Autoimmune diseases reflect the layered complexity of the human immune system and, correspondingly, the presence of immune cells and noncellular components throughout the body. Thus, any organ system can be affected by autoimmune disease. Autoimmunity underlies the pathology of a vast array of diseases, although specific diseases may occur rarely. Autoimmune diseases in general are caused by a breakdown in normal self-tolerance. Some diseases implicate the adaptive immune system and are characterized by reactivity to self-antigens and production of self-directed autoantibodies. In other illnesses, the problem lies primarily within the innate immune system, with corresponding inflammation but without detectable autoantibodies. In yet other entities, the precise immunopathophysiology remains to be determined. In this issue of Pediatric Annals, I am pleased to present articles detailing the clinical presentation, diagnosis, and treatment of five different autoimmune diseases: N-methyl-D-aspartate receptor (NMDA-R) associated encephalitis, autoimmune inner ear disease, macrophage activation syndrome, Kawasaki disease, and Kikuchi-Fujimoto disease.

Specific autoantibodies play an important role in NMDA-R associated autoimmune encephalitis. This illness has only been recently understood as an autoimmune process. Patients with the affliction develop rapid onset of profound personality and behavioral changes, sometimes accompanied by abnormal motor movements. In previous decades, many patients with NMDA-R encephalitis were likely misdiagnosed with schizophrenia or other psychiatric illnesses—even, in some cases, demonic possession. Fortunately, delineation of the autoimmune basis of NMDA-R encephalitis has led to effective treatment aimed at removing the pathogenic autoantibody (via plasma exchange), decreasing autoantibody production and immune hyperreactivity generally (via steroids and other immunosuppressants), and preventing further production of the damaging autoantibody (via B cell depletion with rituximab). However, not all patients respond to treatment. Early diagnosis and treatment are critical to optimize outcomes. In the article, “Pediatric Anti-NMDA-R Encephalitis: Presentation, Diagnosis, and Management,” Drs. Karyn Gerstle, Moon Hee Hur, and Taha Moussa provide an excellent overview of the typical clinical presentation and approach to treatment, including the role of electroconvulsive therapy in recalcitrant cases.

Autoimmune inner ear disease (AIED), which typically presents as sudden onset sensorineural hearing loss, can also be associated with production of specific autoantibodies. The role of autoantibody production in pathogenesis of AIED is unclear. However, as clearly laid out in the article, “Pediatric Autoimmune Inner Ear Disease: A Rare, But Treatable Condition,” by Drs. Rotem Semo Oz, Michael Gluth, and myself, the pediatric clinician must be alert to the possibility of an autoimmune cause in any child with sudden onset sensorineural hearing loss. AIED is most notably distinguished from other causes of sudden onset sensorineural hearing loss by a good response to immunosuppressive treatment. Thus, a high index of suspicion can potentially lead to preservation of hearing in a child with this rare but important condition.

Macrophage activation syndrome (MAS), in turn, is primarily a dysfunction of the innate immune system. MAS arises from an acquired defect in the function of natural killer (NK) cells, usually triggered by an underlying systemic inflammatory condition. Hemophagocytic lymphohistiocytosis is a similar syndrome in which the NK cell dysfunction is genetically mediated and present from birth. In the article, “New Onset Autoimmune Disease or Macrophage Activation Syndrome?,” Drs. J. Palmer Greene and Bridget M. Wild provide an illustrative case of MAS occurring in an adolescent girl concurrently with the onset of systemic lupus erythematosus (SLE). The authors emphasize the need to consider MAS early in evaluation, given the significant mortality rate.
Kawasaki disease is encountered relatively frequently in the pediatric hospital setting, and often considered in the differential diagnosis of persistent high fever in a young child. The diagnostic criteria and initial treatment, with aspirin and intravenous immunoglobulin, are well established. However, the management of resistant Kawasaki disease, in which the child does not respond to standard treatment, is more challenging. In the article, “Kawasaki Disease: Beyond IVIG and Aspirin,” Drs. Taha Moussa and Linda Wagner-Weiner provide a step-by-step overview of the approach to recalcitrant Kawasaki disease and potential complications. Incomplete Kawasaki disease, in which the full clinical criteria for Kawasaki disease are not fulfilled, is associated with a higher risk of treatment resistance. Hence, the clinician must be wary of treatment-resistant disease in precisely the group that is most difficult to diagnose. Cardiac complications are far more likely when treatment for Kawasaki disease is delayed or ineffective, and may not evolve for years, underscoring the importance of timely diagnosis and treatment.

Kikuchi-Fujimoto disease, unlike many other autoimmune diseases, is usually benign and self-limited. Kikuchi-Fujimoto disease typically presents with lymphadenopathy associated with fever and other systemic inflammatory signs and symptoms. As detailed in the article, “Kikuchi-Fujimoto Disease in Children: An Important Diagnostic Consideration for Cervical Lymphadenitis,” by Drs. Emily Batton, Muayad Alali, Joseph R. Hageman, Megan Parilla, and Karl O.A. Yu, the cause is thought to be T-cell hyperreactivity to antigen, possibly from an infectious source. Diagnosis is typically pathologic via lymph node biopsy. Although the illness itself is usually benign, Kikuchi-Fujimoto disease must be considered to prevent misdiagnosis, especially of hematologic malignancies. Additionally, a history of Kikuchi-Fujimoto disease is associated with a small but important risk of the later development of systemic lupus erythematosus.

Although the full scope of autoimmune disease is too vast to cover in this issue, my hope is that the articles provide a helpful review of the spectrum of autoimmune disease. These entities range from the benign and self-limited to the urgently life-threatening. Consideration of these illnesses is essential to enable prompt diagnosis and treatment of dangerous—yet often reversible—conditions and to avoid misdiagnosis.

Disclosure: The author has no relevant financial relationships to disclose.

doi:10.3928/19382359-20190924-02