Infectious Triggers of Hemophagocytic Syndrome in Children

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Hematologic abnormalities complicating childhood infectious diseases have been recognized as a common feature for many decades. In 1979, Risdall et al[1] described 19 patients with a distinct clinical syndrome that occurred in a setting of viral infection and named the disorder virus-associated hemophagocytic syndrome. Following the original report, cases of hemophagocytic syndrome triggered by bacteria, fungi and parasites were reported, ultimately leading to a change in the name of the condition to infection-associated hemophagocytic syndrome.[2] Today the formal designation for this group of disorders is hemophagocytic lymphohistiocytosis (HLH), although the informal designations of hemophagocytic or "macrophage activation" syndrome are still commonly used.

HLH is a proliferative disease that affects antigen-processing macrophages resulting in uncontrolled hemophagocytosis. Primary hemophagocytic lymphohistiocytosis comprises a group of autosomal recessive genetic disorders including mutations in the genes encoding perforin and Munc13-4 protein, and immunodeficiency syndromes such as X-linked lymphoproliferative disorder and the autosomal recessive Chediak-Higashi syndrome. Acquired, or secondary HLH is a reactive disorder causing robust immune activation resulting from infection, autoimmune diseases (especially systemic lupus erythematosus), malignancy or medication. Both primary and secondary hemophagocytic lymphohistiocytosis are associated with marked inflammation, driven in part by the overproduction of proinflammatory cytokines including interleukins-1 and -6 and tumor necrosis factor-α. Infection-associated HLH represents an important subset of all causes of HLH because the identification and treatment of the infectious trigger can, in some cases, lead to complete resolution of the proliferative disorder. Hemophagocytic lymphohistiocytosis appears to affect all ages, with an estimated 40 cases per 100,000 people per year.

The formal diagnostic criteria for primary (or genetic) hemophagocytic lymphohistiocytosis are fulfilled if there is molecular confirmation of the perforin gene or Munc 13-4 gene mutation. HLH is diagnosed in the absence of genetic confirmation if 5 of the following features of the disease are identified: fever; splenomegaly; cytopenias involving 2 or more cell lines; hypertriglyceridemia or hypofibrinogenemia; hyperferritinemia; elevated interleukin-2 receptor (sCD25); reduced or absent NK cell activity; and hemophagocytosis in bone marrow, cerebrospinal fluid or lymph nodes. There is increasing evidence that some patients do not meet all of these criteria and that many patients do so only late in the course of the disease. Because it is not possible to differentiate primary from secondary HLH until the result of genetic testing are available, early and aggressive pursuit of an infectious trigger is logical.

Viruses were the first and remain the most common group of infectious agents to be implicated as triggers of hemophagocytic lymphohistiocytosis, with Epstein-Barr virus (EBV) being the single most common cause.[3] In a recent review of 19 U.S. children with HLH,[4] an infectious trigger was documented in 42%. Similarly 61% of 18 Taiwanese children had a documented infectious provocation.[5] Viruses (EBV, cytomegalovirus (CMV), adenovirus, respiratory syncytial virus, parainfluenza virus and enteroviruses) accounted for all of the documented infectious triggers in both series. In addition, given the recognized hematologic manifestations of parvovirus B19 infection, it is not surprising that it can also be associated with the development of HLH.[6]

In a report of 18 pediatric cases of infection-associated hemophagocytic lymphohistiocytosis from Turkey,[7] the syndrome was caused by viruses (EBV, CMV and herpes simplex virus) in 8 patients, bacteria (*Pseudomonas aeruginosa*, staphylococci, streptococci, *Escherichia coli* and *Brucella abortus*) in 8 patients and by a parasite (*Leishmania donovani*) in the remaining 2 patients. A report of 50 Thai children[8] demonstrated that, in addition to the agents described above, other viruses (human immunodeficiency, dengue viruses), bacteria (*Mycobacterium tuberculosis*), fungi (*Histoplasma capsulatum*, *Penicillium marneffei*) and parasites (*Plasmodium* spp.) can trigger this illness and suggested that as many as 10% of patients have 2 or more concurrent infections. A pediatric cohort of 15 Thai children[9] with infection-associated hemophagocytic lymphohistiocytosis reidentified several of the infections known to be associated with the disorder including salmonellosis, dengue virus and *P. marneffei* infection.

To date, fungal infections that elicit hemophagocytic lymphohistiocytosis in children are described only as single case reports so the precise distribution and spectrum of fungi associated with this disorder are largely unknown. Existing reports include cases of disseminated aspergillosis in an HIV-infected child,[10] cryptococcal meningitis,[11] disseminated histoplasmosis in an immunocompromised adolescent[12] and disseminated *Trichosporon beigelii* (now *Trichosporon asahii*) infection in a newborn.[13] These and other

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case reports and case series on infection-triggered HLH are summarized at URL: http://www.cdc.gov/ncidod/eid/vol6no6/fisman_refs.htm.

All patients who meet the diagnostic criteria for hemophagocytic lymphohistiocytosis should have genetic testing performed because it is impossible to distinguish primary from secondary HLH on clinical grounds, and familial HLH is uniformly fatal without bone marrow transplantation. At the same time, an attempt should be made to uncover an infectious trigger. At a minimum, blood and bone marrow should be cultured for bacteria, fungi and viruses. In addition, serologic and/or nucleic acid-based diagnostic testing for EBV, CMV and parvovirus B19 should be obtained. Additional testing for infectious causes should be guided by epidemiologic data and the patient's medical and travel history. For example, history of travel to an endemic area might require testing for leishmaniasis, dengue fever or malaria. A high level of vigilance and a comprehensive search for a potential infection is particularly important because treatment of the infection can result in rapid resolution of hemophagocytic lymphohistiocytosis-associated signs and symptoms.

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