Familial Hemophagocytic Lymphohistiocytosis

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KEYWORDS

- Hemophagocytic lymphohistiocytosis
- Familial hemophagocytic lymphohistiocytosis • HLH • FHL • Perforin • XLP

KEY POINTS

- Familial hemophagocytic lymphohistiocytosis (FHL) is a rare hyperinflammatory condition that is genetically heterogeneous. FHL is typically diagnosed in infancy but may present much later in life.
- Approximately 70% of individuals diagnosed with FHL have mutations identified in a hemophagocytic lymphohistiocytosis (HLH)–associated gene.
- FHL bears resemblance to secondary forms of HLH, including Epstein-Barr virus–associated HLH and macrophage activation syndrome. The approach to initial treatment is similar.
- Hematopoietic cell transplantation is necessary to cure FHL. Reduced-intensity conditioning before transplantation is associated with lower risk of toxicity and higher likelihood of survival.

INTRODUCTION

Familial hemophagocytic lymphohistiocytosis (FHL) is a rare, life-threatening, inherited hyperinflammatory syndrome that may be clinically indistinguishable from secondary forms of hemophagocytic lymphohistiocytosis (HLH). The molecular basis of FHL is heterogeneous, with defects occurring in 1 or more of several proteins that participate in lymphocyte cytotoxicity. In most but not all cases of FHL, the genetic defect responsible for the disease can be identified. However, in some cases, the diagnosis of FHL is presumed from a relapsing or unremitting course or a positive family history. There is still much more to be learned about the interplay between genetics and environmental factors that underlie FHL.

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INCIDENCE

FHL is estimated to affect approximately 1 in 50,000 live births or 0.12 to 0.15 per 100,000 children per year.[1] The disease occurs worldwide among all races and ethnic groups. The absolute frequency of disease-causing mutations in specific HLH-associated genes varies among populations. A slight male preponderance may be attributable to the occurrence of FHL in association with X-linked lymphoproliferative disorders (XLPs).

FHL is a conditional disease in the sense that affected individuals are healthy until they encounter a trigger, such as an ordinary viral infection. Once initiated, the cycle of inflammation and the signs and symptoms that are elicited usually progress very rapidly. Secondary HLH is more prevalent than FHL; however, the true incidence of secondary HLH in children and adults remains undefined.[2]

FAMILIAL HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SUBTYPES

FHL was first described in 1952 in 2 infant brothers[3] and was recognized as a rare, fatal familial disease with an autosomal recessive inheritance pattern. It was not until 1999 that Stepp and colleagues[4] discovered the association of FHL with mutations in the perforin gene, establishing the molecular basis for FHL-2. In the years since, the molecular basis for FHL-3, FLH-4, and FHL-5 has been determined. The gene responsible for FHL-1, which is linked to chromosome 9q22,[5] remains a mystery. In addition, 2 distinct X-linked syndromes, XLP-1 and XLP-2, are typically associated with HLH and individuals with Griscelli syndrome, Chédiak-Higashi syndrome, Hermansky-Pudlak syndrome, and certain glycogen storage disorders sometimes develop HLH.

The underlying defect in patients with FHL can be ascribed to a defect in the primary cytotoxicity effector pathway in lymphocytes and natural killer (NK) cells, leading to poor clearance of target cells and a perpetual state of immune activation (**Fig. 1**). The genetic variants of FHL are presented in **Table 1**.

Perforin is a critical component of cytotoxic granules in effector T and NK cells. Upon effector cell degranulation, perforin and granzymes are released from the cytotoxic granules in close proximity to a target cell, such as a virally infected cell. Perforin creates a pore in the membrane of the target cell, allowing granzymes to initiate target cell death by apoptosis. Abnormal or absent perforin function leads to impaired killing of target cells and uncontrolled T-cell activation and high levels of inflammatory cytokines. This so-called cytokine storm is responsible for the tissue damage and clinical symptoms seen in HLH. Interferon (IFN) gamma is an essential player in this cascade. Blockade of IFN gamma activity using a neutralizing antibody abrogates the clinical features of HLH in perforin-deficient mice.[6]

The median age of onset of FHL-2 is 3 months. However, there is a wide range of disease onset and severity that correlates with the degree of perforin deficiency. Residual cytotoxic function and later age of onset are observed in patients with at least 1 missense mutation.[7] Among African Americans, FHL-2 accounts for most FHL cases. The 50delT is the most common mutation observed in this population and is associated with profound perforin deficiency and early disease onset.[8]

The process of effector cell cytotoxicity depends on the regulated transport, docking, priming, and fusion of perforin-containing lytic granules at the effector–target cell interface. Munc13-4 participates in preparing lytic vesicles that are docked at the cell surface for fusion with the membrane. Impaired lymphocyte cytotoxicity results from Munc13-4 deficiency[9] and biallelic mutation in Munc13-4 causes FHL-3. Disease-causing Munc13-4 mutations, which may be classified as nonsense, missense, or