Neonatal Hemophagocytic Lymphohistiocytosis

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Education Gaps

1. Hemophagocytic lymphohistiocytosis is rarely seen in the neonatal population.
2. Clinicians should be able to identify and evaluate neonates with disorders of immune regulation.

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is extremely rare in the neonatal period. The incidence of neonatal HLH is not confirmed and may range from 1 in 50,000 to 150,000. The incidence varies based on ethnicity, particularly in populations in which consanguinity is common. HLH is associated with a high fatality rate and poor prognosis, making it important to recognize and diagnose it early. This review will concentrate primarily on the diagnosis and management of neonatal HLH.

Objectives After completing this article, readers should be able to:

1. Review the pathophysiology and clinical features of hemophagocytic lymphohistiocytosis (HLH).
2. Describe the criteria for diagnosis of HLH in the neonatal population.
3. Review the management recommendations for neonates with HLH.

AUTHOR DISCLOSURE Drs McLean, Katebian, Suh, Mirza, and Amin have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

FDA	Food and Drug Administration
fHLH	familial hemophagocytic lymphohistiocytosis
HLH	hemophagocytic lymphohistiocytosis
IFNγ	interferon γ
NK	natural killer
sCD25/sIL-2R	concentration of soluble interleukin 2 receptor
SCT	stem cell transplantation

INTRODUCTION/EPIDEMIOLOGY

Hemophagocytic lymphohistiocytosis (HLH) belongs to a group of disorders known as histiocytosis, which is characterized by an overabundance of tissue macrophages or histiocytes. Histiocytes are phagocytic cells present in connective tissue, which normally participate in the innate immune system by triggering cell signaling and activation. (1)(2) In effect, HLH can concisely be defined as a hyperinflammatory syndrome of pathologic immune activation. (3) The term HLH originated from its distinct histomorphologic findings described as an accumulation of lymphocytes and histiocytes containing phagocytosed cells in various tissues (Fig 1). (3)(4)(5)(6) This syndrome could be either familial or sporadic, which can be difficult to differentiate at the time of initial presentation. (3)(5)

Clinical presentation of HLH in the neonatal period is extremely rare. (7) The incidence of neonatal HLH is not confirmed and may range from 1 in 50,000 to 150,000. Tertiary care pediatric centers should expect 1 case per 3,000 inpatient admissions. (2)(8) The incidence varies based on ethnicity, particularly in populations in which consanguinity is common. (2)(9) In North America, blacks may represent up to 1 in 5 cases of familial HLH. (10)

HLH is associated with a high fatality rate and poor prognosis, pointing to the importance of early recognition and diagnosis. This review will concentrate primarily on the diagnosis and management of neonatal HLH.

PATHOPHYSIOLOGY

The terms "familial" (fHLH) or "primary HLH" are often used to indicate cases of HLH caused by an underlying genetic disorder. The genetic mutation can be autosomal recessive or X-linked, based on whether the gene mutation occurred within the fHLH loci or in a gene responsible for an immune deficiency. Of all cases of fHLH, 70% to 80% present before 1 year of age. (11) Of those with fHLH presenting before 1 year of age, 90% are asymptomatic in the first month after birth. (1)(3)(8)(11) It is estimated that 20% to 40% of FHLH cases result from mutations at the fHLH2 loci within the perforin gene (*PRF1*) on chromosome 10q22.1. (5)(7) More than 40 perforin gene mutations have been identified, many of which are reported as recurring in consanguineous families of Turkish, African, African American, and Japanese descent. (4)(9)(10)

Perforin is secreted by both cytotoxic T lymphocytes and natural killer (NK) cells. Perforin enables these cells to perforate cell membranes, allowing granzyme B to enter and initiate cell death via an apoptotic pathway. (Fig 2) When perforin is absent, cytotoxic T cell and NK cell signaling remains activated, resulting in the continual production of inflammatory cytokines and activated macrophages. Subsequent accumulation of lymphohistiocytic infiltrates in almost all organ systems leads to the clinical signs and symptoms of HLH frequently seen at diagnosis. (4)(9)

Studies have also identified mutations in genes as causes of fHLH, including FHL3: *UNC13D* (codes for Munc13-4), FHL4: *STX11* (Syntaxin 11), and FHL5: *STXBP2 (*Munc18-2). These genes play critical roles in the initial steps of cytolytic granule secretions and in their absence, cytolytic granule exocytosis and activity remain ineffective. (1)(5)

In North America, 7 genes are found to be commonly associated with HLH: *PRF1, UNC13D, RAB27A, STX11, SH2D1A, BIRC4*, or *STXBP2*. (1)(8)(12) As stated before, *PRF1* codes for perforin/granzyme B proteins. *SH2D1A* codes for Sap protein expression and *BIRC4* codes for XIAP protein expression; both of these are required for polarization of cytolytic granules. All others code for CD107a mobilization (Fig 2). Deficiencies in these genes lead to abnormal cytotoxic function by NK and T cells. (8)(13) Of note, the *LYST* gene is also considered diagnostic but is not commercially available, though it is available for testing by next-generation sequencing at Cincinnati Children's Hospital in Cincinnati, OH. Suspected boys should be tested for all 7 genes whereas girls do not need to be tested for *SH2D1A* and *BIRC4* because they do not carry these genes. (8)

Of the numerous genes associated with HLH, few gene mutations have been linked to HLH in children younger than 1 month. (8) According to a review of neonates with HLH, the only genes found to be associated were *PRF1* and *UNC13D*. Of the 2, *PRF1* was found to be the predominant gene and more likely to be found in black and Hispanic patients, whereas mutations in *UNC13D* were more common in white patients. (8) These findings are similar to those from other studies reporting *PRF1* in older black patients with HLH. (10)

Genetic mutations associated with immune deficiency syndromes have also been implicated in fHLH. Mutations in *RAB27A* are associated with Griscelli syndrome, *SH2DIA* and *BIRC4* with X-linked lymphoproliferative disease, and *LYST* with Chediak-Higashi syndrome. Continued gene

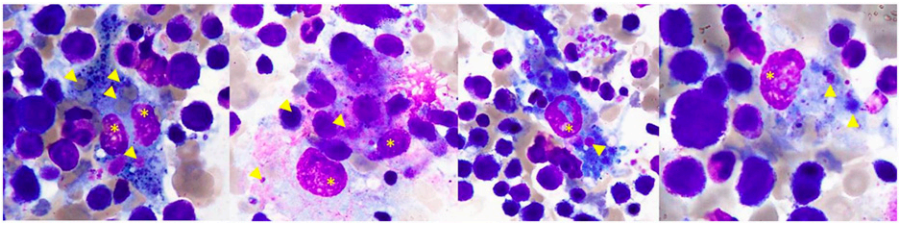

Figure 1. Representative bone marrow aspirate images from a suspected case of hemophagocytic lymphohistiocytosis demonstrating numerous histiocytes (asterisk indicates histiocyte nuclei) that show engulfed debris. Areas of specific erythrocyte debris (yellow arrowheads) confirm hemophagocytic activity. (Wright-Geimsa stain, original magnification ×1,000)

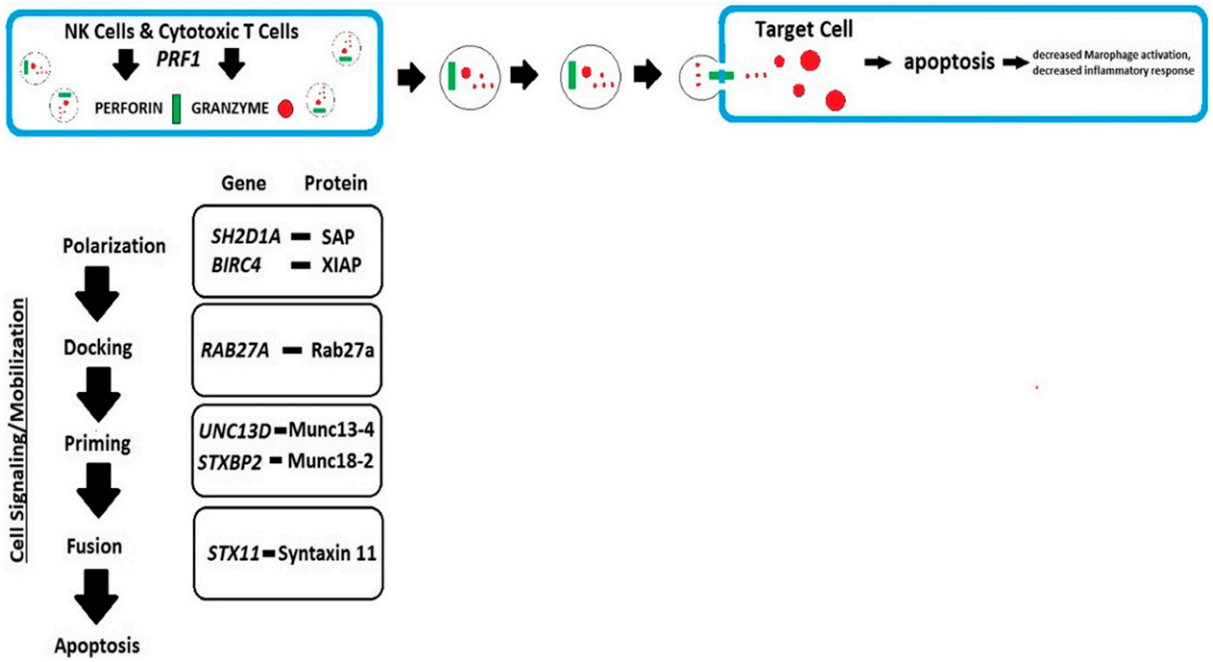

Figure 2. Perforin is secreted by both cytotoxic T lymphocytes and natural killer (NK) cells. Perforin plays a critical role in enabling proapoptotic granzymes to perforate cell membranes and initiate cell death via an apoptotic pathway. When perforin is absent, cytotoxic T cell and NK cell signaling remains activated, resulting in the continual production of inflammatory cytokines and activated macrophages. Hemophagocytic lymphohistiocytosis (HLH)–associated gene mutations may disrupt the normal cell signaling and mobilization process at the level of polarization, docking, priming, or fusion. Mutations in this pathway lead to similar HLH phenotypes with varying degrees of severity.

discovery related to fHLH will expand our understanding of its pathophysiology and lead to earlier diagnosis of neonatal HLH.

The term "secondary HLH" is used to indicate HLH acquired after a strong immunologic activation resulting from severe infection, rheumatoid disorders, malignancies, metabolic disorders, or prolonged intravenous nutrition (fat overload syndrome). (5) Infections known to cause excessive immune stimulation include Epstein-Barr virus, parvovirus B19, and cytomegalovirus. Bacteria, parasites, and fungi may have similar effects as well. (14) Neonatal cases are almost exclusively primary, and an analysis of these infectious etiologies is out of the scope of this review.

DIAGNOSIS

To establish the diagnosis of HLH, a molecular diagnosis must be made consistent with HLH or the presence of at least 5 of the 8 diagnostic criteria. Diagnostic criteria were first published by the Histiocyte Society in 1994. (15) After the first identifiable gene linked to HLH was found in 1999 (16) and additional causative genes were subsequently identified, the committee revised its recommendations in 2004. The committee endorsed the suggestion that any molecular finding of primary HLH would no longer require further clinical or laboratory criteria for diagnosis.

The 8 criteria for diagnosis are persistent fever, splenomegaly, cytopenias, hypofibrinogenemia and/or hypertriglyceridemia, hyperferritinemia, hemophagocytosis, low NK cell activity, and high concentration of soluble interleukin 2 receptor (sCD25/sIL-2R) (Table 1). Low NK cell activity is the result of disruption of NK activity. Hemophagocytosis results from the deposition of lymphocytes/histocytes in tissues. Cytopenias are caused by high levels of specific inflammatory markers suppressing hematopoiesis and increasing overall apoptosis. Splenic macrophage proliferation and activation lead to splenomegaly. Secretion of plasminogen activator causes lysis of fibrinogen, leading to an overall decrease in fibrinogen levels. (17)(18) Hyperferritinemia is thought to be secondary to increased levels of the enzyme heme-oxygenase released from macrophages, which releases ferritin as a by-product during heme degradation. (17)(19) Other inflammatory markers found in excess inhibit lipoprotein lipase, leading to increased triglycerides. (17)(18) sCD25 can reflect activated T-cell activity because it is a transmembrane protein that is upregulated with T-cell activation. (19) Hyperthermia found in patients with HLH is from an overabundance of inflammatory mediators. (20)

Data on the best clinical diagnostic approach are conflicting. (8)(21)(22) Some consider sCD25/sIL-2R as the most useful biomarker, because it indicates inflammatory

TABLE 1. **2004 Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis (5)**

Must fulfill either 1 or 2:
1. Molecular diagnosis: perforin, hMUNC 13-4, other relevant genes, flow cytometery for perforin in NK cells and cytotoxic T cells
2. 5 of 8 of the following criteria
a. Persistent fever*
b. Splenomegaly*
c. Cytopenias*†
d. Hypofibrinogenemia (<150 mg/dL [<4.4 μmol/L]) and/or hypertriglyceridemia (>265 mg/dL [>3.0 mmol/L])*
e. Hyperferritinemia (>500 ng/mL [>1,123 pmol/Lng/mL])
f. Hemophagocytosis*
g. Low natural killer cell activity
h. High concentration of soluble interleukin 2 receptor (sCD25/sIL-2R)

**1994 criteria.*
†Hemoglobin concentration less than 9 g/dL (90 g/L), neutrophils less than $1.0\times10^3/\mu L$ (1.0×10^9/L), or platelets less than $100\times10^3/\mu L$ (100×10^9/L) are considered diagnostic.

activity and disease process more accurately than ferritin and fibrinogen. (8)(20)(22)(23) However, ferritin levels greater than 10,000 g/dL (>22,470 pmol/Lng/mL) have been shown to be highly sensitive and specific for HLH diagnosis. (24) Others report that triglycerides are more useful and cost-effective indicators of HLH, but case studies have shown that triglycerides are elevated less often in neonatal HLH (likely because of rates of lipid metabolism). (21)(25)

The pathologic evaluation for hemophagocyosis is difficult because of the lack of consistent guidelines and absence of established criteria for quantifying hemophagocytic histiocytes in marrow aspirates. (26) Compounding this difficulty is the lack of specificity of finding hemophagocytic histiocytes because many common NICU events, such as blood transfusions, recovery from major surgical procedures, and sepsis, can all show a significant increase in hemophagocytic histiocytes. (26)(27)(28)(29) According to published literature, the presence of hemophagocytosis has a sensitivity of 83% and a specificity of only 60% in diagnosing HLH. (30)

This nonspecific occurrence of hemophagocytic histiocytes in the marrow (even when numerous) underscores the importance of caution that an isolated finding of hemophagocytosis lacks specificity and does not necessarily implicate a diagnosis of HLH immediately. Despite this, bone marrow biopsy examination remains valuable in cases in which clinical suspicion for HLH is high. In such cases, bone marrow evaluation helps to exclude other processes involving the marrow, or other primary marrow disease.

Changes have been proposed to the current diagnostic principles because many of the criteria do not depict common features of the disease process. (8) Liver enzymes are currently not taken into account even though almost all cases have some level of liver inflammation. (7)(9)(31) Others have also raised concerns that neurologic criteria have not been considered even though neurologic abnormalities are a common clinical finding in children with HLH. (8)(23)(32) Similarly, there is no consideration for a family history for HLH even though there are proven genetic components of the disorder. (1)(12)(33)(34)(35)

CLINICAL MANIFESTATIONS

If genetic testing is unavailable, inconclusive, or pending, the diagnosis of HLH can be made based only on clinical and laboratory criteria. The signs and symptoms of HLH vary in all ages and often are mistaken for other common disorders. In a review of 113 patients younger than 15 years for the anticipated 2004 updates, the Histiocyte Society found that the most common clinical signs in all cases were fever, hepatosplenomegaly, and cytopenias. (5) Numerous published reports have found hydrops and elevated transaminases to be the most common findings in the neonatal population. (5)(9)(31)(36)(37)

In contrast with the findings of the HLH Society, hypothermia is more common than hyperthermia in neonates with HLH (4)(31)(32)(38); however, data are limited on hypothermia duration and severity. Nonenvironmental fevers in the newborn period in the setting of other HLH findings should trigger a clinical suspicion of HLH after sepsis and other common causes have been ruled out.

One of the largest reviews of HLH in neonates was part of a 2009 case report of a twin pregnancy with fetal hydrops. (31) An extensive literature search from this review resulted in a total of 13 cases of HLH diagnosed prenatally or within the first week after birth. Significant findings included abnormal perforin and NK function, hepatosplenomegaly, cytopenias, and increased ferritin/fibrinogen in all 13 cases (1 twin died in the delivery room and testing was incomplete). In addition, 10 of 14 patients were male, 11 of 13 had respiratory issues requiring support, 10 had elevated bilirubin levels, 4 had fever, and 2 had hypothermia. Elevated liver function tests were noted in 12 patients with 1 unknown, coagulopathies were noted in 9 cases, and 7 patients had abnormal triglycerides. Only 4 fetuses developed hydrops between 28 and 36 weeks' gestation.

A 2009 case series also confirmed that hemophagocytosis is neither sensitive nor specific in diagnosing HLH. (39) Of the 14 neonatal cases, 8 had hemophagocytosis in the bone marrow, 4 had infiltration in the liver, 2 had splenic involvement, and 2 had hemophagocytosis in the placenta. Few of these neonates had biological testing, and sCD25/sIL-2R testing was available at the time of the report's publication. (31) Since then, several other case reports have been published about neonates with HLH with similar presentations.

As stated in numerous publications, the diagnosis of HLH is often camouflaged as other conditions commonly found in newborns. (22)(40)(41) Sepsis is a common consideration in the differential diagnosis (6)(22)(42) because both sepsis and HLH can present with characteristic multiorgan failure. (23)(41)(42) In older children, neurologic abnormalities and coagulopathies can be easily mistaken for a nonaccidental trauma. (43)(44)(45) Clinicians should consider HLH in their differential if a full diagnostic evaluation for child abuse is inconclusive.

An additional clinical consideration in the diagnosis of HLH is the presence of dermatologic abnormalities. Up to 65% of all patients with HLH in any age group will have some type of dermatologic finding. (34)(46)(47) Findings may vary and the skin lesions are highly pleomorphic. These findings can range from a simple erythematous rash to conditions as complex as edema and purpura. (8)(48) The variations in skin presentation can often mimic common newborn rashes or exanthems, leading to a delayed diagnosis. (48) Physicians should consider HLH in infants with skin findings in the setting of other diagnostic criteria for HLH.

MANAGEMENT

Once the diagnosis is confirmed, management should be aimed promptly at reducing the hyperinflammation and immune dysregulation. A delay in diagnosis and treatment results in increased mortality. (25) Clinicians should work closely with oncological services that are specialized in neonatal HLH at a care center that is equipped to administer treatment. Because most neonatal HLH cases are familial, allogeneic stem cell transplantation (SCT) is the only curative solution. (49) As such, HLA typing of the patient and search for an appropriate SCT donor should be conducted immediately. Therapy should be initiated based on Histiocyte Society treatment protocols, such as HLH-94, or enrollment in a clinical trial may be considered while waiting for

TABLE 2. **Potential Medications for Use in Patients with Hemophagocytic Lymphohistiocytosis**

DRUG	DRUG CLASSIFICATION	MECHANISM OF ACTION	SIDE EFFECTS
Etoposide	Antineoplastic agent; topoisomerase II inhibitor	Causes breaks in DNA when interacting with the DNA/topoisomerase II complex, preventing further replication of DNA in late S and early G2 phase and inhibiting cell proliferation	Alopecia, nausea and vomiting, diarrhea, anorexia, leukopenia, thrombocytopenia, anemia, hypotension secondary to rapid infusion, hepatotoxicity, anaphylactoid reaction
Dexamethasone	Corticosteroid	Decreases inflammation by modulating the production of inflammatory mediators and suppressing neutrophil migration	Arrhythmia, embolism, hypertension, emotional lability, edema, hyperglycemia, hypokalemia, adrenal suppression, growth suppression, nausea and vomiting, increased appetite, increased serum transaminases, hypersensitivity
Cyclosporine A	Immunosuppressant; calcineurin inhibitor	Suppresses cell-mediated immune reactions by blocking transcription of cytokine genes in activated T cells	Hypertension, edema, headache, paresthesia, tremor, hypertrichosis, hirsutism, increased serum triglycerides, gingival hyperplasia, gastrointestinal upset, increased susceptibility to infection, renal insufficiency
Emapalumab	Monoclonal antibody	Inhibits interferon γ	Hypertension, tachycardia, irritability, skin rash, hypokalemia, appendicitis, constipation, abdominal pain, diarrhea, lymphocytosis, increased susceptibility to infection, infusion-related reaction, fever

an SCT donor. (50) Induction therapy consists of 8 weeks of chemotherapy including etoposide and dexamethasone with or without cyclosporine A. Intrathecal therapy is administered if there is central nervous system involvement. The primary goal of therapy is to maximize T-cell function while decreasing inflammation until SCT can be performed.

The antineoplastic etoposide is used to inhibit topoisomerase II, which is crucial for DNA replication and repair. Etoposide causes breaks in the DNA when interacting with the DNA/topoisomerase II complex, preventing further replication of DNA in the late S and early G2 phases and inhibiting cell proliferation. (51) The glucocorticoid dexamethasone is used to decrease inflammation by modulating protein production intracellularly. (52) Cyclosporine A suppresses cell-mediated immune reactions by blocking transcription of cytokine genes in activated T cells. (53) Table 2 provides a summary of possible medications to use in patients with HLH.

Specific protocols for treatment failure, relapse, and remission should follow the 2004 Histiocyte Society HLH guidelines; clinicians are advised to work closely with an oncologist on long-term treatment plans after initial treatment.

In November 2018, the US Food and Drug Administration (FDA) approved emapalumab, a monoclonal antibody directed against interferon γ (IFNγ). Emapalumab is the first FDA-approved drug for HLH, specifically for the treatment of adult and pediatric patients with primary HLH that is refractory, recurrent, progressive, or intolerant to conventional therapy. (54) Mean age of all pediatric patients in the study at the time of diagnosis was 0.85 years and 79% lived to SCT. Although HLH is a hyperinflammatory disorder involving multiple cytokines, IFNγ, specifically, has been found to play a pivotal role in disease activity. As a result, blocking IFNγ was found to be effective in achieving responses in a clinical trial of emapalumab. (54)

PROGNOSIS

As stated earlier, the only curative treatment for fHLH is hematopoietic SCT. Data are extremely limited, but children who achieved remission before transplantation did better than those who did not; even under optimal circumstances, the disease was often terminal. (55) With no intervention, the median survival is 2 months from the time of diagnosis. Multiorgan failure and systemic infection are the most common causes of mortality. (56) Because neonatal presentation of HLH is extremely rare, the outcomes data are limited and variable. Remission status, time to transplantation, and other comorbid factors affect overall survival. Delay in control of disease with chemotherapeutic agents before transplantation has been shown to affect overall survival. (15)(32) Early diagnosis via genetic testing, treatment, and transplantation offer best chances for survival.

CONCLUSION

Neonatal presentation of HLH is extremely rare. Clinicians should consider HLH in their differential diagnosis in neonates with unexplained fever, hepatosplenomegaly, and pancytopenia. Genetic testing should be considered if there is a clinical suspicion of HLH.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Recognize the clinical features and know the evaluation and management of disorders associated with T-cell dysfunction, including DiGeorge sequence and HIV infection.
- Know the initial screening tests and subsequent specific diagnostic tests used to evaluate neonates with possible defects in host defense mechanisms.

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1. Hemophagocytic lymphohistiocytosis (HLH) is a severe disorder that rarely presents in the neonatal period and can be defined as a hyperinflammatory syndrome of pathologic immune activation. HLH can be inherited (familial HLH [fHLH]) or acquired. Which of the following statements regarding the pathophysiology of fHLH is correct?
    A. Genes identified as causes of HLH play a critical role in the initial steps of cytolytic granule secretion.
    B. Mutations in the perforin gene (*PRF1*) on chromosome 10q22.1 represent the most commonly identified mutation, accounting for 60% of cases.
    C. *STX11* and *BIRC4* are the only genes that have been associated with HLH in neonatal patients.
    D. The majority of fHLH cases present after the first year of age.
    E. *UNC13D* is the predominant mutation found in Hispanic patients.
2. HLH is associated with poor prognosis, emphasizing the need for early diagnosis and intervention in affected patients. The diagnostic criteria for HLH were initially published in 1999 by the Histiocyte Society and revised in 2004. Which of the following statements regarding the diagnosis of HLH is correct?
    A. High natural killer cell activity is a diagnostic criterion for HLH.
    B. Hypertriglyceridemia is the most helpful criterion in neonatal HLH.
    C. Hyperferritinemia represents one of the criteria for the diagnosis of HLH.
    D. The presence of low concentrations of soluble interleukin 2 receptor represents one of the criteria for the diagnosis of HLH.
    E. There are 10 diagnostic criteria and the diagnosis of HLH can be established if at least 4 of these criteria are present.
3. The clinical manifestations of HLH are variable and can be mistaken for other common disorders. Which of the following statements regarding the clinical presentation of HLH is correct?
    A. An elevated ferritin level is an uncommon finding in neonates with HLH.
    B. Dermatologic abnormalities are uncommon at the time of presentation.
    C. Hyperthermia is the most common presenting symptom in both neonates and older infants.
    D. In children younger than 15 years, the most common clinical signs include fever, hepatosplenomegaly, and coagulopathies.
    E. In neonates, hydrops and elevated transaminases represent the most common findings.
4. A prompt diagnosis of HLH in affected neonates is critical to initiate therapies aimed at reducing inflammation and immune dysregulation, and decrease mortality. Which of the following statements regarding the management of HLH is false?
    A. Allogeneic stem cell transplantation is the only curative solution.
    B. Cyclosporine A can be used to block transcription of cytokine genes in activated T cells and suppress cell-mediated immune reactions.
    C. Dexamethasone can be used to modulate intracellular protein production and decrease inflammation.
    D. Emapalumab, a monoclonal antibody directed against interferon γ, was recently approved for the treatment of adult and pediatric patients with primary refractory HLH.
    E. Etoposide is used to inhibit topoisomerase I, thereby causing breaks in the DNA and inhibiting cell proliferation.

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5. Since November 2018, emapalumab has been approved by the US Food and Drug Administration, and is specifically targeted at primary HLH that is refractory, recurrent, progressive, or intolerant to conventional therapy. Of the following, the purported mechanism of action of emapalumab in modulating disease activity is:

   A. As a competing agonist toward complement.
   B. As a monoclonal antibody directed against and blocking interferon γ.
   C. Binding to signaling proteins in B and T cells.
   D. By increasing the production of several coagulation factors in the liver.
   E. By stimulating erythropoiesis as well as other cell lines in the bone marrow.

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NeoReviews 2019;20;e316
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