

Introduction: the biological basis

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History of discovery

Throughout the course of history, people have been ill with diseases affecting their mobility. This could take the form of increasing paralysis over time. For many, this was associated with other symptoms, such as numbness, dizziness, and blurred vision. In the eighteenth century, physicians began to classify such cases into broad groups. The term paraplegia was used for people who had progressive paralysis. A major advance was made in 1868 by the physician Jean-Martin Charcot and his colleague Edmé Vulpian. They studied the tremors of younger patients and differentiated a condition from that described by James Parkinson in 1817. At autopsy such patients were found to have grey patches (plaques) scattered throughout the spinal cord and brain. Charcot gave a series of lectures on the features of this disease, which he termed *sclérose en plaque disseminée* and which we now know as multiple sclerosis (MS). Since then, a large amount of research has been carried out on this disease, and much progress has been made in understanding its pathogenesis. However, the primary cause of the disease still remains elusive (1).

Characteristics of the disease

MS is an inflammatory disease of the human central nervous system (CNS) leading to damage to myelin and axons; this damage occurs in localised plaques. Early in the disease demyelination of myelinated axons is followed by remyelination leading to transient recovery, but later extensive and chronic neurodegeneration occurs, including axonal loss, leading to irreversible disability.

MS occurs in three forms: relapsing and remitting (about 90% of cases), primary progressive (about 10% of cases), and secondary progressive (derived from relapsing-remitting). Relapsing and remitting MS is characterised by clinical episodes, which may be of progressive severity, interspersed by periods of stability. In primary progressive MS the course of the disease is continuous from the onset. Secondary progressive MS develops later in the course of the relapsing-remitting disease, usually 6–10 years after onset.

The age of onset of MS is usually between 20 and 40 years, making it the most common cause of neurological disability in young adults in areas of high prevalence, although childhood MS also occurs. Except for a minority with aggressive MS, life expectancy for MS patients is near normal. Although the majority of MS patients experience progressive disability, a minority has benign MS in which progression of the disease has halted.

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The prevalence of MS is highest among white populations in temperate regions, and in Europe and North America it is 1/800. Multiple sclerosis is thus a common disease in developed countries. However, it is clear from epidemiological studies that it shows regional variation in prevalence, that clusters have occurred, and that there is a genetic basis to MS. Study of these phenomena has provided circumstantial evidence concerning the etiology of MS, although the evidence from any one aspect may be tenuous and often contradictory (see reference (2) for a general review of MS). It is therefore necessary to take an overview of the factors involved in the etiology of MS and to formulate a general hypothesis, before specific etiological agents are considered.

Diagnosis

Clinical signs

Most patients present with an acute episode affecting one (or occasionally several) site (Table 1.1); the symptoms increase in number and severity with time.

Electrophoresis of the cerebral spinal fluid (CSF) shows the presence of oligoclonal bands of immunoglobulin in MS patients, although this is only diagnostic in conjunction with other criteria such as those shown in Table 1.1 and magnetic resonance imaging (MRI). However, there are no other reliable biomarkers for the progression of disease in MS (3).

Magnetic resonance imaging

In 1981 an advance was made in the diagnosis of MS by the first description of MS lesions detected by MRI (Figure 1.1) (4). It was later confirmed that MRI corresponds to lesions in the brain from studies of autopsy tissue (5). During the 1990s, drug studies in MS incorporated MRI assessment, providing information about the underlying disease (1). However, it was clear that the changes that resemble MS lesions could occur in other conditions, and also in apparently healthy people, so MRI is not a sole diagnostic criterion but is correlated with other clinical signs occurring in the patient. Repeated MRIs on the same patient showed that the disease has continuous activity, even when the patient is not experiencing new symptoms, and computer models were developed to measure disease burden based on the number and volume of lesions (6).

In 1986 it was shown that the enhancing agent gadolinium-DPTA caused some lesions to enhance whereas others did not. The enhancement identified breakdown of the blood-brain barrier, indicating areas of inflammation (7). Thus gadolinium enhancement has become a useful technique to demonstrate new and active MS lesions, effectively monitoring disease activity (8).

Autopsy

The diagnostic tests mentioned above are not specific, but are used in conjunction with clinical findings to reach a diagnosis. However, the final and unequivocal diagnosis of MS is by autopsy. The characteristic changes noted in the CNS at autopsy are scattered lesions in the white matter (plaques), with the features of inflammation (Figure 1.2), demyelination, some axonal damage, and gliosis.

Evidence for an environmental factor

Some of the earliest studies on the prevalence and epidemiology of MS are the immigration studies carried out by Dean and colleagues (9-12). Although the numbers of patients used were small, immigration to the UK from the Indian subcontinent and the Caribbean, and

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Table 1.1 Symptoms of MS

Site affected	Symptoms
Cerebrum	Cognitive impairment Hemisensory and motor Affective (mainly depression) Epilepsy (rare) Focal cortical deficits (rare)
Optic nerve	Unilateral painful loss of vision
Cerebellum	Tremor Clumsiness and poor balance
Brainstem	Diplopia, oscillopsia Vertigo Impaired swallowing Impaired speech and emotional lability Paroxysmal symptoms
Spinal cord	Weakness Stiffness and painful spasms Bladder dysfunction Erectile impotence Constipation
Other	Pain Fatigue Temperature sensitivity and exercise intolerance
Derived in part from (2).	



Figure 1.1. Two representative T2-weighted MR images of an MS patient. Thick arrows indicate typical periventricular (round or ovoid) white matter lesions; thin arrow in the right panel indicates a juxtacortical lesion in the insula region.

from other countries to South Africa, was studied (Figure 1.3A). On the basis of this data, it was postulated that immigration before the age of puberty results in a prevalence of MS reflecting the region of origin, whereas immigration after the age of puberty results in a prevalence in keeping with the destination region. This has been interpreted as indicating that an environmental factor exerts its effect at or around the age of puberty.

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Figure 1.2. This MS autopsy section shows a vessel filled with red blood cells and surrounded by lymphocytes (arrow). Haematoxylin and eosin × 60. (Courtesy Dr. F. Brett, Beaumont Hospital, Dublin.)



Figure 1.3. Diagrammatic representation of the immigration studies carried out by Dean and others and the hypothesis derived from these and other studies. (A) Some regions involved in the immigration studies; prevalence of MS is proportional to the degree of shading. (B) Schematic diagram showing how the interaction between an environmental factor and genetic susceptibility could result in MS.

This hypothesis has been substantiated by a study of Caribbean immigrants moving to France and their return migration (13,14), but is not consistent with a study of UK and Irish immigrants moving to Australia (15).

Consistent with the idea of an environmental factor is the occurrence of 'clusters' of MS. Very generally, the prevalence of MS varies by latitude, being most common further away from the equator (about 1 in 800 in Northern Europe and Australia). Clusters of MS have been described in Iceland, Key West (Florida), and the Faroe Islands and smaller divergences in prevalence have been found in several other areas. In the Faroe Islands, the increase in incidence of MS occurred following the occupation of the islands for 5 years by British troops during the Second World War. Multiple sclerosis on the Faroe Islands occurred in four successive epidemics after 1943. It has been postulated

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Virus	Family	Nucleic acid
Measles	Paramyxovirus	RNA(-ve)
Rubella	Togavirus	RNA(+ve)
Epstein–Barr	Herpesvirus	DNA
Varicella-zoster	Herpesvirus	DNA
Herpes 6	Herpesvirus	DNA
Endogenous retrovirus	Retrovirus	RNA/DNA*

*RNA replicated via DNA integrated into the genome, or present as a DNA copy (provirus) integrated into the genome and replicated with the cellular DNA.

that this occurred through the spread of an unknown infectious agent which is asymptomatic and which triggered MS in only a minority of infections. Clearly this could have been a virus introduced by the British troops, but this has not been unequivocally established (16).

Nature of the environmental factor

Most studies have concentrated on identifying a virus infection as the trigger for MS. Some studies have suggested other environmental factors in the etiology of MS. These include smoking, diet, and bacteria (17–20). There is also a possible influence of sunlight and vitamin D.

Viruses

Several viruses have been implicated, including measles virus, rubella virus, Epstein-Barr virus, varicella-zoster virus, human herpesvirus type 6, and human retrovirus (Table 1.2).

Unspecified infections (mainly respiratory tract infections), occurring before relapses of MS, have also been implicated (17). The evidence for the involvement of specific viruses will be reviewed in Chapter 6.

Vitamin D

The hypothesis that vitamin D deficiency is a risk factor for MS is based on the immunomodulatory effects of vitamin D (21). The hypothesis of an increased risk among individuals with low vitamin D concentrations derives from epidemiological evidence similar to that described above, i.e. that the risk for both MS and vitamin D deficiency may be related to sunlight exposure (see reference 22 for a general review).

Vitamin D is available from two sources: skin exposure to ultraviolet B (UVB) radiation in sunlight and diet (Figure 1.4). Compared to UVB exposure, diet (e.g. fatty fish) is a poor source of vitamin D. Vitamin D is biologically inactive and is converted in the liver to 25-hydroxyvitamin D. This then undergoes a second hydroxylation in the kidney or other tissues to give the active form, 1,25-dihydroxyvitamin D. This binds and activates the vitamin D receptor (VDR), a transcription factor that regulates the expression of as many as 500 genes (23). These include the regulation of calcium physiology, effects on



brain development and function, regulation of blood pressure and insulin secretion, and particularly in this context, effects on the differentiation of immune cells and modulation of immune responses (24).

The reasons that vitamin D deficiency may be a risk factor for MS are based on: (1) the fact that MS frequency generally increases with increasing latitude, which is inversely correlated with duration and intensity of UVB from sunlight and vitamin D concentrations; (2) the fact that the prevalence of MS is lower than expected at high latitudes in populations with high consumption of fatty fish, which is high in vitamin D (25); and (3) the data on MS risk associated with migration (described above).

If vitamin D has an effect on MS risk, MS incidence would be expected to decrease with increasing serum 25-hydroxyvitamin D concentrations. It is known that 25-hydroxyvitamin D concentrations decline after MS onset (26). One longitudinal study on 25-hydroxyvitamin D concentrations before the onset of MS has been conducted (27). This sampled a cohort from 7 million individuals from the US military who had at least two serum samples stored. Individuals with more than 99.2 nmol/l 25-hydroxyvitamin D (top quintile) had a 62% lower odds of developing MS than those in the bottom quintile (less than 63.3 nmol/l). Thus it was concluded that the serum concentration of 25-hydroxyvitamin D in healthy white adults is a predictor of their risk of developing MS. This association could be due either to a true protective effect of vitamin D or confounded by a factor affecting both 25-hydroxyvitamin D concentration and MS risk, such as UVB exposure, which could have immunosuppressive effects.

In another study, using 200 000 women, vitamin D intake was measured every 4 years by a comprehensive food frequency questionnaire (28). The validity of the estimated vitamin D intake was assessed in a subgroup of 300. The incidence of MS during the 30-year follow-up decreased with increasing vitamin D intake (p=0.03) and was 33% lower among women in the highest quintile compared to those in the lowest. Thus it can be concluded that vitamin D intake is a predictor of MS risk.

A further study has analysed 132 patients with MS, 58 with relapsing-remitting MS (RRMS) during remission, 34 RRMS patients during relapse, and 40 primary progressive MS cases (PPMS). Sixty healthy individuals matched with respect to place of residence, race/ethnicity, age, and gender were used as controls. Levels of 25-hydroxyvitamin D and

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1,25-dihydroxyvitamin D were lower in RRMS patients than in controls. Also, levels in patients suffering relapses were lower than those during remissions. PPMS patients showed similar values to controls. Proliferation of both freshly isolated CD4+ T cells and MBP-specific T cells was inhibited by 1,25-dihydroxyvitamin D. T cells were able to metabolise 25-hydroxyvitamin D into biologically active 1,25-dihydroxyvitamin D, since T cells express 1α -hydroxylase constitutively (29).

A protective effect of vitamin D is in agreement with most data on the geographical distribution of MS, including the latitude gradient, although the data is not yet unequivocal. A Canadian study has shown no apparent association between vitamin D metabolic pathway genes and MS susceptibility (30). However, one study has identified weak evidence of an association between a common variation within the vitamin D receptor gene and MS (31).

It has been suggested that population-wide diet supplementation programmes might be a prevention strategy for MS (32). However, diet supplementation with vitamin D to prevent not only MS but other diseases has been questioned. A panel put together by the Institute of Medicine has issued a report that challenged this view. They asserted that blood levels of vitamin D need not be as high as had been advocated, and high doses of the vitamin could actually cause harm (33).

Evidence for a genetic factor

MS is more common in White people than in other racial groups, and is also more common in women than men. It has a higher familial risk in first- or second-degree relatives than unrelated individuals (2,34), and monozygotic twins have a higher concordance rate than dizygotic twins (2,35). These facts taken together indicate a genetic predisposition to MS.

Further evidence for a genetic basis for MS susceptibility has been obtained by studying the association between MS and alleles of the multiple histocompatibility complex. Initially, a relationship was established between MS and genotypes HLA-DRB1, HLA-DRB5, HLA-DQA1, and HLA-DQB2 (2,36). This relationship holds for most Europeans except some Mediterranean groups. More recently, it has been shown that a complex epistatic interaction between HLA-DRB1, HLA-DQA1, and HLA-DQB1 determines susceptibility to MS (37). A genomewide study of risk alleles for MS using microarray technology has identified alleles of the interleukin-2 receptor alpha gene, interleukin-7 receptor alpha gene, and multiple alleles in the HLA locus as heritable risk factors (38). In a collaborative study involving 9772 cases of European descent collected by 23 research groups working in 15 different countries, almost all of the previously suggested associations were replicated and at least a further 29 susceptibility loci identified (39). Within the MHC the identity of the HLA-DRB1 risk alleles was refined. Immunologically relevant genes were significantly over-represented among those mapping close to the identified loci, and T helper cell differentiation was particularly implicated in the pathogenesis of MS. These studies indicate that susceptibility to MS is probably polygenic and the result of complex interactions between alleles.

Disease mechanisms

The primary disease lesions in MS are sclerotic plaques that occur in the brain and spinal cord. These are areas of inflammation, demyelination, and neuronal degeneration that probably result from increased migration of autoreactive lymphocytes across the

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blood-brain barrier (2). These disease processes result in loss of axonal conduction. The immune specificity of the autoreactive lymphocytes has not yet been determined, although there have been many proposals. The main problem is that autoreactive lymphocytes are also present in normal individuals, but it has been shown that regulatory lymphocytes from MS patients fail to suppress effector cells (40).

Detailed studies of the pathology of MS lesions from a large number of patients indicate that a number of different mechanisms of demyelination may operate (41,42). It is possible therefore that MS may be a disease with a number of different etiologies, all of which have a common pathological end point.

Conclusion

A generally accepted mechanism for the etiology of MS is that the disease results from interaction between an environmental factor and genetic susceptibility (Figure 1.3B), although the environmental factor is still unknown and the genetics is complex. It is not known how the genetic determinants of the disease result in the disease phenotype.

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