This review also highlights the diagnostic challenges associated with HLH and emphasizes that early identification, low threshold for suspicion, thorough diagnostic work up and multidisciplinary approach are crucial for timely diagnosis and optimal management.

Keywords: Haemophagocytic Lymphohistiocytosis; Hyperinflammatory syndromes; Macrophage activating syndrome

INTRODUCTION

Haemophagocytic Lymphohistiocytosis (HLH) has gathered much attention in recent years especially during the COVID19 era. HLH is characterized by an ineffective hyperstimulation of the immune system which leads to a pathologic rise in cytokine levels and to a hyperinflammatory state. This Hyperinflammation leads to multiorgan dysfunction and carries a grave prognosis. HLH can be secondary to an underlying etiology or inherited due to genetic causes termed familial HLH. Familial HLH is generally reported in infants and children, although has recently been increasingly reported in adults; while secondary HLH (sHLH) is described in the setting of infections, malignancy, autoimmune conditions, or related to an immunodeficiency state.

HLH shares pathophysiologic, clinical, and laboratory findings with other hyper inflammatory conditions, such as Macrophage Activation Syndrome (MAS) in rheumatologic illness, which carries a poor prognosis, [1] and COVID19 hyper inflammatory syndrome. Furthermore, it shares clinical features with severe bacterial sepsis or malignancies, which makes HLH clinical diagnosis convoluted and a feasible scenario for the use of diagnostic scales [2,3].

COVID19 hyper inflammatory syndrome is associated with a cytokine storm leading to a hyper inflammatory syndrome and in some cases to sHLH. There are some differences in the clinical presentation of COVID19 related sHLH vs. COVID19 hyper inflammatory syndrome such as hepatomegaly, splenomegaly, and hypertriglyceridemia which are not commonly seen in the latter. The use of the HScore in COVID19 s. HLH is recommended in patients with hypertriglyceridemia, raised ferritin level and low platelet count as it may aid in an early HLH detection and prompt management [4]. Our review aims to provide updated clinical-practical generalities of HLH in terms of epidemiology, pathophysiology, clinical features, and management particularly in light of COVID19.

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LITERATURE REVIEW

Definition

HLH is a clinical illness characterized by extreme hypercytokinemia induced by an overactive but inefficient immune response. HLH is not a sickness of itself, it is a resultant from an underlying anomaly of the immune system's genetics or an acquired incapacity to deal appropriately with a trigger [5]. In most situations, the trigger is an infectious agent

Epidemiology

HLH is a rare disease with an annual incidence of one in 800,000 individuals and one to ten per million children in the United States [6-8]. It is typically described as a childhood illness; however, it can affect people of any age, including young adults, and elders [9,10]. Geographical variation is a classically described epidemiological feature of HLH, as the most common causes varies by nation, implying a distinct genetic background and/or differences in probable triggering factors, notably infections [11]. Since the emergence of the SARS-CoV2 pandemic, the number of reported cases of HLH in patients with COVID19 has progressively increased [12].

Pathophysiology

Generalities: The exact cellular and molecular processes behind HLH are yet unknown. Decades of clinical observation, genetic analysis, and fundamental scientific study have yielded three significant findings: 1) In HLH, the disease is driven primarily by an abnormal immune response rather than underlying triggers; 2) immune responses in HLH do not appear to target self-antigens, as seen in autoimmune diseases; and 3) uncontrolled activation of T cells (especially CD8 cytotoxic T cells), rather than macrophages, is the root abnormality in most forms of HLH [13]. Susceptibility to HLH is genetically centered on genes whose products are involved in cell-mediated cytotoxicity and lymphocyte activation/survival. Immunosuppression and persistent inflammation are other risk factors for HLH; in these circumstances, HLH is frequently induced by infection, viruses like EBV and COVID19, and other intracellular pathogens. They are a rare entity in adults and are generally reported in the pediatric population [14].

DISCUSSION

Etiology

Classically HLH is classified into familial HLH and secondary/sporadic/reactive HLH. Different causes have been implicated in sHLH, such as infections (49%), malignancies (27%), rheumatic conditions (7%), primary or acquired immunodeficiencies (6%), and others (I.e. HLH in the setting of drug hypersensitivities, or with immune-activating therapies). Among the infectious sHLH, viral illnesses are the main described microorganisms. Among the implicated viruses EBV and CMV are the most isolated, other described viruses are HSV, RSV, rotavirus, influenza, parvovirus B19, and HIV. Cases of HIV associated HLH secondary to triggering opportunistic infections are described, particularly secondary to tuberculosis. Other implicated microorganisms are rickettsia, Brucella, Leptospira, malaria, and systemic fungal infections. COVID19 causes HLH, as is described to cause severe inflammatory syndromes with pathophysiologic similarities to HLH. Malignancy associated HLH can be seen in up to 1% of cancers in adults and is mainly to be seen in cases of hematologic malignancy, particularly in NK, T, and B-cell lymphomas. The most common reported rheumatic conditions to be associated with HLH are adult Still's disease and systemic lupus erythematosus.

Genetics

Genetic abnormalities significantly impact juvenile HLH and are increasingly being discovered in adult disease [15-18]. Up to one-quarter of HLH cases are familial. Genetic information can predict recurrence, the requirement for hematopoietic stem-cell transplantation, and the risk of HLH in family members. Most of the first implicated "HLH-linked" genes encode components of the perforin-dependent cytotoxicity mechanism [19]. Many HLH gene mutations can be mapped to a locus that transcribes to the formation of cytokine granules and release pathways and has been labeled familial hemophagocytic lymphohistiocytosis loci. The chances of detecting a gene mutation are most remarkable in younger patients. In a study of 476 North American children, a gene mutation was found in 45 percent of those under the age of one month. The rates of finding a gene mutation in individuals aged two months to one year, one to two years, and more than two years were 39, 20, and 6%, respectively [20]. The most often implicated genes are PRF1 null mutations and genes that impact degranulation (e.g., UNC13D, STX11, STXBP2). Adult individuals with hypomorphic PRF1, MUNC13-4, and STXBP2 mutations have a less severe course than pediatric patients [21].

Immunology

In HLH, there is absence of the normal inflammatory downregulation by activated macrophages and lymphocytes. Natural Killer cells and/or Cytotoxic lymphocytes (CD8+) fail to remove activated macrophages. The lack of feedback control, leads to an excessive CD8+ T cell and macrophage activation, as well as to significantly increased levels of interferon-gamma (IFNγ) and other cytokines, which are thought to be accountable for multiorgan failure and the syndrome's high mortality [22-24]. IFNγ, the chemokine CXCL9 (which is controlled by IFNγ), tumor necrosis factor-alpha (TNF alpha), interleukins (IL) particularly IL-6, IL-10, IL-12, and the soluble IL-2 receptor (CD25) have all been described at exceptionally high levels in the plasma of HLH patients [25-26]. In a study by Gursoy et al., severe COVID19 with cytokine storm displays symptoms comparable to hyperinflammatory syndromes but differs in the cytokine storm and certain clinical characteristics seen in MAS/sHLH [27].

Clinical characteristics

Like other viral infections such as CMV and EBV, SARS-CoV2 infection, regardless of vaccination status, can also cause secondary HLH, especially in immunocompromised patients with autoimmune disease, organ transplant, or receiving immunosuppressive therapy. There is a significant overlap between features of severe COVID-19 and those included in the HLH-2004 diagnostic criteria, such as fever, cytopenia and hyperferritinemia. Physical exam or imaging might show lymphadenopathy and/or splenomegaly, but those are less frequently reported [28,29]. Hypertriglyceridemia and/or hyperfibrinogenemia can be present and might be related to poor prognosis [30,31]. While lymphopenia is a key feature of severe COVID-19 and has prognostic values, bicytopenia and pancytopenia are relatively less common in COVID-19 patients

without complications [32,33]. Thus, multiple cell line involvement in severe COVID-19 might indicate progression or complication of the disease [34]. Multisystem inflammatory syndrome or cytokine release syndrome can present as complications of severe COVID-19 independent of HLH but share similar pathophysiology [35,36]. Qiurong Ruan et al. reported that common risk factors of mortality in COVID-19 infection are elevated ferritin and IL-6 level, which are crucial features in patients with HLH [37,38].

Diagnosis

Diagnosis of HLH in COVID-19 is mainly based on the HLH-2004 diagnosis criteria [39]. Elevated serum soluble CD25 (i.e., interleukin-2 receptor) level and low/absent NK cell activity are specific for HLH diagnosis and prognosis but might not be routinely performed due to laboratory limitations [40]. Pathologic evidence of HLH through tissue biopsies such as bone marrow, lymph node or liver biopsy is diagnostic. However, due to the high morbidity and mortality of the illness, HLH-specific treatment should not be delayed if five out of eight HLH-2004 diagnostic criteria (Table 1) are met even without a tissue biopsy. A more practical method is to use the HScore (Table 2) to predict the likelihood of HLH and initiate treatment [41]. Mei Meng et al. reported that a high HScore (>98 instead off the commonly used cutoff 169) was an independent predictor of mortality in severe COVID-19 patients with HLH. However, clinicians should understand the limitations of the HScore system, such as possible lack of sensitivity and inadequate published data when utilizing it for a presumed diagnosis of HLH in COVID-19 patients. The CDC criteria and the Brighton Collaboration Case Definition can help differentiate Multi inflammatory response syndrome after COVID 19 infection from HLH.

Table 1: Diagnostic criteria of hemophagocytic lymphohistiocytosis -HLH-2004.

Eight Hemophagocytic Lympho Histiocytosis-2004 diagnostic criteria
1. Molecular diagnosis consistent with HLH
2. Fulfill HLH diagnostic criteria (5 out of the 8 criteria shown below)
(1) Fever ≥ 38.5°C for ≥ 7 days
(2) Splenomegaly (usually based on radiographic evidence)
(3) Cytopenia affecting ≥ 2 of 3 lineages in peripheral blood (Hemoglobin <9 g/L*, Platelets <100×10^9/L, or Absolute Neutrophil Count (ANC) <1.0 × 10^9/L)
(4) Hypertriglyceridemia (Fasting triglycerides ≥ 265 mg/dL), and/or hypofibrinogenemia (Serum fibrinogen ≤ 1.5 g/L)
(5) Evidence of hemophagocytosis in the bone marrow or spleen or lymph node
(6) Low or absent NK cell activity (according to the local laboratory reference)
(7) Ferritin ≥ 500 µg/L
(8) Soluble CD25 (sIL-2 receptor) ≥ 2,400 U/mL

Note: Diagnosis will be established if one of either (1) or (2) is fulfilled. *According to HLH-2004 diagnostic criteria, in infants <4 weeks the cutoff hemoglobin is 100 g/L)
Abbreviations: HLH, hemophagocytic lymphohistiocytosis; NK, natural killer; sIL-2, soluble interleukin-2.

Table 2: H-Score for diagnosis of hemophagocytic lymphohistiocytosis.

A more practical method is to use the H Score		
Variable		Points
Known underlying immunosuppression*	No	0
	Yes	18
Temperature, °F (°C)	<101.1 (<38.4)	0
	101.1-102.9 (38.4-39.4)	33
	>102.9 (>39.4)	49
Organomegaly	No	0
	Hepatomegaly or splenomegaly	23
	Hepatomegaly and splenomegaly	38
Numbers of Cytopenias**	1 lineage	0
	2 lineages	24
	3 lineages	34
Ferritin, ng/Ml (µg/L)	<2,000	0
	2,000–6,000	35
	>6,000	50
Triglyceride, mg/dL (mmol/L)	<132.7 (<1.5)	0
	132.7-354 (1.5-4)	44
	>354 (>4)	64
Fibrinogen, mg/dL (g/L)	>250 (>2.5)	0
	≤ 250 (≤ 2.5)	30
AST, U/L	< 30	0
	≥ 30	19
Hemophagocytosis features on bone marrow aspirate	No	0
	Yes	35

Note: Interpretation: the best cutoff value for H-Score was 169, corresponding to a sensitivity of 93%, specificity of 86%, and accurate classification of 90% of the patients. *HIV positive for receiving long-term immunosuppressive therapy (i.e. glucosteroids, cyclosporine, azathioprine). **Defined as hemoglobin ≤ 9.2 g/dL (≤ 5.71 mmol/L), and/or WBC ≤ 5,000/mm^3 and or platelets ≤ 110,000/mm^3.

Management

Management consists of anti-viral treatment for COVID-19 and immuno-chemotherapy for HLH. Corticosteroids, especially dexamethasone given its long duration and central venous system permeability is the mainstay of treatment, targeting the hyperactivation of inflammatory factors seen in both COVID-19 and HLH. Etoposide-based chemotherapy has shown to be effective in inducing remission. It acts as a cytotoxic agent that directly kills excessively proliferated T cells [42]. Cytokine-specific treatments such as IL-1 inhibitor Anakinra or IL-6 inhibitor tocilizumab [43,44] are being used, but more prospective data are needed to solidify the mortality and prognosis benefit in those patients [45,46]. Most of the time, patients with COVID-19-induced HLH are critically ill and are prone to opportunistic infection due to lymphopenia/neutropenia related to COVID-19 infection and cytotoxic agent. Supportive treatments such as antibiotics/antifungals, ventilation, and pressor support are crucial and case specific. Allogeneic Hematopoietic Stem Cell Treatment (HSCT) is the last resort for refractory disease despite induction therapy or reactivated HLH. Continuation therapy using the same dose of dexamethasone and etoposide are commonly used before HSCT. However, the efficacy and benefit of HSCT in COVID-19-induced HLH are not well studied [47,48].

CONCLUSION

HLH is a rare, life-threatening condition that can be triggered by diverse etiologies including severe and life-threatening COVID-19. Given its dismal prognosis, and increased incidence in COVID19 times, a low threshold for suspicion should be considered in patients with COVID19 or other etiologies associated with HLH who presents with high grade fever, cytopenias, organomegaly, ARDS, and/or marked dysregulation of inflammatory markers. It is worth noting that Multi inflammatory response syndromes that occur after COVID 19 infection are difficult to differentiate from HLH and may occur in a fully vaccinated adult with COVID 19 infection.

Early identification of cases should lead to a rapid multidisciplinary approach. This approach should comprehend hematology and oncology specialists, rheumatologists, critical care and pulmonary specialists, internists, and infectious diseases specialists, with the end goal to rapidly start an aggressive and specialty-consensus antiviral and immunochemotherapeutic individual-tailored treatment. Although studies are limited to validate the use of scores for the diagnosis of HLH in SARS-CoV2 infection, the use of HScore, and/or the HLH-2004 diagnosis criteria may aid the clinician in an earlier detection of this devastating disease.

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