JIA Flare Triggers Macrophage Activation

BY PATRICE WENDLING

CHICAGO — Disease flare rather than infection or treatment complication may explain most cases of macrophage activation syndrome, and the wider use of new biologic agents may significantly reduce its incidence.

Epstein-Barr virus and cytomegalovirus infections are the most commonly reported causes of macrophage activation syndrome (MAS), and several case reports have implicated gold preparations and sulfa drugs. But most cases of this potentially lethal complication of systemic juvenile idiopathic arthritis (JIA) have remained unexplained, pediatric rheumatologist Alexi Grom said at a symposium sponsored by the American College of Rheumatology.

"If we treat systemic JIA better with new biologics, we are less likely to see MAS because the underlying disease is the setup for this complication," he said in an interview.

Subclinical MAS may occur in up to 40% of children with active JIA. Its more severe form is devastating.

DR. GROM

Although MAS has been reported in association with almost any rheumatic disease, it is by far most common in systemic JIA, affecting about 10% of these patients. It may occur at any stage of the disease, even in remission. Recent research suggests that a mild subclinical form of MAS may occur in about 30%-40% of children with active systemic JIA.

"Macrophage activation syndrome is the most devastating aspect" of JIA, Dr. Grom of Cincinnati Children's Hospital Medical Center told the audience.

There are strong clinical similarities between MAS and the genetic disorder familial hemophagocytic lymphohistiocytosis, both of which are characterized by uncontrolled proliferation of T cells and macrophages that exhibit hemophagocytic activity. Recent observations also suggest that dysfunction of the natural killer cell function is relevant to the pathogenesis of both disorders, Dr. Grom said. These cellular abnormalities in MAS patients result in a massive systemic inflammatory response marked by liver dysfunction, cytopenias, and coagulopathy consistent with disseminated intravascular coagulopathy.

The first laboratory signs of MAS are sharp falls in white blood count, hemoglobin count, and platelet count, as well as some evidence of coagulopathy, including a significant elevation of D-dimers and alterations in clotting times. Because liver function is impaired, decreasing serum fibrinogen activity often results in a sharp fall in the erythrocyte sedimentation rate despite persistently elevated C-reactive protein, he said.

Two other important diagnostic features are hypertriglyceridemia, which reflects increased tumor necrosis factor–alpha activity, and extreme hyperferritinemia, with levels of serum ferritin in excess of 10,000 ng/mL in some patients. The diagnosis of MAS is typically confirmed with bone marrow studies, although Dr. Grom noted that abnormalities may not be evident in the early phase. Children with MAS often present with persistent fevers. They usually have enlarged nodes and hepatosplenomegaly, and at later stages bruising, purpura, and mucosal bleeding may be present. In severe cases, there are mental status changes or seizures.

There is no definitive treatment for MAS, but high-dose IV methylprednisolone (30 mg/kg; maximum, 1,000 mg), and cyclosporine oral or IV (2-5 mg/kg) are typically used. If the MAS severity does not lessen with this treatment, clinicians may want to consider chemotherapy with etoposide, which induces apoptosis of various immune cells including macrophages. Data show success with rabbit antithymocyte globulin, which takes aim at the T cells rather than the macrophages (Clin. Immunol. 2009 March 16 [Epub ahead of print]).

Dr. Grom reported no relevant conflicts of interest. ■