Multiple sclerosis

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Abstract

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) and the most common cause of disability among young adults. Most patients present with a relapsing–remitting illness, characterized by discrete episodes of focal neurological deficit with temporal and anatomical dispersion in the CNS. The introduction of diagnostic criteria integrating magnetic resonance imaging has enabled earlier diagnosis and guides earlier intervention in this chronic disease. Although the underlying cause of MS remains unknown, recent advances in molecular immunology have brought about a new wave of immunotherapies that can stop relapses and may delay progression. Given the emergence of more effective therapies, the recognition of relapses and the symptom management of continuing complications are important roles for all clinicians who encounter patients with MS.

Keywords Clinically isolated syndrome; demyelination; multiple sclerosis; relapsing–remitting; secondary progressive

Key points

- Multiple sclerosis has both genetic and environmental risk factors
- Around 90% of patients initially have relapsing–remitting disease, most of them ultimately developing secondary progression
- Around 10% of patients have primary progressive multiple sclerosis, for which there is currently no disease-modifying treatment
- Diagnosis must demonstrate central nervous system damage disseminated in time and space. Clinical history, examination and magnetic resonance imaging are the key diagnostic tools, supplemented by lumbar puncture and visually evoked potentials
- The McDonald Criteria are used for diagnosis
- Corticosteroids hasten recovery from relapses but do not modify underlying disease
- In recent years, disease-modifying treatments have become available, with variable efficacy and adverse effects. Prompt treatment, tailored to a patient's disease activity, is probably important in limiting long-term accumulation of disability

Epidemiology

The prevalence of multiple sclerosis (MS) in the UK is approximately 1 per 1000, and as with other autoimmune diseases, there is a female preponderance; MS is 2–3 times more common in women, and the incidence among women is increasing. Peak age of onset is around 30 years, and alternative diagnoses should be sought in young children and in adults >60 years of age. Although the cause of MS remains unknown, certain risk factors have now been identified (Table 1) and there is mounting evidence that immune dysregulation may play a role in genetically susceptible individuals.[1]

Genetics

The strongest genetic association for MS lies within the *HLA* gene locus on chromosome 6, and certain human leukocyte antigen (HLA) types, particularly HLA DR15 and DQ6, play an important role in the pathogenesis of the disease. These genes are involved in antigen recognition by T cells and may determine whether or not abnormal responses are made to myelin proteins. Genome-wide studies reveal that many other genes, mostly with immunological roles, can contribute to the risk of disease. MS is polygenic and does not follow any obvious Mendelian pattern of inheritance. Those with first-degree relatives with MS are 5–7 times more likely to develop MS than the general population. MS is more common in certain ethnic groups, being relatively high among white patients, low among Afro-Caribbean and lower still in East-Asian populations, the latter being more susceptible to neuromyelitis optica (Devic's disease).

Environmental risk factors

Large-scale epidemiological and migration studies indicate that certain environmental risk factors are associated with the

Genetic and environmental risk factors in MS

Genetics	Genes:	*HLA* DR15/DQ
		Multiple immunological candidate genes
	Ethnicity:	White patients > Afro-Caribbean > Chinese
	Sex:	Female > male
Environment	Epstein–Barr virus/infectious mononucleosis	
	Smoking	
	Vitamin D deficiency/reduced sunlight exposure/ geographical latitude	

Table 1

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development of MS. These factors are thought to affect the immune system and include prior infection with Epstein–Barr virus (especially with a history of infectious mononucleosis), smoking and sunlight exposure/vitamin D deficiency. The prevalence of MS increases in areas further from the equator, including within Britain, where the incidence is highest in Northern Scotland and lowest in Southern England. Migration studies have shown that disease risk is acquired by the age of 15 years and does not change with subsequent relocation.

Pathogenesis

Relapsing–remitting MS (RRMS) has traditionally been characterized as a predominantly T-cell-driven autoimmune disease against components of the myelin sheath. In recent years, the contribution of B cells has been recognized. In genetically susceptible individuals, through immune dysregulation and probably mistaken antigen identity, CD4 T cells become primed in the peripheral blood and cross the blood–brain barrier, where they recognize components of the myelin sheath (Figure 1). The subsequent release of cytokines, such as interferon-γ (IFN-γ) and tumour necrosis factor-alpha, activates macrophages and B cells; local inflammation ensues, resulting in destruction of oligodendrocytes with demyelination of axons.[2] Disruption of the myelin sheath leads to reduced saltatory conduction and reduced conduction velocities along nerve fibres. In some cases, this results in the focal neurological symptoms known as 'relapses'. Although local inflammation generally resolves and remyelination occurs, the underlying nerve fibres can accumulate damage over time, resulting in progressive axonal loss and brain atrophy. Inflammatory episodes can be frequent in early disease but often subside, and patients can enter a secondary progressive phase, in which gradual axonal loss is the main cause of increased disability. Although once considered a disease primarily affecting central nervous system (CNS) white matter, high-resolution magnetic resonance imaging (MRI) and histological studies indicate that inflammation also occurs within the cortical grey matter and in some cases the overlying meninges.

Natural history

A patient's first symptom caused by focal CNS demyelination is known as a clinically isolated syndrome (CIS). Approximately 60% of individuals with CIS have a further relapse and are diagnosed with MS; this increases to 80% if the baseline MRI shows evidence of inflammatory lesions.

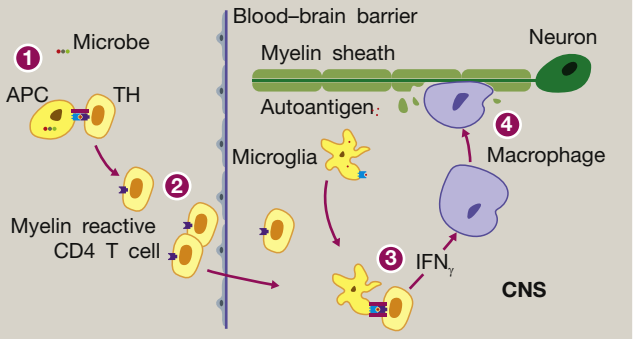
Most patients with MS (90%) present with a relapsing–remitting illness, characterized by relapses with focal neurological deficits. Patients with frequent relapses in early disease often experience a more malignant disease course (rapidly evolving RRMS or highly active RRMS). With time, the frequency of relapses decreases until they stop altogether. During this transition phase, a high proportion of patients gradually deteriorate in the absence of clear-cut relapses and develop secondary progressive disease (Figure 2). Around 50% of patients are unable to work 10 years after disease onset, 30% of patients with MS are ultimately rendered wheelchair-bound, and life expectancy is currently reduced by on average 5–10 years. Approximately 5% of patients experience relapsing–remitting symptoms but have a benign disease course with infrequent relapses and very limited disability.

Approximately 10% of patients show gradual disease progression from the outset; in the absence of clear-cut relapses, this is known as primary progressive MS.

Clinical features

MS patients present with a wide range of symptoms and signs, and these can often be directly related to the underlying anatomical site of focal inflammation within the CNS. Patients can present with fatigue, generalized weakness, diffuse paraesthesia, clumsiness, dizziness or visual disturbance, which can pre-date the diagnosis by months or years and make the diagnosis on clinical grounds alone difficult.

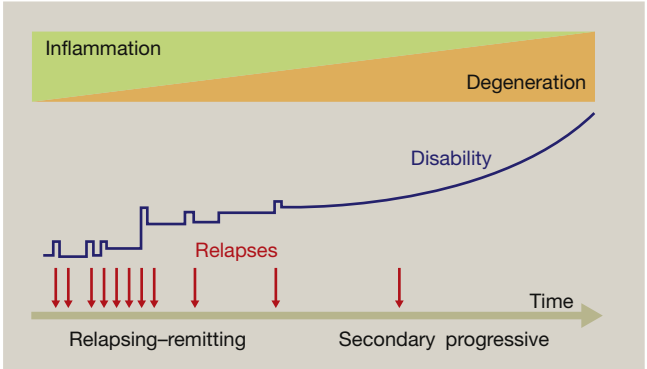
Half of MS patients present with weakness or numbness in one or more limbs, while a quarter present with optic neuritis. Others experience brainstem symptoms, such as diplopia or vertigo, or, in



In multiple sclerosis, it is postulated that CD4 T cells specific for certain microbial antigens are able to cross-react and recognize proteins on the surface of the myelin sheath. In genetically susceptible individuals who lack immunoregulatory mechanisms, these autoreactive cells are allowed to persist; they eventually recognize and destroy myelin after crossing the blood–brain barrier.

APC, antigen presenting cell; TH, T helper cell.

Figure 1



The majority of multiple sclerosis patients have a relapsing–remitting disease course, which is characterized at first by regular clinical attacks. With time, attacks become less frequent and recovery is incomplete, and patients gradually acquire more disability and develop secondary progressive disease.

Figure 2