Pediatric Multiple Sclerosis

From Recognition to Practical Clinical Management

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KEYWORDS

• Multiple sclerosis • Children • Demyelination • Diagnosis • Treatment

KEY POINTS

- Pediatric multiple sclerosis (MS) (before age 18) makes up approximately 5% to 10% of MS.
- Risks factors for pediatric MS are similar to those of adults, and include vitamin D deficiency, history of Epstein-Barr virus exposure, obesity, and exposure to cigarette smoke.
- Characteristics that argue against a diagnosis of MS include history of developmental delay, progressive course, encephalopathy, monofocal lesion, and prepubertal onset.
- Children with MS take longer to acquire significant disability but arrive at significant disability at a chronologically younger age compared with adults with MS.
- Selection of disease-modifying therapies should focus on compliance, safety, and impact of therapies on a developing central nervous system and immune system.

INTRODUCTION

There has been increasing recognition that multiple sclerosis (MS) can present in childhood, prompting growing efforts to characterize the spectrum of pediatric-onset disease. This chronic inflammatory, demyelinating disease of the central nervous system is thought to develop when genetically susceptible individuals are exposed to specific environmental factors at a critical time in development. Recent studies have explored the similarities and differences in pediatric versus adult-onset MS, and elucidated early risk factors in disease pathogenesis. Recognition and diagnosis of pediatric MS can be challenging given a broad differential of possible MS mimics. There has also been concern about the safety and generalizability of using immunomodulatory treatments, studied almost exclusively in adults, in children.

Disclosures: Dr B.M. Greenberg has received research funding from the NIH (5R01NS071463-02), PCORI, MedImmune, Chugai, Genentech and the Guthy Jackson Charitable Foundation. He has received consulting fees from Novartis, Alexion and EMD Serono. C.X. Wang: No disclosures.
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Neurol Clin 36 (2018) 135–149
https://doi.org/10.1016/j.ncl.2017.08.005
neurologic.theclinics.com

In this review, we discuss the epidemiology, clinical presentation, diagnostic evaluation, and treatment approach to pediatric MS. In particular, we highlight the areas in which pediatric disease may differ from adult-onset MS and review the differential diagnoses for MS in the pediatric population. We discuss the management of acute relapses and explore the potentially difficult long-term therapy decisions in patients with immature and developing nervous and immune systems. Last, we will discuss supportive care for patients with pediatric MS, with attention to how symptoms including fatigue, cognitive impairment, and mood dysfunction can manifest and impact younger patients.

EPIDEMIOLOGIC FACTORS

Although fewer than 10% of individuals with MS experience their first clinical demyelinating event before the age of 18, exposure to key environmental factors leading to an eventual adult diagnosis of MS likely occur during childhood.[1,2] Past studies have found that individuals carry the MS risk profile of their place of residence during childhood and that there is a latitude gradient to MS incidence, perhaps explained by direct sunlight exposure and vitamin D level.[3,4] Early viral exposures, specifically Epstein-Barr virus (EBV) infections, appear to confer increased MS risk in both children and adults.[4] In contrast, early exposure to cytomegalovirus may be protective against development of MS.[5] The genetic locus HLA DRB1*15 in children, like adults, appears to increase risk of developing MS, up to twofold to fourfold.[6] Disease pathogenesis likely involves interaction of multiple risk factors, as evidenced by observations that remote infection with HSV-1 can increase MS risk in HLA DRB1*15 negative individuals, but attenuate MS risk in DRB1*15 positive individuals.[7]

It is rare for demyelinating events to begin before puberty and only 20% of pediatric MS is diagnosed before age 10.[8] Before puberty, the ratio of females to males with MS is roughly even, but increases to 2 to 3:1 in adolescents.[9] This observation suggests that hormonal changes, menarche in particular, may play an important role in the pathogenesis of MS. Obesity has been associated with higher risk for MS,[10] although this may be somewhat confounded by its association with lower bioavailability of vitamin D and a younger age of menarche.[11] Vitamin D level appears not only to determine risk of developing MS but also influence relapse risk.[12,13] Children with MS are exposed to passive smoking twice as frequently as a control population.[14] Initial studies of gut microbiota in children with MS show a perturbation in flora indicative of a proinflammatory milieu.[15] Dietary intake of salt has yielded mixed results.[16]

CLINICAL PRESENTATION

The heralding event of pediatric multiple sclerosis can involve gait disturbance, vision loss, weakness, or sensory change, among other symptoms. Children may present with forms of clinically isolated syndrome, including optic neuritis, transverse myelitis, and cerebellar, brainstem, and cerebral hemispheric lesions. Approximately one-third of children who have an acute demyelinating event are later diagnosed with a relapsing disease such as MS or neuromyelitis optica spectrum disorder (NMOSD).[17] Encephalopathy, seizures, and polyfocal symptoms, which can be atypical for adult MS, can be seen in children. At onset, pediatric MS is nearly universally relapsing-remitting (85%–100% of cases)[18]; a progressive disease course should raise suspicion for an alternative diagnosis.

DIAGNOSIS

Similar to adult MS, making a diagnosis of pediatric MS is centered on identifying recurrent demyelinating events separated in space and time. The International