Acquired Demyelinating and Other Autoimmune Disorders of the Central Nervous System in Children

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Received August 14, 2012. Accepted for publication August 14, 2012.

Over the past 5 years, our knowledge has been significantly enhanced in the field of immune-mediated inflammatory disorders of central nervous system in children. These exciting developments along with identification of novel autoimmune markers have provided new diagnostic approaches and, more important, have led to appropriate immunotherapy to halt disease progression and prevent relapses. Recognition of immune-mediated disorders of the central nervous system is important because these disorders are highly responsive to immunotherapy. We child neurologists have been introduced to several novel agents of immunotherapy (both immunomodulatory and immunosuppressive) for the management of immune-mediated inflammation.

Pediatric multiple sclerosis and other immune-mediated demyelinating disorders of the central nervous system in children are increasingly recognized in recent years in the United States and worldwide. An estimated 3% to 10% of all patients with multiple sclerosis have onset before the age of 18 years. Pediatric multiple sclerosis is rare, but it has a profound impact on the health of young children and adolescents. As a result of developing this disorder at an early age, individuals reaching any given level of impairment will be younger than individuals with adult-onset disease.

The autoimmune inflammatory demyelinating disorders of the central nervous system represent a broad spectrum of conditions that vary in their clinical course, regional distribution within the central nervous system, and prognosis. Many features overlap among these various disorders: multiple sclerosis, acute disseminated encephalomyelitis, and neuromyelitis optica, and clinically isolated syndromes of childhood. The consensus definitions by the IPMSSG help to minimize the risk of inconsistency in diagnosis, identify the patients with high risk of multiple sclerosis, and provide a platform for future research and clinical trials. Since the dissemination of these diagnostic criteria in 2007, knowledge in the field has expanded significantly, and excellent review articles published in the past 5 years provide guidance for the diagnosis and care of these children. Several pediatric cohort studies using the consensus definitions have provided data on the long-term outcomes of children presenting with the first demyelinating event. Furthermore, the International Study Group has expanded as an organization with increasing numbers of members worldwide. Through the efforts of IPMSSG, systematic multicenter therapeutic trials in children with acquired demyelinating disorders are now under way for the first time.

In the light of these developments and the expanding knowledge in the field of childhood acquired demyelinating disorders, this special issue of the Journal of Child Neurology is devoted to pediatric autoimmune inflammatory disorders of central nervous system, including both demyelinating and non-demyelinating conditions. I would like to express my sincere appreciation to the authors who participated in this issue and provided the most updated and comprehensive reviews on their topics.

The first 6 articles cover the acquired demyelinating syndromes in children. In the first article, Bigi and Banwell provide an overview of the childhood multiple sclerosis including clinically isolated syndromes, neuropsychological prognosis of childhood multiple sclerosis, environmental risk factors, and differential diagnosis. The management of childhood multiple sclerosis is reviewed separately in the article written by Yeh.

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and Weinstock-Guttman, with specific discussion of therapies for acute exacerbations, disease-modifying therapies that can prevent relapses and slow disease progression, and future directions in symptomatic interventions for cognitive decline, fatigue, and depression. The article also discusses the status of second-line therapies for breakthrough disease (monoclonal-based antibody therapies, cyclophosphamide, and mitoxantrone).

The pathogenesis of multiple sclerosis remains to be elucidated, and there is no curative therapy against multiple sclerosis, although we have several disease modifying drugs. The exact factors that initiate inflammation are unknown, but generally multiple sclerosis is considered to be an immune-mediated disease. Tissue injury in inflammatory demyelinating lesions, such as those seen in multiple sclerosis, is very complex and can be mediated by a variety of different immunological mechanisms involving cytotoxic T-cells, B-cells, and auto-antibodies and activated macrophages or microglia cells. “Can pediatric multiple sclerosis inform us about factors related to disease initiation and propagation?” “Does pediatric multiple sclerosis pathogenesis differ from adult MS?” “Can pediatric multiple sclerosis provide insights into environmental risk factors for multiple sclerosis?” Vargas-Lowy and Chitnis address these central questions by providing data obtained from immunological studies conducted in children. Distinguishing features of the pediatric immune system are reviewed. Pediatric acquired demyelinating disorders provide an opportunity to investigate disease pathogenesis in the pediatric immune system.

The article on the acute disseminated encephalitis provides a comprehensive review of the differential diagnosis. In terms of acute demyelination, the first attack of multiple sclerosis is the main differential diagnosis of acute demyelinating encephalomyelitis. However, acute demyelinating encephalomyelitis-like presentation can also occur in numerous non-demyelinating entities of childhood in which encephalopathy is a common feature. In the absence of specific biological markers, the magnetic resonance imaging patterns have become the most important tool in diagnosing acquired demyelinating syndromes of central nervous system. The differential diagnosis section provides an extensive discussion on the acute demyelinating encephalomyelitis mimics classified by different radiological patterns.

The article on acute transverse myelitis written by Wolf, Lupo, and Lotze is a comprehensive overview that describes idiopathic and disease-associated acute transverse myelitis, along with differential diagnosis, treatment, prognosis, and rehabilitation, and highlights infantile acute transverse myelitis. Tillema and McKeon review neuromyelitis optica. The discovery of the neuromyelitis optica (NMO)-IgG antibody targeting the CNS-predominant water channel aquaporin-4 (AQP4) greatly enhanced our understanding of autoimmunity and immunopathogenesis. Neuromyelitis optica is the only acquired demyelinating disease with an available disease marker. This discovery has not only accelerated our understanding of the pathogenesis but also improved our understanding of all inflammatory central nervous system diseases. Their article not only provides comprehensive clinical information, but also discusses studies of NMO-IgG (AQP4-IgG) serology, along with other autoimmune serologic and immunohistopathologic findings of neuromyelitis optica that are distinct from multiple sclerosis.

Primary central nervous system vasculitis is a rare disorder that is in the differential diagnosis of nonvascular inflammatory demyelinating central nervous system disorders. Its treatment requires immunosuppressive and immune modulatory therapies. Understanding central nervous system vasculitis also provides new insights into pediatric stroke. Gowdie, Twilt, and Benseler indicate that inflammatory immune mediated vasculitis is the most common cause of stroke in children beyond the neonatal period. This information has crucial implications for the management of stroke in the young: for example, should the child be treated with immunosuppressive agents? How can inflammatory vasculopathy (vasculitis) be distinguished from noninflammatory vasculopathies in the presence of abnormal MR angiography? This article addresses such questions that are highly relevant to management.

Over the past 5 years, the discovery of immune-mediated encephalitis has changed the approach to the diagnosis and treatment in children with unknown encephalitides. There is an emerging group of patients with treatment-responsive autoimmune encephalitis. Armanique, Petit, and Dalmaz focus on several forms of encephalitis that occur in children, and for which an autoimmune etiology has been demonstrated (eg, anti-NMDAR receptorencephalitis) or is strongly suspected (eg, Rasmussen’s encephalitis, limbic encephalitis, opsoclonus-myoclonus). The authors also review several disorders that could be immune mediated, such as the “rapid onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation,” and some encephalopathies with fever and status epilepticus. Recognition of novel immune-mediated encephalitis is important because some such disorders are highly responsive to immunotherapy.

A number of different autoimmune disorders predominantly involve the basal ganglia and can result in movement and psychiatric disorders. Autoimmune basal ganglia disorders can now be better classified, particularly following discovery of antibodies against neuronal proteins. Dale and Brilot discuss the autoantibody hypothesis and the role of systemic inflammation in autoimmune basal ganglia disorders. Identification of these entities is important since clinicians have an increasing therapeutic repertoire to modulate or suppress the aberrant immune system. Acute cerebellar ataxia and acute cerebellitis are associated with paras-infectious, postinfectious, or postvaccination cerebellar inflammation. Although there is lack of clinical trials to answer many questions regarding management approach, it is important to explore the current status in this field. Desai and Mitchell provide an overview of the spectrum of acute cerebellar ataxia and acute cerebellitis and summarize the results of current experience, along with discussing paraneoplastic opsoclonus-myoclonus syndrome.
I would like to thank the expert authors who contributed to this special issue concerning pediatric autoimmune inflammatory disorders of the central nervous system. I hope this issue will be a useful resource for child neurologists, neurology residents, and pediatricians.

References