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Multiple Sclerosis Re-Examined: Essential and Emerging Clinical Concepts

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ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by exacerbations of neurological dysfunction due to inflammatory demyelination. Neurologic symptoms typically present in young adulthood and vary based on the site of inflammation, although weakness, sensory impairment, brainstem dysfunction, and vision loss are common. MS occurs more frequently in women and its development is complex—genetics, hormones, geography, vitamin D, and viral exposure all play roles. Early MS is characterized by relapsing-remitting course and inflammation of the white matter, although as patients age, the disease often transitions to a pathologically distinct secondary progressive phase with gradual disability accrual affecting gait, coordination, and bladder function. A minority of patients (10%) have disease that is progressive at onset. In the past decade, there has been a remarkable expansion in disease-modifying therapy for MS, but treatment of progressive disease remains a challenge. This article reviews foundational concepts in MS and emerging work that has reshaped understanding of the disease, providing new insight for therapeutic advance.

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INTRODUCTION

In 1868, Jean-Martin Charcot provided the first detailed anatomical illustrations of "la sclérose en plaques," characteristic periventricular white matter lesions now appreciated as a pathological hallmark of multiple sclerosis (MS), the most common autoimmune demyelinating disease of the central nervous system. Although MS is commonly classified as "relapsing" or "progressive," the disease is best understood as heterogeneous, with considerable overlap between stages. This is hypothesized as due to a complex immune response whereby the adaptive immune system drives pathology in early stages of disease but eventually wanes to be overtaken by other disease processes (mediated by the innate immune system, mitochondrial dysfunction, glutamate toxicity, and reduced compensatory ability, among other pathology), leading to gradual disability accumulation in older age.[1,2] Treatment of MS remains a clinical challenge, as it is the most frequent cause of permanent disability in young adults, and annual health care costs total more than $10 billion in the United States.[3-5]

EPIDEMIOLOGY

MS prevalence varies with geography: an estimated 400,000 people in the United States (150 people per 100,000) and 2.5 million people worldwide are affected.[5,6] The mean age of diagnosis is 28 to 31 years, although patients may present from the first to the seventh decades of life.[3,7] MS affects women disproportionately, with an estimated female-to-male incidence ratio of 2.3:1, skewing further toward female predominance in more recent studies for unclear reasons.[8,9]

MS prevalence increases the further one moves from the equator, hypothesized related to differences in genetic background, infection exposure, and vitamin D levels. In many countries with a high prevalence of MS (US, Northern Europe,

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Russia, Canada, and New Zealand) there is a latitude gradient of MS risk; however, in regions with lower prevalence this relationship does not always hold.[9-12] Classic MS migration studies have shown that individuals moving from low- to high-prevalence regions after age 15 years maintain the low risk of the area that they migrated from, whereas individuals migrating before this age assume the risk of the region they move to.[13] Several lines of evidence point to the importance of puberty in MS risk, potentially contributing to this effect: 1) increased female MS risk develops around age 11 years (near puberty onset); and 2) earlier menarche correlates with earlier MS onset in multicenter case-control studies of pediatric MS.[14]

Epstein-Barr virus exposure is a hypothesized trigger for the development of MS. Though Epstein-Barr virus infection is ubiquitous, studies have demonstrated near 100% seropositivity in MS patients, and in pediatric-onset MS there is an unexpectedly high rate of asymptomatic Epstein-Barr virus seropositivity.[15,16] Mononucleosis in adolescence is also associated with increased subsequent risk of MS (relative risk 2.3, 95% CI 1.7-3.0).[17] Epstein-Barr virus-mediated MS risk is hypothesized due to "molecular mimicry" (amino acid sequence homology between virus proteins and myelin basic protein causing autoreactivity) and also infection of B cells, which may mediate chronic inflammation in MS.[18,19]

The recognition of a gradient latitude MS risk led to the hypothesis that vitamin D might be another important mediator of susceptibility. Vitamin D is predominantly synthesized in the skin in response to ultraviolet light. Its receptors are expressed ubiquitously on immune cells, and function to reduce immune activation of autoreactive T and B cells in MS.[20] There is a clear relationship between low vitamin D levels and increased risk of MS,[21-24] clinical relapse/progression,[25,26] and new magnetic resonance imaging (MRI) activity.[27] Furthermore, vitamin D is an important developmental immunomodulator involved in immune system maturation and self-antigen recognition during critical developmental windows.[28,29]

MS genetic susceptibility is complex and multifactorial. Twin studies demonstrate a 25% concordance rate among monozygotic twins and 5.4% concordance rate among dizygotic twins.[30-32] A growing number of genes have been linked to MS risk, with recent genome-wide studies identifying over 100 alleles of significance with immune function that alter disease risk,[33] supporting the notion of MS as an autoimmune disease. Perhaps the best-studied genetic association is the link between MS and major histocompatibility complex class I and class II alleles, particularly HLA-DRB1.[34-39] Recent work has characterized protective and risk alleles,[40] although no combination can be used to definitively predict development of MS, and genetic testing is not clinically available.

CLINICAL SIGNIFICANCE

- Multiple sclerosis is the most common demyelinating disease of the central nervous system.
- MS is an autoimmune-mediated condition with genetic basis, however, environmental factors more strongly influence disease development.
- Diagnosis of MS requires specific magnetic resonance imaging and clinical criteria.
- MS consists of relapsing and progressive phases driven by distinct pathophysiology. There are 15 Food and Drug Administration-approved therapies for relapsing MS, but treatment of progressive MS remains a challenge and there is no cure.

MS PATHOPHYSIOLOGY: A CLOSER LOOK AND A NEW CHAPTER AHEAD

The acute MS lesion is the pathophysiologic end result of a highly coordinated cascade of inflammatory activity. Active blood–brain barrier breakdown is mediated by the recruitment of perivascular inflammatory infiltrates comprised of myelin-reactive T cells, B cells, and macrophages.[41] The pathological hallmark of acute MS is focal white matter demyelination and relative sparing of axons with a variable amount of associated perivascular inflammation or gliosis.[42] Areas commonly affected in MS include the periventricular and juxtacortical white matter (regions with dense perivenular topography), although lesions may occur throughout the central nervous system, including the optic nerves, cerebellum, and spinal cord.[42,43]

Although MS is commonly described as a disease of focal white matter demyelination, histological studies have illustrated a more complex picture. We now know that there is diffuse injury of the "normal"-appearing white matter in MS even at disease onset.[44] Axonal degeneration is present in MS lesions of all ages, frequently in regions of active demyelination.[45] Cortical gray matter demyelination is prevalent in MS, with type III/IV "subpial" cortical lesions considered as a unique, specific feature of the disease.[46-48] Initial postmortem histological studies demonstrated cortical demyelination in progressive MS;[49] however, subsequent work has shown it can be prevalent in early disease course (nearly 40% of patients undergoing brain biopsy at MS-symptom onset) and has an interesting spatial relationship to leptomeningeal inflammation.[50] The meninges are hypothesized immunologic regulatory sites for the inflammatory response in MS, and meningeal B-cell follicles (present in 40% of patients with progressive MS) may act as sites of smoldering subarachnoid antibody production necessary for sustaining chronic inflammation of progressive disease.[51-53] Additional mechanisms likely sustain chronic MS inflammation in parallel, including microglia/astrocyte activation, glutamate excitotoxicity, iron accumulation, and oxidative/mitochondrial injury.[2]