

# Hemophagocytic Lymphohistiocytosis, A Syndrome of Excessive Immune Activation: Review of the Literature

Georges EI Hachem\*

*Institut Jules Bordet, Université Libre de Bruxelles, Belgium*

## Article Information

Received date: Aug 31, 2017

Accepted date: Sep 11, 2017

Published date: Sep 18, 2017

### \*Corresponding author

Georges Ei Hachem, Institut Jules  
Bordet, Université Libre de Bruxelles,  
Belgium,

Email(s): georges.elhachem@bordet.be  
(or) George.el.hashem@hotmail.com

**Distributed under** Creative Commons  
CC-BY 4.0

**Keywords** Hemophagocytic  
lymphohistiocytosis; Macrophage  
activation syndrome

## Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a rare and life threatening syndrome caused by excessive and dis-regulated immune activation. It can present as a primary sporadic disorder or be secondary to a trigger disrupting the immune homeostasis, such as auto-immune disorders, malignancies and mainly infections. It is usually of low suspicion index, and has variable presentations lacking specific pathognomonic clinical or laboratory signs. HLH is a medical emergency, and is associated with poor prognosis in most of the cases. An early diagnosis and initiation of appropriate treatment may change the outcome. Here I present a review of the literature concerning HLH, and one related pathologically similar disorder, the Macrophage Activation Syndrome (MAS), emphasizing on the clinical presentation, associated etiologies, diagnosis, treatment and prognosis, thus making the clinicians more aware of this fatal syndrome in order to decrease the related mortality.

## Introduction

Hemophagocytic Lymphohistiocytosis (HLH) and its related syndromes are a life threatening medical diagnosis with serious outcome secondary to excessive and inadequate immune activation. In the English and French literatures, the terms Hemophagocytic Lymphohistiocytosis (HLH) and Lymphohistiocytic Activation Syndrome (LHAS) are equivalent [1]. However, the macrophage activation syndrome is commonly used to describe the HLH secondary to auto-immune disorders, especially juvenile rheumatoid arthritis [2]. HLH was first described in 1952 as a “familial hemophagocytic reticulosis”. In the literature, HLH are divided into primary and secondary syndromes. The primary HLH denotes the Familial Hemophagocytic Lymphohistiocytosis (FLH) with mutation of the FLH gene and other genetic disorders associated with immunodeficiency syndromes. The secondary disorders are not associated with known genetic mutations and can be sporadic or acquired with associated triggers, such as auto-immune disorders, infections and malignancies [3]. However, this classification may create confusion because many patients affected by secondary HLH may have a genetic dysfunction. Furthermore, the patients having primary HLH may experience their symptoms in response to a certain trigger. HLH affects primarily pediatric population, mainly infants of less than 3 months of age. The male to female ratio is close to 1:1, with a slight male predisposition in adults [4]. The incidence is unknown as there is a wide spectrum of clinical presentation, and many episodes may remain undiagnosed.

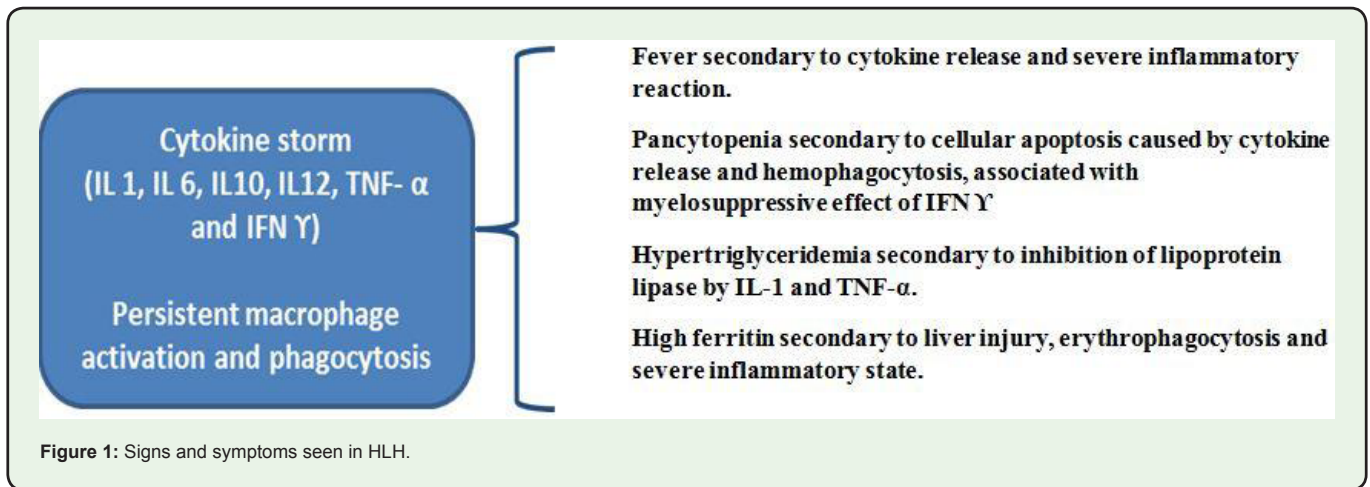
## Pathophysiology

HLH is not a malignant disorder. It can be resumed as an excessive immune activation leading to a severe inflammatory syndrome and tissue destruction. The major immune dysfunction is an absence of down-regulation of abnormally activated lymphocytes and macrophages [5].

Macrophages become activated and secrete cytokines, leading to tissue damage and a severe inflammatory reaction. At same time, cytotoxic T cells and NK cells are unable to eliminate the overactivated macrophages leading to their further activation, associated with increased levels of interferon gamma and other cytokines: Tumor Necrosis Factor Alpha (TNF  $\alpha$ ), soluble receptor of Interleukin (IL) 2 or CD25, IL-6 and IL-10 ( Figure 1) [6-8]. In addition to this inflammatory reaction, macrophages are able to phagocytize or “eat” host cells, in a picture of macrophages engulfing host white blood cells, red blood cells and platelets within their cytoplasm (Figure 2). This is called hemophagocytosis and is seen in biopsies of immune tissues and bone marrow aspirate or biopsy. It is highly supportive for the diagnosis of HLH, but its presence alone is neither diagnostic nor pathognomonic.

## Etiologies

Primary HLH are mainly caused by familial disorders and other immunodeficiencies. Four main genetic disorders are associated with primary HLH: familial lymphohistiocytosis, Griscelli syndrome, Purtillo syndrome, Chediak-Higashi syndrome [1]. Secondary HLH are mainly related



to infectious etiologies, malignancies and auto-immune disorders. Among infections, viruses (especially Herpes Simplex Virus, Epstein Barr Virus, Cytomegalovirus, Human Immunodeficiency Virus) are responsible for half of the cases, followed by mycobacteria, then other bacterial and parasitic infections [1,9,10].

High grade lymphomas, mainly T cell and Natural killer (NK) non Hodgkin lymphomas are the most common malignant causes of secondary HLH. Other hematologic malignancies are represented by acute leukemia and myeloproliferative syndromes. Solid tumors may play the role of trigger to HLH, such as colon carcinoma, gastric cancer, small cell lung carcinoma and others [11]. Between systemic and auto-immune disorders, Still’s disease and Lupus are mostly associated with MAS, which is a pathologically similar to HLH: an excessive dis-inhibited cytokine storm [1].

**Clinical Presentation and Diagnosis**

Patients are usually acutely and severely ill with multi-organ failure and without specific etiology despite prolonged hospital stay and evaluation. Common features include clinical deterioration, associated with persistent fever, high ferritin, hypertriglyceridemia, rash, lymphadenopathies, hepatosplenomegaly, neurologic symptoms, abnormal liver function tests, pancytopenia, coagulopathies, and sometimes acute kidney injury. Initial work up includes complete blood count, liver function tests, chemistry, kidney function, coagulation studies (PT-INR, PTT, fibrinogen and d-dimer), serum triglycerides, ferritin, viral serologies and blood cultures. Bone marrow examination should be done to evaluate pancytopenia, to rule out lymphoproliferative disorders, leukemia, and to asses infiltration by hemophagocytes (macrophages engulfing the three lineages and “eating the host cells”). All patients should also have cerebral spinal fluid studies, brain MRI and CT scan of the neck, chest, abdomen and pelvis to exclude any Central Nervous System (CNS) pathology or other malignant etiology [12-14].

Hyperferritinemia, mainly more than 10,000 g/dL is of high sensitive and specific value in diagnosing HLH (Figure 1).

After this initial evaluation, patients highly suspected of having HLH should undergo specialized immunologic profile testing with the following findings consistent with LHAS: elevated levels of soluble IL-2 receptor alpha; reduced NK function or cell surface expression of

CD107 alpha; elevated soluble levels of the hemoglobin-haptoglobin scavenger receptor (sCD163), and reduced perforin [15,16].

Diagnostic criteria, based on the HLH-2004 trial, requires five of the eight criteria reported in table 1 [17].

Diagnostic criteria are usually used for clinical trials and are unlikely to be detected in every case of HLH. Clinicians should never wait to meet these criteria to make the diagnosis and start the adequate treatment. The earlier the diagnosis is made, the quicker the treatment is given, and the better will be the prognosis. It is a fatal syndrome with high mortality rate, so treatment should never be delayed while awaiting some genetic tests or other specific immunologic profile testing. Administration of the adequate treatment can dramatically increase the survival.

**Treatment and Prognosis**

HLH cases should be referred to hematologic centers. Triggering conditions including infectious and auto-immune disorders should

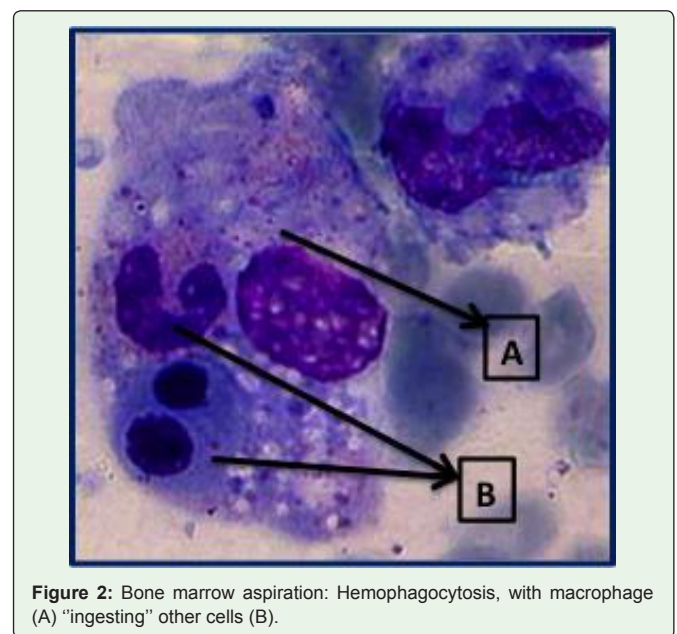


Figure 2: Bone marrow aspiration: Hemophagocytosis, with macrophage (A) “ingesting” other cells (B).

**Table 1:** Diagnostic criteria according to HLH-2004 trial.

Diagnostic criteria according to HLH-2004 trial
1- Fever > 38.5 °C
2- Splenomegaly
3- Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/d l; platelets <100,000/µl; absolute neutrophil count <1000/µl
4- Hypertriglyceridemia (fasting triglycerides >265 mg/d l) and/or hypofibrinogenemia (fibrinogen <150 mg/dl)
<b>5- Hemophagocytosis in bone marrow, spleen, lymph node, or liver</b>
6- Low or absent NK cell activity
7- Ferritin >500 ng/ml
8- Elevated soluble C025 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms (> 2400 U l/ml).

be evaluated. Patients with high risk features are those having HLH mutations, CNS disease and hematologic malignancies. Management of hemophagocytic lymphohistiocytosis is resumed in figure 3.

HLH specific treatment is mainly based on the HLH-94 protocol, or enrollment in clinical trials rather than treatment based on the HLH-2004 protocol. Therapy based on the HLH-94 protocol consists of eight weeks of induction therapy with Etoposide and Dexametahsone, with intrathecal therapy for those with CNS involvement. For the intrathecal therapy, Methotrexate with Hydrocortisone are usually used. Etoposide is given at a dose of 150 mg/m<sup>2</sup> for adults. The dose is given twice weekly for the first two weeks, and once weekly for weeks three through eight with adequate dose adjustment for hyperbilirubinemia, neutropenia and creatinine clearance. Dexamethasone is the preferred corticosteroid because it can cross the blood-brain barrier. It is given intravenously or orally and tapered over the eight-weeks induction, as following: start with 10 mg/m<sup>2</sup> daily for weeks 1 and 2, then 5 mg/m<sup>2</sup> daily for weeks 3 and 4, then 2.5 mg/m<sup>2</sup> daily for weeks 5 and 6, then 1.25 mg/m<sup>2</sup> daily during week 7, and then taper dose to zero on week 8 [18]. The

HLH-2004 protocol was initiated by the Histiocyte Society in 2004 and closed in December 2011, and the study results are awaited. The major modifications were to add Cyclosporin simultaneously with Etoposide.

Cases that are refractory to induction therapy are treated with additional anti-CD52 monoclonal antibody Alemtuzumab before transplant [19]. In cases of HLH secondary to lymphoproliferative disorders, Etoposide is included in the polychemotherapy protocols. Adequate supportive care with transfusion management, antibiotherapy, and appropriate prophylactic anti-viral and anti-fungal drugs are essential.

The response to initial induction treatment is a major determinant prognostic factor and defines the later need of allogeneic transplantation. Response to treatment is evaluated by clinical and biological assessment mainly the evolution of the ferritin and other cytokines which are disease specific markers.

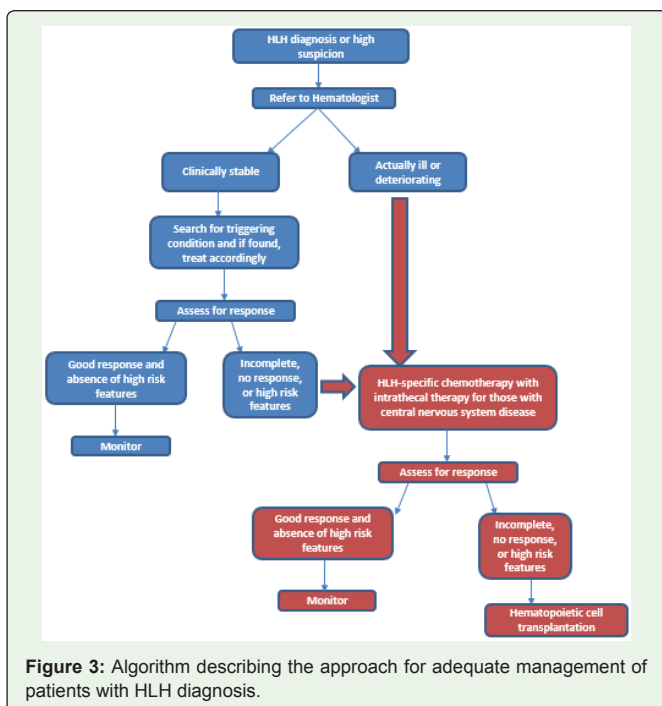
Median survival for patients with HLH is approximately 50 percents with HLH-94-based treatment. Poor prognostic factors include younger age, CNS involvement, and failure of therapy to induce a remission prior to HCT [20].

**Conclusion**

HLH is a life threatening condition that is hereditary in most infantile or pediatric cases, and acquired or secondary to infectious, auto-immune and malignant triggers in adults. MAS with its multi-organ failure and severe inflammatory reaction remain a diagnostic challenge, and must be suspected every time there is an acute rapid deterioration of the general status, even in the absence of the HLH-2004 typical diagnostic criteria. Early suspicion and diagnosis with referral to hematologic centers may change the outcome of this highly morbid and fatal syndrome.

**References**

1. Karras A, Hermine O. Hemophagocytic syndrome. Rev Med Interne. 2002; 23: 768-778.
2. Janka GE. Hemophagocytic syndromes. Blood Rev. 2007; 21: 245-253.
3. Larroche C. Hemophagocyticlymphohistiocytosis in adults: diagnosis and treatment. Joint Bone Spine. 2012; 79: 356-361.
4. Henter JI, Elinder G, Söder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocyticlymphohistiocytosis. Acta Paediatr Scand. 1991; 80: 428.
5. Filipovich A, McClain K, Grom A. Histiocytic disorders: recent insights into



**Figure 3:** Algorithm describing the approach for adequate management of patients with HLH diagnosis.

- pathophysiology and practical guidelines. *Biol Blood Marrow Transplant*. 2010; 16: S82.
6. Pachlopnik Schmid J, Côte M, Ménager MM, Burgess A, Nehme N, Ménasché G, et al. Inherited defects in lymphocyte cytotoxic activity. *Immunol Rev*. 2010; 235: 10-23.
  7. Risma K, Jordan MB. Hemophagocytic lymphohistiocytosis: updates and evolving concepts. *Curr Opin Pediatr*. 2012; 24: 9.
  8. Aricò M, Danesino C, Daniela Pende, Lorenzo Moretta. Pathogenesis of haemophagocytic lymphohistiocytosis. *Br J Haematol*. 2001; 114: 761.
  9. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH Jr, Simmons RL, et al. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. *Cancer*. 1979; 44: 993-1002.
  10. JM Michot, Hié M, Galicier L, Lambotte O, Michel M, Bloch-Queyrat C, et al. Hemophagocytic lymphohistiocytosis. *La Revue de médecine interne*. 2013; 34: 85-93.
  11. Machaczka M, Vaktnäs J, Klimkowska M, Hägglund H. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: a retrospective population based analysis from a single center. *Leuk Lymphoma*. 2011; 52: 613-619.
  12. Henter JI, Home A, Aricò M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007; 48: 124-131.
  13. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011; 118: 4041-4052.
  14. Gupta A, Tyrrell P, Valani R, Benseler S, Weitzman S, Abdelhaleem M. The role of hemophagocytosis in bone marrow aspirates in the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatric Blood Cancer*. 2008; 50: 192-194.
  15. Egeler RM, Shapiro R, Loechelt B, Filipovich A. Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. *J Pediatr Hematol Oncol*. 1996; 18: 340.
  16. Bleesing J, Prada A, Siegel DM, Villanueva J, Olson J, Ilowite NT, et al. The diagnostic significance of soluble CD163 and soluble interleukin-2 receptor alpha-chain in macrophage activation syndrome and untreated new-onset systemic juvenile idiopathic arthritis. *Arthritis Rheum*. 2007; 56: 965-971.
  17. Josh Farkas. Pulmcrit-Understanding sepsis - HLH overlap syndrome, Wikipedia picture. 2006.
  18. Henter JI, Aricò M, Egeler RM, Elinder G, Favara BE, Filipovich AH, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. *Med Pediatr Oncol*. 1997; 28: 342.
  19. Strout MP, Seropian S, Berliner N. Alemtuzumab as a bridge to allogeneic SCT in atypical hemophagocytic lymphohistiocytosis. *Nat Rev Clin Oncol*. 2010; 7: 415-420.
  20. Rivière S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, et al. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. *Am J Med*. 2014; 127: 1118-1125.