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Review

Contemporary diagnostic methods for hemophagocytic lymphohistiocytic disorders

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ABSTRACT

Hemophagocytic lymphohistiocytosis is a life-threatening multi-system hyperinflammatory disorder characterized by dysfunctional cytolytic lymphocyte responses, hypercytokinemia, and widespread lymphohistiocytic tissue infiltration and destruction. Diagnosis and definitive therapy are often delayed as clinical efforts are directed toward treatment of presumed overwhelming infection. Sporadic cases occur in association with underlying immune dysfunction related to autoimmune disease, malignancy, or severe infection. However, familial cases predominate with remarkable associations between underlying genetic defects and dysregulation of immune responses. Here, we review the genetic and immunologic basis of contemporary diagnostic methods for hemophagocytic lymphohistiocytosis.

Contents

Abbreviations: CNS, central nervous system; Cr, chromium; CRP, c-reactive protein; CTL, cytotoxic T lymphocyte; EBV, Epstein–Barr virus; ELISA, Enzyme-linked immunosorbant assay; ESR, erythrocyte sedimentation rate; E:T, effector:target ratio; FHL, familial hemophagocytic lymphohistiocytosis; HCT, hematopoietic cell transplant; HLH, hemophagocytic lymphohistiocytosis; IL2, interleukin-2; LAMP, lysosomal associated membrane glycoprotein; MAS, macrophage activation syndrome; MFI, mean fluorescence intensity; NK, natural killer; PBMC, peripheral blood mononuclear cell; SAP, SLAM-associated protein; sIL2R, soluble IL2 receptor-alpha chain; SLAM, signaling lymphocyte activation molecule; TCR, T cell receptor; XIAP, X-linked inhibitor of apoptosis; XLP, X-linked lymphoproliferative syndrome.

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1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) was first described by Farquhar and Claireaux using the term familial hemophagocytic reticulosis (Farquhar and Claireaux, 1952). Histopathological analyses led them to conclude that disease pathogenesis was related to a primary defect of the reticuloendothelial system. Since that time, great advances have been made in our understanding of the underlying mechanisms of HLH disease evolution. It is now recognized that fundamental defects in lymphocyte cytolytic effector function lead to dysregulated immune responses that ultimately manifest as HLH. Although sporadic forms exist, it has long been appreciated that a familial predilection predominates, with an incidence of 1.2 per million (Henter et al., 1991).

HLH is a systemic hyperinflammatory syndrome in which dysfunctional cytolytic lymphocyte responses lead to ineffective down-modulation of stimulatory signals provided by antigen presenting cells. Thus, a positive feedback loop is initiated in which excessive stimulation of T cells leads to massive cytokine production that drives systemic macrophage activation, lymphohistiocytic infiltration of tissues, destruction of vital organs, and death. Diagnostic guidelines require either a genetic diagnosis (http://www.cincinnatichildrens.org/svc/alpha/m/molecular-genetics/hlh-spec.htm) or five of the following clinical criteria: fever, splenomegally, bicytopenia, either hypofibrinoginemia or hypertriglyceridemia, hyperferritinemia, elevated soluble interleukin-2 receptor, impaired natural killer (NK) cell cytolytic function, or the observation of hemophagocytosis in bone marrow, spleen, or lymph nodes (Henter et al., 2007). Hepatic dysfunction and failure can also be a presenting manifestation of HLH and may greatly complicate the clinical course. In addition, development of subtle or overt CNS findings may be related to CNS involvement with HLH.

HLH is often fulminant at the time of diagnosis and familial disease is uniformly fatal with mean survival of 1 to 2 months in the absence of therapy. The advent of etoposide based induction therapy led to an 8-week survival rate of 89%, with 85% either resolved (53%) or improved (32%), and introduction of hematopoietic cell transplant (HCT) for familial disease achieved 3-year overall survival of 55% and a 3-year post-transplant survival of 62% (Henter et al., 2002). Long term post-transplant outcomes have since improved, achieving survival rates of 75% to 84% with introduction of reduced-intensity conditioning regimens (Cooper et al., 2006, 2008). However, the presence of active disease at the time of HCT remains an ominous prognostic factor, and effective pre-transplant induction therapy is extremely important in optimizing transplant outcomes. Thus, prompt and accurate diagnosis based on a combination of immunologic, genetic, and clinical criteria is critical to avoid unnecessary delays in the initiation of definitive therapy.

2. Genetic testing in the diagnosis of HLH

2.1. Familial HLH

First reported by Farquhar and Claireaux (1952), familial HLH (FHL) is inherited in an autosomal recessive fashion, presenting as a primary syndrome of hyperimmune dysfunction with an incidence of 1.2 per million (Henter et al., 1991). Linkage analyses of FHL patients have demonstrated at least five distinct genetic loci (Cetica et al., 2010a): FHL1 at 9q21.3-22 with an as yet undefined gene (Ohadi et al., 1999), FHL2 at 10q21-22 affecting the *PRF1* gene (Dufourcq-Lagelouse et al., 1999; Stepp et al., 1999), FHL3 at 17q25 affecting the *UNC13D* gene (Feldmann et al., 2003), FHL4 at 6q24 affecting the *STX11* gene (zur Stadt et al., 2005), and FHL5 at 19p13.2-13.3 affecting the *MUNC18-2* gene (zur Stadt et al., 2009). Among these familial forms of HLH, the common pathway of HLH pathogenesis is defective NK cell and CD8+ T cell cytolytic effector function with respect to cytotoxic vesicle degranulation and perforin-dependent killing of target cells. Normal granule-mediated cytotoxicity occurs as cytolytic granules containing perforin and granzymes are delivered to the inner leaflet of the cytotoxic effector lymphocyte membrane at the immunological synapse via microtubule-dependent vesicular transport. Granules must then undergo vesicular priming prior to fusion with the cell membrane, whereupon their contents are released into the intercellular space at the point of contact between the two cells. Once in the intercellular space, perforin plays a critical role in delivering granzymes through the target cell membrane where they induce apoptosis by caspase-dependent and caspase-independent mechanisms. The genes known to cause FHL each have a protein product which is critical for normal cytotoxic lymphocyte degranulation.