Multiple sclerosis
symptoms and diagnosis

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Multiple sclerosis (MS) is a common neurological disease of young adults affecting approximately one in 800 people in the UK. It is a multifocal inflammatory disease of the central nervous system (CNS) characterised by nerve demyelination (see “Pathogenesis”, p437). Limited remyelination occurs in the early stages of the disease followed by progressive loss of nerve fibres (axons) during the chronic, progressive phase. It was first described in the 19th century and by 1868 the French neurologist Jean-Martin Charcot had provided a series of lectures detailing the clinical and pathological aspects of the disease, formerly known as disseminated sclerosis.

As with many autoimmune diseases, MS is more common among females than males (2:1). The usual age of onset is within the third and fourth decades, although some cases present before the age of 16 years (5%) or after 60 years of age.

The distribution of MS varies worldwide, with the highest prevalence seen in northern and central Europe, Canada, North America and south-eastern Australia. The prevalence of MS increases with distance from the equator on both hemispheres and as such has fuelled much research into identifying a cause for the relationship. Additionally, there are racial differences, with a higher frequency in Caucasians, especially of northern European descent, and a lower prevalence in people of black African or Asian descent.

Classification

By consensus, four main clinical categories of MS have been established. The most common is relapsing remitting MS (RRMS) occurring in about 80% of patients. This form of the disease is characterised by a relapse followed by remission, which can take days or months to occur. Patients are clinically stable between relapses. However, each relapse can be associated with residual disability.

After several years, 50–60% of patients with RRMS develop secondary progressive MS (SPMS), whereby they experience a progressive neurological deterioration (see Figure 1, p436). A small proportion of these patients may also experience mild, superimposed flares of inflammation. It has been estimated that another 15–20%
of the RRMS group follow a benign course in which they experience mild and infrequent relapses with minimal or no disability.

If patients have no relapses but have an insidious development of progressive neurological deterioration from the onset they are said to fall into the category of primary progressive MS (PPMS). This form often presents late to neurologists owing to the patient having adapted to the gradual onset of symptoms such as mild gait disturbance. PPMS commonly presents in men around the age of 40 years and is associated with a poor prognosis. It tends to affect areas of the spine rather than the brain, with progressive spastic paraparesis (lower limb weakness) typical.\(^1\)\(^,\)\(^3\)

PPMS is regarded by some neurologists as a separate disease since axon loss is an early and dominant characteristic of this form combined with evidence to suggest immunogenetic differences between the primary and secondary types of progressive MS.\(^3\)\(^,\)\(^5\)

Progressive relapsing MS (PRMS) occurs in less than 5% of MS cases, whereby patients suffer ongoing axonal degeneration along with subtle flares of inflammation.

**Causes**

The cause of MS remains an enigma. A variety of genetic, environmental and immunological factors have been implicated in triggering its onset and progression.\(^6\)

**Genetics** Support for a genetic component is significant. Twin studies have shown an increased risk of 31% among monozygotic and around 5% in dizygotic twins. A first degree relative of a patient with MS has a less than 5% risk of developing the disease but this is some 20 to 40 times higher than in the rest of the population.\(^7\)

It is believed that MS may have a polygenic mode of inheritance.\(^7\) There are several documented associations between MS and a genetic region known as the major histocompatibility complex (MHC) — in particular, the human leukocyte antigen (HLA)-DR2, HLA-DR4 and DQW1.\(^3\)\(^,\)\(^7\) Evidence suggests a high proportion of MS sufferers possess HLA-DR2. In populations where there is a high frequency of HLA-DR2 the prevalence of MS is greater.\(^8\)

A recently published study has demonstrated a strong link between MS and the expression of the MHC class II allele HLA-DRB1*1501. The allele is regulated by vitamin D, which contributes further to the implication that vitamin D (obtained through sun exposure) acts as a strong environmental factor when determining people’s genetic susceptibility to MS.\(^9\)

**Environmental factors** Environmental factors are considered to be highly influential in the development of MS in genetically susceptible individuals. The momentum for this argument derives from the fact that in 70% of cases where one monozygotic twin develops MS the other does not.\(^4\)

The premise of environmental influence is supported further by a study which found that, in families migrating from a region of high-risk population to a region of low-risk population, children took on the lower risk of the new population whereas their parents did not. This could also support the idea of a possible viral infection conditioning the disease in childhood.\(^3\)

**Viral pathogens** Much attention has been focused on establishing a viral cause. The current thinking is that a virus activates an autoimmune process through a phenomenon known as “molecular mimicry” in which a viral antigen shares characteristics with myelin. Subsequently the immune system incorrectly identifies and targets myelin as an antigen.\(^3\)

Epstein-Barr virus (EBV) is one of many viruses implicated. Nearly all patients with MS have circulating...
antibodies to EBV, compared with 60% in the general population. Herpes viruses (human herpes virus 6 in particular) have also been studied as possible causes. It is unlikely that a specific infectious agent is directly responsible for inducing MS since numerous viruses have been suggested over the years (but not proven) as causative pathogens for MS. It is plausible to suggest from current knowledge and research that environmental factors, possibly combined with chance, trigger an autoimmune reaction against CNS myelin in genetically susceptible individuals.

**Pathogenesis**

The pathogenesis of MS is not certain but there is considerable evidence to suggest an autoimmune mechanism. The oligodendrocyte (CNS axonal insulator) is responsible for the synthesis and maintenance of around 40 neighbouring nerve axons and appears to be the principal target of immune attack. Oligodendrocytes form what are known as “myelin sheaths” — condensed membranes wrapped around the axons. This facilitates saltatory conduction of action potentials along the intervening nodes of Ranvier where voltage-gated sodium channels propagate depolarisation of that segment of the axon (see Figure 2). The loss of saltatory conduction due to demyelination explains many clinical and laboratory features of MS. In the peripheral nervous system (not affected by MS), Schwann cells are responsible for axonal insulation.

Early symptoms of MS are the result of demyelination with associated oedema and inflammation. Over time these symptoms can abate as the inflammation resolves and partial remyelination takes place. Progressive deterioration appears to be related to axonal loss, which, although present in the early stages, is more characteristic of advanced and progressive forms of MS.

Plaques (or lesions) are the pathological hallmark of MS. These are areas of axonal loss and hardening characterised by oligodendrocyte (and myelin) depletion for which no pathogenic mechanism has been identified formally. During an acute inflammatory attack the plaque is infiltrated predominantly by T lymphocytes, macrophages and (to a lesser degree) B lymphocytes. Conversely, immune cells are not a feature of inactive, chronic plaques.

**Blood-brain barrier integrity** Compromised integrity of the blood-brain barrier (BBB) was first described in MS during the 1940s, with the discovery of leakage of the pigment tryptan blue into active CNS plaques and, to a lesser extent, chronic ones following injection. Normally, most tissues and organs in the body would stain except the brain because of the protection of the BBB. There are several cytokines that are believed to be implicated with the breach of the BBB, including interleukins and tumour necrosis factor (TNF) alpha, with sensitisation of the endothelial cells occurring via interferon gamma (IFN-γ). Conversely, interferon beta has been shown in studies to oppose these effects.

Certain T lymphocytes have been shown to play proinflammatory roles in MS and experimental allergic
encephalomyelitis (see Box “Animal model”, p436). The sensitisation of CD4-positive T cells in the periphery may be responsible for the immunological cascade that leads to MS. There, presentation of an autoantigen by an antigen-presenting cell to specific T cells occurs. In the CNS these CD4 cells upregulate on encountering the associated antigen and secrete IFN-γ, interleukins, TNF and other cytokines. This leads to the breakdown of the BBB, activation of microglia (CNS macrophages) and subsequent damage of oligodendrocytes and myelin. Other molecules that may contribute to this destructive process include nitric oxide and free radicals.

Clinical features
The clinical features of MS depend on the pattern of lesions within the nervous system. Indeed, almost any neurological symptom or sign might be attributed to MS. Nonetheless, certain symptoms are characteristic and tend to appear early in the course of MS; others are typical of longer duration of, and more established, disease.

The CNS is divided into motor and sensory pathways. The motor pathways (upper and lower motor neurones) begin at CNS centres and end at the effectors they control. Conversely, the sensory pathways distribute information from peripheral receptors and relay the information to the brain for processing.

Somatosensory symptoms
Somatosensory symptoms are a common initial complaint occurring in up to 70% of patients. These may include numbness, which is often a positive subjective sensation rather than an absent or diminished feeling. Others include tightness, burning and a feeling similar to lidocaine wearing off. These complaints are often unaccompanied by objective neurological signs (such as reduced sensitivity to light touch and pinprick) on examination. Less common are diminished pain and temperature sensations.

Lhermitte’s sign
A symptom known as “Lhermitte’s sign” is highly characteristic of MS. Virtually any movement of the neck can precipitate it but flexion does so most often and causes an electric-like sensation to radiate down the spine or extremities. It reflects involvement of the posterior cervical column.

Pain
Pain that is a direct manifestation of MS is referred to as primary pain. Types of primary pain include neuralgic, dyesthetic (severe burning), spastic and radicular pain, as well as pain associated with optic neuritis (see below). Secondary pain, such as lower back pain, can arise from poor gait and postural changes. Osteoporosis can occur due to poor mobility and regular use of corticosteroids (see accompanying article, p441).

Optic neuritis
Optic neuritis often occurs as an initial symptom in MS, with one in five patients presenting this way. However, many more will have optic nerve involvement and subsequent optic atrophy during the course of the disease.

The optic nerves are usually involved bilaterally and visual acuity is often affected measurably. Decreased colour perception, visual field abnormalities and blind spots (which tend to be central or paracentral) can occur. The optic discs are usually pale (on ophthalmoscopy) unless the patient has retrobulbar neuritis (in which the optic nerve becomes inflamed).

The patient may describe a sharp pain at the back of the eye, which is exacerbated on movement. Recovery of vision can be good, even if the vision loss has been severe during a relapse.

Uhthoff’s phenomenon is a temporary worsening of MS symptoms that occurs when the patient’s body temperature increases (eg, during exercise or a hot bath). A temporary blurring of vision is commonly noted.

Motor symptoms
Motor symptoms are a common initial manifestation of MS. They occur in over a third of patients often with unilateral rather than bilateral involvement of the lower extremities. Patients complain of weakness or stiffness and sometimes pain. Hyperreflexia...
and extensor plantar responses may be present and severe spastic paraparesis develops frequently.11

**Spasticity** Spasticity is often present in the legs and the patient may describe stiffness, spasms, cramps and pains.27 Over-enthusiastic treatment of spasticity with muscle relaxants should be avoided to prevent deterioration of patients’ ability to walk. This is because the increased muscle tone that occurs with spasticity may be acting as a “leg stent” and when this is abolished patients’ underlying muscle strength may not be sufficient to sustain their weight.11

**Fatigue** Patients often describe fatigue as the most disabling symptom of MS. It is encountered in over 90% of patients, is difficult to treat and is compounded by the physical restrictions patients face to function in daily life.7,13

**Cerebellar involvement** Involvement of the cerebellum, which affects co-ordination, ultimately occurs in up to 50% of patients despite its infrequency as an initial symptom. Cerebellar vermis involvement manifests as gait ataxia whereas hemispheric involvement affects the lateral extremities. Examination may reveal intention tremor (increased tremor as the patient’s finger approaches the examiner’s finger), dysmetria (over- or undershooting the examiner’s finger), dysdiadochokinesia (observed as clumsiness of alternating movements of the hands) and, less commonly, hypotonia. Slurred speech is another cerebellar manifestation and warrants referral to a speech and language therapist.22

**Brainstem effects** Brainstem disturbances are another feature of MS.13 Nystagmus is common, often of the horizontal type. Some patients report diplopia (double vision) and oscillopsia (jerky eye movements). Internuclear ophthalmoplegia is characteristic of MS. This is where patients with a unilateral brainstem lesion are unable to turn the eye inwards (adduct) on the side of the lesion.13

**Pseudobulbar palsy** Pseudobulbar palsy is an upper motor neuron lesion affecting the nerves innervating the muscles responsible for eating, swallowing and talking. This can cause explosive, poorly modulated (nasal sounding) speech disturbances. Although hearing loss is uncommon (but not rare), vestibular disturbances are more frequent, especially during relapses, with patients reporting vertigo.

**Cognitive impairment** Patients with MS sometimes describe difficulty with concentration and memory. Frank dementia can occur but is less common.11

**Genitourinary and bowel dysfunction** Bladder dysfunction can affect as much as 80% of MS patients. Many of these complain of urgency and frequency. Urinary incontinence occurs in some patients and the cause must be determined to decide the appropriate treatment (see p447 of accompanying article). Patients can also suffer constipation and occasionally faecal incontinence. Sexual dysfunction is common.11

**Diagnosis** Other autoimmune conditions that affect the CNS must be excluded as differential diagnoses. These include systemic lupus erythematosus, Sjogren’s syndrome and sarcoidosis. It is necessary to rule out vasculitis if suspected. Acute disseminated encephalomyelitis (which also damages myelin) and transverse myelitis (which affects a discreet region of the spinal cord) should also be considered.2,4

A relapse is the occurrence of new MS symptoms, which must last for more than 24 hours at normal body temperature. However, for two relapses to be considered as such, a period of 30 days must have elapsed between the onset of new symptoms for each event.1

On examination (see below), involvement of “multiple” areas of the CNS are looked for. Typically, ophthalmoscopy may reveal pale optic discs, demonstrating a history of optic neuritis. There are three main investigations that can help yield a diagnosis of MS due to their high specificity and sensitivity. These are magnetic resonance imaging (MRI), visual evoked potentials (VEPs) using electroencephalogram; and cerebrospinal fluid (CSF) examination.1

**Magnetic resonance imaging** In clinically definite MS around 95% of patients have an abnormal brain MRI. However, caution must always be exercised when interpreting MRI results since around 4% of normal healthy controls have periventricular lesions indistinguishable from those observed in MS. In PPMS, brain MRIs are more often normal compared with other forms of MS, reflecting a possible different pathological picture (such as axonal loss in addition to more frequent lesions in the spinal cord).1

The breakdown of the BBB in MS has allowed the use of gadolinium enhancement with MRI, which can help identify early active lesions within six weeks. Although this rarely adds much information in clinical practice, it
can be useful for differentiating MS from sarcoidosis (which can cause meningeal irritation) and is a more sensitive method for evaluating the effects of treatments in clinical trials. Gadolinium enhancement is also expensive and requires the patient to be cannulated."1,5,7

**Visual evoked potentials** Evoked potentials measure (using electroencephalogram) the amplitude and rate of conduction of a nerve impulse from a site of stimulus (eg, visual [VEPs]; auditory, sensory posterior column, motor systems) to the cortex.1

VEPs are investigated most often when MS is suspected since these contribute most to the diagnosis. Evidence of a reduction in amplitude due to axonal loss or a decrease in the rate of conduction of a few milliseconds indicates demyelination.1

VEP abnormalities remain in 85% of patients following recovery from an episode of optic neuritis that has become clinically undetectable and, therefore, VEPs provide a useful and sensitive method of confirming MS.1

**Cerebrospinal fluid examination** Patients with clinically definite MS are reported to have oligoclonal bands (OCBs — immunoglobulins produced by inflammation) in their CSF in 95% of cases. Identification of OCBs in the CNS but not in the serum suggests CNS inflammation and can support (but not confirm) an MS diagnosis. It should be noted that the CSF can be OCB-positive in many inflammatory diseases and 4% of patients with a non-inflammatory neurological pathology can have OCBs in their CSF.1

In 1983, the diagnostic criteria for MS were established following the efforts of a committee that looked at the degree of certainty of an MS relapse.1 However, it was not until 2001 that an international panel on MS diagnosis presented new criteria that focused specifically on the use of MRI as a diagnostic aid. The resulting McDonald criteria have been used worldwide since their publication in 2001 and subsequent revision in March 2005.

The new revisions have made confirmation of MS, using objective clinical, imaging and laboratory evidence, more accurate and speedy, while recognising that diagnosis is still partly subjective.1

**Progression and prognosis**

A patient with MS can expect an overall reduction in life expectancy of five to 10 years, corresponding to a median survival of 30 years from symptom onset. A third of patients with MS will die an unrelated death (eg, from cardiovascular causes). However, patients with advancing disability are predisposed to potentially fatal infections such as bronchopneumonia (due to poor respiratory effort), recurrent urinary tract infections (from poor bladder control) and skin-related infections or pressure sores.1

The following are indicators of poor MS prognosis:1

- Older age of onset
- Male sex
- Cerebellar or motor involvement early in course
- Progressive course after onset

The "Extended status disability scale" (EDSS) was devised in 1983 to objectively score the level of deterioration of MS patients’ functioning. It is used widely in trials to monitor disease activity but is not without limitations since it focuses mainly on ambulatory ability and neglects other forms of disability (see Figure 3).15

**References**