HAVE YOU SEEN

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

IN YOUR PRACTICE?

The first step to life-saving intervention is diagnosis.[1,2]

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What is hemophagocytic lymphohistiocytosis (HLH)?

HLH is a life-threatening hyperinflammatory disorder that is often characterized by persistent fevers, hepatosplenomegaly, cytopenia, coagulopathy, hepatitis, and liver failure.[1,3] HLH can be subcategorized as either primary or secondary HLH.[1]

PRIMARY HLH,

also known as genetic HLH or familial HLH (FHL), is associated with genetic mutations and typically presents in infancy and early childhood, although cases among teens and adults have also been identified.[1,2] A family history of the disease may or may not exist.[4]

SECONDARY HLH,

also known as acquired HLH, is not associated with any identified genetic mutation or a family history of the disease.[1,4] Rather, most cases are triggered by infections, malignancies, or rheumatologic disorders in older children, teens, and adults.[1,2]

- The heterogeneous presentation of HLH can lead to delayed diagnosis and treatment, **CONTRIBUTING TO A HIGH MORTALITY RATE (50%-100%).**[1,2]

RECOGNIZING THE CONSTELLATION OF SIGNS AND SYMPTOMS associated with the disease is the first clue on the road to diagnosis and life-saving treatment.[1]

Primary HLH: A diagnostic challenge

The diagnosis of HLH can be challenging due to its variable presentation.[1] The signs and symptoms of this rapidly progressive and life-threatening hyperinflammatory disorder can be mistaken for other conditions such as infections and malignancies.[3,4] Note that before an accurate diagnosis is made, a patient with HLH may see many physicians, including those specializing in emergency/intensive medicine, gastroenterology/hepatology, rheumatology, and hematology/oncology.[5]

The signs and symptoms of primary HLH include [1,3]:

- High fever (above 102°F, lasting 4-41 days)
- Hepatosplenomegaly
- Severe cytopenias
- Hyperferritinemia
- Coagulation defects
- Liver function impairment
- Infection
- Rash
- Jaundiced appearance
- Seizures and central nervous system involvement

Many of these signs and symptoms appear in the following diseases that should be ruled out to avoid misdiagnosis[5]:

- Sepsis
- EBV infection
- CMV infection
- Non-specific viral illnesses
- Macrophage Activation Syndrome (MAS)
- Juvenile rheumatoid arthritis (JRA)
- Lupus
- Liver dysfunction
- Hepatitis
- Immunodeficiencies
- Metabolic disorders
- Kawasaki disease

IT IS IMPORTANT TO RULE OUT MALIGNANCIES in all suspected cases of primary HLH.[6]

WITHOUT TREATMENT, the median survival of patients with HLH is less than 2 months from diagnosis.[1,4]

Your impact begins at diagnosis

According to current guidelines, fulfillment of

5 OF THE FOLLOWING **8**

criteria may be the basis for a clinical finding of HLH[1]:

- **FEVER** ≥ 38.5°C
- **SPLENOMEGALY**
- **CYTOPENIAS (AFFECTING AT LEAST 2 OF 3 LINEAGES IN THE PERIPHERAL BLOOD)**
  - Hemoglobin < 90 g/L (in infants < 4 weeks: hemoglobin < 100 g/L)
  - Platelets < 100 x 10^9/L
  - Neutrophils < 1.0 x 10^9/L
- **LOW OR ABSENT NATURAL KILLER (NK)-CELL ACTIVITY**
- **HEMOPHAGOCYTOSIS IN BONE MARROW, SPLEEN, OR LYMPH NODES**
- **FERRITIN** ≥ 500 µg/L
- **HYPERTRIGLYCERIDEMIA** (fasting, ≥ 265 mg/dL) **AND/OR HYPOFIBRINOGENEMIA** (≤ 1.5 g/L)
- **SOLUBLE CD25** (interleukin [IL]-2 receptor) > 2400 U/mL (or per local reference laboratory)

ANCILLARY TESTING AND FLOW CYTOMETRY can facilitate diagnosis and help prevent misdiagnoses and treatment delays.[1,6,7]

Diagnosis: A process of elimination and confirmation

Beyond the guideline criteria, ancillary testing and flow cytometry can help narrow possible diagnoses to more accurately find primary HLH.[1,6,7] Due to the rapid and severe nature of the disease, these methods should be explored if possible.[1,6]

ANCILLARY TESTING

To help rule out secondary HLH, you may consider running the following tests[7]:

- CT of chest/abdomen/neck
- MRI of brain
- Viral PCRs – EBV, CMV, adenovirus, etc.
- PET-CT to evaluate lymphoma
- Test for tick- or mosquito-borne diseases in areas at risk

FLOW CYTOMETRY

To help find primary HLH, you may consider checking for decreased levels of[7]:

- Perforin/granzyme B
- SAP protein (in males)
- XIAP protein (in males)
- CD107a

THE FINAL STEP IS GENETIC TESTING

A positive genetic test for any of the following mutations can assist a primary HLH diagnosis, although additional, unknown mutations may also exist[1]:

SUBTYPE	MUTATION
FHL1	Unknown
FHL2	*PRF1**
FHL3	*UNC13D**
FHL4	*STX11*
FHL5	*STXBP2 (UNC18B)*
Griscelli Syndrome type 2	*RAB27A*
Chédiak-Hagashi syndrome	*LYST*
X-linked Lymphoproliferative Disorder 1	*SH2D1A*
X-linked Lymphoproliferative Disorder 2	*BIRC4*

*Approximately 40% to 60% of primary HLH have been attributed to mutations in the *PRF1* (perforin) and *UNC13D* genes.[1]

THE MEDICAL CONSENSUS IS CLEAR: Once a case of primary HLH is suspected, treatment should begin immediately, regardless of genetic confirmation.[1]

RAPIDLY PROGRESSIVE. FATAL. TREATABLE.

Request more information about primary HLH by contacting your Sobi representative today.

Sobi Patient Support Services

833.597.6530

REFERENCES

1. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood.* 2011;118(15):4041-4052. doi:10.1182/blood-2011-03-278127. **2.** Price B, Lines J, Lewis D, Holland N. Haemophagocytic lymphohistiocytosis: a fulminant syndrome associate with multiorgan failure and high mortality that frequently masquerades as sepsis and shock. *S Afr Med J.* 2014;104(6):401-406. doi:7196/samj.7810. **3.** Marsh RA, Haddad E. How I treat primary haemophagocytic lymphohistiocytosis. *Br J Haematol.* 2018;182(2):185-199. doi:10.1111/bjh.15274. **4.** Henter J-I, Arico M, Egeler RM, et al; HLH Study Group of the Histiocyte Society. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. *Med Pediatr Oncol.* 1997;28:342-347. **5.** Data on file. Stockholm, Sweden: Swedish Orphan Biovitrum AB. **6.** Gurunathan A, Boucher A, Mark M, et al. Limitations of HLH-2004 criteria in distinguishing malignancy-associated hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2018;65:e27400. doi:10.1002/pbc.27400. **7.** Cincinnati Children's Hospital. HLH diagnostic strategy. https://www.cincinnatichildrens.org/service/h/hlh/clinical/test. Accessed June 14, 2019.

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