Pediatric Neurology 75 (2017) 17–28

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Pediatric Multiple Sclerosis: Genes, Environment, and a Comprehensive Therapeutic Approach

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ABSTRACT

BACKGROUND: Pediatric multiple sclerosis is an increasingly recognized and studied disorder that accounts for 3% to 10% of all patients with multiple sclerosis. The risk for pediatric multiple sclerosis is thought to reflect a complex interplay between environmental and genetic risk factors. **MAIN FINDINGS:** Environmental exposures, including sunlight (ultraviolet radiation, vitamin D levels), infections (Epstein-Barr virus), passive smoking, and obesity, have been identified as potential risk factors in youth. Genetic predisposition contributes to the risk of multiple sclerosis, and the major histocompatibility complex on chromosome 6 makes the single largest contribution to susceptibility to multiple sclerosis. With the use of large-scale genome-wide association studies, other non-major histocompatibility complex alleles have been identified as independent risk factors for the disease. The bridge between environment and genes likely lies in the study of epigenetic processes, which are environmentally-influenced mechanisms through which gene expression may be modified. **CONCLUSIONS:** This article will review these topics to provide a framework for discussion of a comprehensive approach to counseling and ultimately treating the pediatric patient with multiple sclerosis.

Keywords: pediatric, multiple sclerosis, demyelinating, genetics, environment, treatment

Pediatr Neurol 2017;75:17–28

Introduction

Multiple sclerosis is a dynamic, inflammatory demyelinating disease of the central nervous system that peaks in incidence in young adulthood. However, 3% to 10% of all patients ultimately diagnosed with multiple sclerosis experience the onset of their disease before age 18 years.[1,2] Pediatric patients with multiple sclerosis often exhibit a more inflammatory disease course within the first several years of diagnosis[3,4] associated with greater frequency of clinical relapses in addition to higher brain T2- and T1-weighted lesion volumes.[5,6] Although pediatric patients often have good recovery with lack of marked disability progression, irreversible disability and secondary progression ultimately occur at an earlier age than their adult-onset counterparts.[7]

A diagnosis of multiple sclerosis in a child can be made at the time of the first clinical attack provided magnetic resonance imaging (MRI) at the time demonstrates evidence of both dissemination in time (ie, presence of a clinically silent, gadolinium-enhancing lesion(s) with simultaneous non-enhancing lesions) and space (ie, presence of at least one T2-hyperintense lesion in at least two of four central nervous system [CNS] areas—periventricular, juxtacortical, brainstem or cerebellum, and spinal cord). As reviewed in Table 1, if these diagnostic criteria are not met at the time of the first demyelinating event, diagnosis may then be made with the presence of a new T2 or gadolinium-enhancing lesion obtained on follow-up imaging.[8,9] These criteria are sensitive and specific when utilized in the context of a child who is older than 11 years; however, the positive predictive value diminishes when used in younger children, and thus diagnostic caution must be exercised.[10]

The risk of pediatric multiple sclerosis is thought to be secondary to a combination of genetic and environmental

Funding: No funding was secured for this study.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Article History:

Received March 24, 2017; Accepted in final from July 6, 2017

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http://dx.doi.org/10.1016/j.pediatrneurol.2017.07.005

TABLE 1.
Current Diagnostic Criteria for Pediatric Multiple Sclerosis

Clinical Presentation	Required Steps to Multiple Sclerosis Diagnosis*
≥2 non-ADEM clinical CNS events with presumed inflammatory cause, occurring >30 days apart and involving more than ≥2 of four CNS areas	None: Patient meets criteria for pediatric multiple sclerosis
A single, non-ADEM clinical CNS event with presumed inflammatory cause meeting criteria for: (a) DIS as evidenced by the presence of at least one T2-hyperintense lesion in at least two of four CNS areas (periventricular, juxtacortical, infratentorial, or spinal cord) **- and –** (b) DIT as demonstrated by the presence of a clinically silent, enhancing lesion, as well as non-enhancing lesion(s)	None: Patient meets criteria for pediatric multiple sclerosis
A single, non-ADEM clinical CNS event with presumed inflammatory cause involving at least 2 of 4 CNS areas but not meeting criteria for DIT	This patient requires either (a) a new non-ADEM clinical CNS event with presumed inflammatory cause occurring >30 days later **- or -** (b) a follow-up MRI showing at least one new enhancing or non-enhancing lesion
A single, non-ADEM clinical CNS event with presumed inflammatory cause and MRI demonstrating the presence of at least one clinically silent, enhancing lesion in addition to non-enhancing lesions but not meeting criteria for DIS (ie, lesions within only 1 of 4 required CNS areas)	This patient requires: a follow-up MRI (with or without new clinical symptoms) that demonstrates ≥1 new lesion in at least one of the previously unaffected CNS areas
A single ADEM event followed by a non-ADEM clinical CNS event with presumed inflammatory cause, occurring ≥3 months after ADEM event that is associated with new MRI lesions that fulfill DIS criteria for multiple sclerosis	None: Patient meets criteria for pediatric multiple sclerosis
A single ADEM event followed by a non-ADEM clinical CNS event with presumed inflammatory cause, occurring ≥3 months after ADEM event that is associated with new MRI lesions that does not fulfill DIS criteria for multiple sclerosis	This patient requires a third non-ADEM clinical CNS event with presumed inflammatory cause, occurring >30 days from second event that fulfills DIS criteria

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
CNS = Central nervous system
DIS = Dissemination in space
DIT = Dissemination in time
MRI = Magnetic resonance imaging

* Important caveats: The 2010 criteria for DIS and DIT at onset in children younger than age 11 years have a lower positive predictive value for diagnosis of multiple sclerosis and should be utilized with caution in this age bracket. For a more detailed synopsis of current diagnostic criteria, readers should review Polman et al. and Krupp et al.[8,9]

risk factors. Although the greatest genetic risk for multiple sclerosis in childhood is related to specific haplotypes in the human leukocyte antigen-D related (HLA-DR) allele of the major histocompatibility complex (MHC),[11] there is an array of environmental contributions that have also been associated with increasing risk. Given the relative rarity of multiple sclerosis in children, studies assessing risk factors, genetics, and treatment stratification have proven challenging, often requiring multicenter collaborations to achieve results of relevance. Despite these challenges, pediatric multiple sclerosis offers a unique opportunity to study early-life exposures and genetic risk factors in patients temporally close to the biologic events thought to contribute to disease onset. This review will focus on the current knowledge of both environmental and genetic risk factors for pediatric-onset multiple sclerosis. Furthermore, we will use this evidence to provide a framework discussion on the concept of longitudinal comprehensive care of the pediatric patient with multiple sclerosis.

Environmental contributions to risk of multiple sclerosis

Lifestyle and environmental factors are established contributors to the risk for multiple sclerosis. Intriguingly, many of the currently identified environmental risk factors for adult-onset multiple sclerosis are thought to exert their effect in adolescence or earlier. Given this, the temporal proximity of pediatric-onset multiple sclerosis with exposure to environmental risk factors provides an excellent opportunity to further define these variables. Detailed exploration of these environmental factors helps to better define the underlying biology of multiple sclerosis and may partly explain the phenotypic heterogeneity of this disease. Although much work is still to be done, identification of, and intervention upon, modifiable environmental risk factors may provide us with the opportunity to reduce incidence in those at high risk or modify disease course for those with already established disease biology.

Geography of residence in early childhood

One of the earliest arguments in favor of an environmental influence on risk of multiple sclerosis is the epidemiologic association with the latitude gradient. There is a positive association between latitude and prevalence of multiple sclerosis at a global level, unexplained by the genetic distribution of high-risk alleles.[12] Although genetic predisposition contributes somewhat to the geographic variations in incidence of multiple sclerosis, genetics cannot fully account for the risk variation observed in those who migrate to areas of higher or lower prevalence of multiple sclerosis. Migrants who move from an area of high risk to an area of lower risk prior to