Hemophagocytic Lymphohistiocytosis and Primary Immunodeficiency Disorders – follow up

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Abstract:

Hemophagocytic lymphohistiocytosis (HLH) is characterized by uncontrolled inflammation that is often lethal if not diagnosed and treated promptly. HLH has often been designated as "primary" (genetic) if mutations in genes important for cytotoxic T and NK cell function or in genes causing primary immunodeficiency disorders (PID) have been identified. Triggers such as infections, malignancy and rheumatic diseases have been implicated as causes for the "secondary" (acquired) form of HLH. The terminology of primary versus secondary HLH, although useful in the past, can be misleading as primary HLH might be triggered by secondary causes such as infections, and conversely, genetic mutations are identified at increasing frequency among patients with HLH that was considered secondary. Here we update the growing list of PID associated with HLH. In addition to the more common defects in granule-mediated cytotoxicity caused by mutations in perforin, UNC13D, STX11, STXBP2), LYST, RAB27A, SH2D1A and XIAP, we describe mutations which disrupt T cell development and function. These include 22q11 deletion syndrome, Wiskott Aldrich syndrome, STAT1 deficiency and others. Interestingly, HLH can also occur among patients with auto-inflammatory disease and immune dysregulation. Importantly, the occurrence of HLH among patients with defects restricted to T cells, suggests that a combination of increased susceptibility to infections with loss of T cell function might be sufficient for development of uncontrolled inflammatory response and HLH.

Abbreviations:

ALPS: Autoimmune lymphoproliferative syndrome

CGD: chronic granulomatous disease

CID: combined immunodeficiency

CVID: common variable immune deficiency

FMF: familial Mediterranean fever

HIS: hemophagocytic inflammatory syndrome

HLH: Hemophagocytic lymphohistiocytosis

PID: primary immunodeficiency disorders

PFR: perforin

SCID: severe combined immunodeficiency

TLR: Toll like receptors

XLA: X-linked agammaglobulinemia

XLP: X-linked lymphoproliferative syndrome

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1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life threatening, hyperinflammatory syndrome. Patients diagnosed with HLH suffer from an uncontrolled inflammatory process accompanied by increased levels of cytokines manifesting with fever, hepatosplenomegaly and damage to multiple organs, including the heart, lungs, kidneys and brain. Most patients will succumb to the disease without intense anti-inflammatory treatment. Mutations in genes responsible for the granule-mediated cytotoxic T and NK cell function or in genes causing primary immunodeficiency disorders (PID) have been identified in patients with the "primary" (genetic) form of HLH. Triggers such as infections, malignancy and rheumatic diseases have been implicated as causes for the "secondary" (acquired) form of HLH [1, 2]. The terminology of primary versus secondary HLH, although useful in the past, can be misleading as primary HLH might be triggered by secondary causes such as infections, and conversely, genetic mutations are identified at increasing frequency among patients with HLH that was considered secondary. Nevertheless, distinguishing the two forms of HLH is important, as prognosis and management differs between primary and secondary HLH [3].

HLH is often diagnosed using clinical and laboratory criteria described in the HLH-2004 protocol (table 1) [4]. Yet, these criteria do not distinguish between primary and secondary HLH. Occurrence of HLH in other family members suggests primary HLH, however such history is often absent. Accordingly, there has been growing reliance on advanced biological and genetic assays to investigate for the possibility of primary HLH. The availability of next generation sequencing, including extensive gene panels and whole exome sequencing, had led to an increase in the number of PID recognized as predisposing to HLH in recent years. In 2014, we reviewed 18 patients with PID who have been diagnosed with HLH [5]. A year later, Bode et al. described additional patients who had HLH and PID [6]. Since then, more PID have been associated with HLH. Accordingly, in August 2017 we performed a thorough search of PubMed for the terms hemophagocytic, lymphohistiocytosis, HLH, macrophage activation syndrome and immune deficiency (individually and in combination). In the current publication, we update the PID associated with HLH, including some of the less common and recognized aetiologies. Detailed reports of these conditions are available in the medical literature, therefore only brief descriptions of each disease will be provided here. Importantly, the broad association of PID and HLH also suggests that a defective immune system might be involved in the pathogenesis of HLH.

2. PID commonly associated with HLH

The PID included here have been associated with HLH more frequently and are responsible for most patients eventually identified with primary HLH (Table 2). Since these conditions are better known and have received excellent reviews previously [7-9], they will be described here only briefly. They have been separated into three sub-categories according to the biological defect leading to HLH:

2.1 Defects in genes important for granule-mediated cytotoxic function of T cells and NK cells. Mutations in the perforin gene (PFR-1) and in genes responsible for the priming and fusion of cytotoxic granules (UNC13D, STX11 and STXBP2) disrupt lymphocyte cytotoxicity [10-13]. Affected patients typically present at early age.

2.2 Disorders in the biogenesis, function and trafficking of secretory lysosomes. Patients suffer from increased susceptibility to infections and HLH, and some may also present with partial oculo-cutaneous albinism, bleeding disorders and/or neutropenia, due to the important role of secretory lysosomes in melanocytes, platelets and neutrophils, respectively [8]. The disorders in this group include Chediak-Higashi and Griscelli type 2. The risk of HLH in Chediak-Higashi is estimated to be up to 85% [14], although in the Japanese population the incidence has been reported to be only 33% [15]. Patients with Griscelli type 2 syndrome often develop HLH in their first year of life, an event that is known as the "accelerated phase" [16]. Patients with Hermansky-Pudlak type 2, despite defects in proteins trafficking to the lysosome resulting in partial oculo-cutaneous albinism, have been reported to have only a small increase in the risk for HLF in comparison to Chediak-Higashi and Griscelli type 2 [17].

2.3 X-linked lymphoproliferative syndrome (XLP) -1 and -2. These disorders are characterized by T- and B- immune deficiencies with high susceptibility to EBV infection [9]. Disruption of the SH2D1A gene, which causes XLP-1, inhibits the cytotoxicity responses of NK and CD8 cells to EBV-infected B cells and allow the inflammatory process to propagate after EBV infection eventually leading to HLH [18]. In contrast to XLP-1, there is no clear explanation for the uncontrolled inflammation caused by mutations in the XIAP gene, which causes XLP-2. XIAP, also known as baculoviral IAP repeat-containing protein 4, has an important anti-apoptotic role however how defects in an anti-apoptotoic protein cause uncontrolled lymphoproliferation is still unknown. HLH tends to be more common in XLP- 2 than in XLP-1 (67-90% vs. 39-55% respectively), although the fatality is higher in former than the later (61% vs. 23%) [19].

3. PID uncommonly associated with HLH

In contrast to the conditions mentioned above, the PID described in this section have been reported uncommonly among patients with HLH, although the frequency is increasing in recent years. In total, 71 patients, affected by 26 distinct PID, have been identified as also suffering from HLH (Table 3 and 4). The PID in this group can be divided into (1) PID with combined immunodeficiency (CID); (2) chronic granulomatous disease (CGD); (3) other PID including auto-inflammatory diseases, immune dysregulation, hypogammaglobulinemia and isolated neutropenia.

3.1 Combined immunodeficiency. This sub-category includes 17 distinct PID ranging from severe combined immunodeficiency (SCID) to common variable immune deficiency (CVID). Infections, usually viruses, have been identified as potential triggers of HLH in up to 77% of these patients. Many patients display T cells function abnormalities, which can be isolated as occurring with IL7R alpha deficiency and the CD3E and CDδ deficiencies, or part of an additional NK or B cells dysfunction as found in patients with gamma common chain or recombination activating gene mutations, respectively [6, 20]. Notably, while some patients had an extremely low T cells and NK cells counts, others had normal numbers but poor T cell function, such as the mutations in the ORAI1 gene disrupting calcium influx in T cells [21]. Mutations in the Purine nucleoside phosphorylase gene may cause T, B and NK cell deficiency, have also been infrequently associated with HLH [22]. The T cell deficiency in HLH is intriguing, as uncontrolled inflammation typically is associated with increased number of activated T cells. In contrast, HLH caused by PID often occurs with low or absent T cells. Some of the PID are associated with multi-organ involvement which might provide clues to establishing the diagnosis. These include neurological and dermatological findings in ataxia telangiectasia, the ectodermal dysplasia in NEMO syndrome or the cardiovascular defects and hypocalcemia in 22q11.2 microdeletion. Importantly, HLH might be the first presentation of the PID and has been associated with a particularly poor prognosis with

71% mortality, emphasizing the need for increased vigilance for this possibility.

3.2 Chronic granulomatous disease. CGD occurs because of defects in the NADPH oxidase complex, impairing phagocytes ability to produce superoxide anions, which are critical for the eradication of catalase-positive organisms. Most of the patients with CGD are males with mutations in the X-linked p91-PHOX gene [6], however mutations in other genes encoding proteins important for the NADPH complex have also been reported. In contrast to CID, HLH is infrequently the presenting feature of CGD, as 60% developed HLH after the diagnosis of CGD was done. Additionally, the mortality in the CGD from HLH is much lower (9%) compared to the CID. Similar to CID, infections were identified as triggers in 87% of CGD patients who developed HLH, however the pathogens leading to HLH in CGD were commonly bacterial or parasites, such as Burkholderia cepacia and Leishmania species [6].

3.3 Auto-inflammatory diseases, immune dysregulation and antibodies deficiency.

3.3.1 HLH has been reported among patients with auto-inflammatory diseases including familial Mediterranean fever (FMF) [23, 24], Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS) [25] and mutations in the NLRC4 gene, which is part of the innate inflammasome complex [26]. Defects in the inflammasome are often associated with normal number and function of T and NK cells, which may explain the infrequent occurrence of HLH, despite the high prevalence of conditions such as FMF. Among the 4 patients reported in this subgroup, HLH appeared primarily at late childhood, without prior diagnosis of PID and without an infectious etiology. Prognosis was favourable with 75% survival.

3.3.2 Immune dysregulation. Patients affected by Immune dysregulation conditions usually suffer from lymphadenopathy, hepatosplenomegaly and haematological cytopenia which are also among the criteria for HLH, thereby complicating the diagnosis of the 2 conditions. Two children were described as having HLH and Autoimmune lymphoproliferative syndrome (ALPS) due to genetic mutation in the FAS gene (causing defective lymphocyte apoptosis). However, one of them fulfilled 5 out of 8 HLH criteria including splenomegaly, cytopenia, hypertriglyceridemia, elevated sCD25 and elevated ferritin, but without fever, which is not common [27]. It is possible that the splenomegaly and cytopenia had resulted from the ALPS, questioning the diagnosis of HLH. The other child had HLH with findings suggestive of CVID such as hypogammaglobulinemia and poor response to vaccination at the time of the diagnosis [28]. Recently a 50-year-old man with CTLA-4 deficiency, which causes immune dysregulation due to abnormal inhibition of T cell by antigen presenting cells, was reported to suffer from HLH after EBV-induced Hodgkin lymphoma. Interestingly, the patient recovered following hemodialysis with hemoadsorption of cytokines using a cytokine removal column [29].

3.3.3 Antibodies deficiency. A 27 years old male with recurrent skin and lung, isolated IgM deficiency and no B cells developed HLH, which resolved with steroids and cyclosporine treatment [30]. Two male siblings with X-linked agammaglobulinemia (XLA), caused by mutations in the BTK gene were reported with HLH after adenovirus infection [31]. A possible explanation for the association of XLA and HLH is the role of BTK in regulating Toll like receptors (TLR) activation of the innate immune system [32, 33]. Hence, a defect in BTK may affect the inflammation cascade in addition to the infections that are caused by the absent immunoglobulins, which together may lead to develop HLH.

4. Discussion

The immune system is required to respond vigorously to invading pathogens such as EBV,

fragments of cells generated during rheumatologic diseases or cancerous cells, yet it is as important to contain and end such responses, in order to prevent damage to bystander cells and organs. Breech of this delicate homeostasis because of acquired or inherited defects in immune regulation is the main culprit in the development of HLH. Identification of mutations in genes important for cytotoxic function, such as Perforin, highlighted the role of NK cells in controlling immune responses. In recent years, identification of other PID leading to HLH has provided additional understanding of HLH pathogenesis. Here we describe 71 patients with 26 different PID who developed HLH, ranging from infants with SCID to adults with immune dysregulation. Importantly, although the number of patients with CID that developed HLH was small, their prognosis was particularly poor, possibly because the recognition of the immune deficiency was delayed, further emphasizing the need to consider PID in all patients presenting with HLH.

The increase in diversity of PID identified as predisposing to HLH, particularly the occurrence of HLH among patients with defects isolated to T cells, such as those involving the CD3 chain, suggests that T cells have a critical role in controlling the immune response and preventing HLH. This hypothesis, which differs than the one proposed by Bode at al [6], who even suggested changing the name of the disorder to "hemophagocytic inflammatory syndrome" (HIS), is also supported by the development of HLH in patients with T cell deficiency secondary to HIV [34, 35].

In conclusion, HLH is being recognized at increased frequency among patients with PID, particularly, although not limited to those, with profound T cell deficiencies. Vigilance among clinicians for the possibility of a predisposing PID among patients with HLH is expected to improve survival of patients and possibly further the understanding of disease pathogenesis.

Table 1. HLH-2004 diagnostic guidelines.

Clinical criteria
Fever
Splenomegaly
Laboratory criteria
Cytopenia (affecting >2 of 3 lineages in peripheral blood)
Hypertriglyceridemia or Hypofibrinogenemia
Low or absent NK cells activity
Hyperferritinemia>500 microgram/Liter
Increased levels of sCD25 >2400 U/ml
Histopathological criteria
Hemophagocytosis in the bone marrow, spleen or lymph nodes
No evidence of malignancy

A diagnosis of HLH is made if: 1. 5/8 criteria are fulfilled. 2. A molecular defect consistent with HLH is demonstrated.

Table 2. Primary immunodeficiency disorders commonly associated with HLH

Primary Immunodeficiency Disorders	Gene (Protein defect)	Function
Familial HLH types (I*-V)	PRF1 (Perofrin), UNC13D (Munc13-4), STX11 (Syntaxin 11), STBBP2 (Syntaxin-binding protein 2)	Priming and fusion of the cytotoxic vesicle, pore formation (Perforin)
Chediak-Higashi	LYST (lysosomal trafficking regulator)	Regulate lysosome size
Griscelli type 2	RAB27A	Regulate vesicular fusion, trafficking and docking
X-linked lymphoproliferative disease 1	SH2D1A (SAP)	Regulate signal transduction
X-linked lymphoproliferative disease 2	XIAP (X-linked inhibitor of apoptosis protein)	Suppression of apoptosis

*The gene responsible to familial HLH type 1 is unknown but is linked to chromosome 9q21.3

Table 3. Cases of patients with PID uncommonly associated with HLH

Primary Immunodeficiency	Number of patients	Number of patients with HLH before PID diagnosis	Number of patients with infection as trigger for HLH	Number of patients who died	Reference
Combined Immunodeficiency					
Ataxia telangiectasia	1	0	1	1	6
CD27 deficiency	2	2	2	0	36
CD3δ deficiency	1	1	0	1	20
CD3ε deficiency	1	1	1	1	6
Common variable Immunodeficiency (CVID)	1	0	1	1	37
Deletion 22q11 syndrome	5	0	4	3	6, 38
Dyskeratosis congenita	1	1	1	0	6
Hermansky-Pudlak type 2	1	0	1	1	17
IL2-inducible T cell kinase deficiency	3	3	3	3	39, 40
IL-2R Gamma deficiency	5	4	4	2	6
IL-7R Alpha deficiency	1	1	1	1	6
Nuclear factor-kappa B Essential Modulator (NEMO) deficiency	1	1	1	0	41
ORAI1 deficiency	1	1	1	1	21
Purine nucleoside phosphorylase (PNP) deficiency	1	1	1	1	22
Recombination-activating gene 1 (RAG1)	3	2	2	2	6
STAT1 (gain of function)	3	2	0	3	6, 42, 43
Undefined combined immunodeficiency	3	2	2	2	6
Wiskott-Aldrich syndrome	4	2	2	4	6
Total combined immunodeficiency	38	25	29	27	
Chronic granulomatous disease (CGD)	22	9	19	2	6
Other Primary Immunodeficiency Disorders					

Autoimmune lymphoproliferative syndrome (ALPS)	2	2	0	0	27, 28
CTLA4 deficiency	1	0	1	0	29
Cyclic neutropenia	1	0	1	?	6
Familial Mediterranean Fever (FMF)	2	1	1	1	23, 24
NLRC4 mutation	1	1	0	0	26
Selective IgM immunodeficiency	1	1	1	0	30
Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)	1	1	0	0	25
X-linked agammaglobulinemia (XLA)	2	2	2	1	31
Total other PID	11	8	6	2	

Table 4. Primary immunodeficiency disorders uncommonly associated with HLH

Primary Immunodeficiency	**Gene (Protein defect)**	**Function**
Combined immunodeficiency		
Ataxia telangiectasia	ATM (ATM protein)	Coordinates the cellular response to DNA double strand breaks
CD27 deficiency	CD27	Important for signal transduction in T and B cells
CD3δ deficiency	CD3D	Part of the T-cell receptor/CD3 complex, essential for T-cell development and signal transduction
CD3ε deficiency	CD3E	Part of the T-cell receptor/CD3 complex, essential for T-cell development and signal transduction
Common variable Immunodeficiency	Mutations in at least 13 genes have been associated with CVID but in most cases the genetic cause is unknown.	Most genes associated with CVID are involved in the function and maturation of B cells and antibodies production.
Deletion 22q11 syndrome	22q11.2 deletion (unknown)	Unknown
Dyskeratosis congenita	TERT (hTERT) TERC (hTR) DKC1 (Dyskerin) TINF2 (TERF1-interacting nuclear factor 2)	Maintaining the length of telomeres.
Hermansky-Pudlak type 2	AP3B1 (subunit of adapter protein 3)	Trafficking of proteins from the Golgi apparatus to the lysosome.
IL2-inducible T cell kinase deficiency	ITK (IL-2 inducible T cell kinase)	CD4 differentiation toward TH2 response
IL-2R Gamma deficiency	IL2RG (interleukin-2 receptor subunit gamma)	Essential for signaling from many interleukin receptors
IL-7R Alpha deficiency	IL7R (interleukin-7 receptor-α)	Essential for T cell development.
Nuclear factor-kappa B Essential Modulator (NEMO) deficiency	IKBKG (NF-κB essential modulator)	Regulates the activity of nuclear factor-kappa-B.
ORAI1 deficiency	ORA1 (Calcium Release-Activated Calcium Modulator 1)	A membrane calcium channel subunit that act as the primary way for calcium influx into T-cells.
Purine nucleoside phosphorylase deficiency	PNP (Purine Nucleoside Phosphorylase)	Reversibly catalyzes the phosphorolysis of purine nucleoside.
Recombination-activating gene 1	RAG1 (Recombination Activating 1)	Activate rearrangement and recombination of the genes of

		immunoglobulin and T cell receptor molecules
STAT1 (gain of function)	STAT 1 (Signal Transducer And Activator Of Transcription 1)	A transcription activator
Wiskott-Aldrich syndrome	WAS (Wiskott-Aldrich syndrome protein)	Essential for transduction of signals from cell receptors to the actin cytoskeleton
Chronic granulomatous disease (CGD)	CYBB (p91-PHOX) CYBA (p22-PHOX)	Part of the NADPH oxidase complex, crucial for the producing reactive oxygen species
Other Primary Immunodeficiency Disorders		
Autoimmune lymphoproliferative syndrome (ALPS)	FAS (Fas Cell Surface Death Receptor)	Play a central role in the physiological regulation of apoptosis
CTLA4 deficiency	CTLA4 (Cytotoxic T-Lymphocyte Associated Protein 4)	Transmits an inhibitory signal to T cells
Cyclic neutropenia	ELANE (Elastase, Neutrophil Expressed)	A protease which hydrolyzes proteins within neutrophil lysosomes and in the extracellular matrix
Familial Mediterranean Fever (FMF)	MEFV (Pyrin Innate Immunity Regulator)	Modulator of the inflammasome complex
NLRC4 mutation	NLRC4 (NLR Family CARD Domain Containing 4)	A key component of inflammasomes complex
Selective IgM immunodeficiency	Unknown	Unknown
Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)	TNFRSF1A (Tumor Necrosis Factor Receptor Superfamily Member 1A)	Receptor for TNF alpha which plays a role in cell survival, apoptosis, and inflammation
X-linked agammaglobulinemia (XLA)	BTK (Bruton tyrosine kinase)	Essential for B cells development

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