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# Multiple sclerosis: diagnostic issues and modern management

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**Abstract**

***Aim:*** **To provide an insight into the current issues in the diagnosis and management of multiple sclerosis (MS).**
***Methods:*** **A literature-based review was undertaken to determine diagnostic criteria, differential diagnosis, and the use of disease-modifying medication and symptomatic treatments for MS. The main source of references was Medline via PubMed but standard major reference works on MS were also used.**
***Results*****: The prevalence of MS may be increasing, especially in women, thereby increasing the need for resources for diagnosis and clinical management of the condition. Clinical diagnosis of MS has changed little since the descriptions of Charcot. However, new diagnostic techniques ranging from neurophysiology and spinal fluid analysis to increasingly sophisticated magnetic resonance imaging have allowed the condition to be diagnosed earlier and with more confidence. New insights in immunology and neuropathology allow differential diagnoses to be excluded and continue to lead to different approaches to managing the condition. New disease-modifying drugs are being used, with the realistic hope of altering the progression of disability. Equally important are new techniques and medications aimed at symptom management, ranging from multidisciplinary team working to drug treatment of pain, fatigue, spasticity, continence and nystagmus.**
***Conclusions*****: There is continuing improvement in many aspects of the care of people with MS. Insights from epidemiology, genetics, pathology and clinical trials have all contributed to this.**

**Key words:** Diagnosis, Multiple sclerosis, Optic neuritis, Treatment

## Introduction

Multiple sclerosis (MS) is a chronic life-changing condition. This literature review aims to summarise research published on MS. The review will highlight the incidence of MS in Britain and Ireland, the current diagnostic criteria and differential diagnosis, and the use of disease-modifying medication and symptomatic treatments. The illustrations presented are from real cases, sourced from personal and colleagues' collections. The main source of references was Medline via PubMed, but standard major reference works on MS were also used.

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## Epidemiological background

MS is common, with the British Isles having one of the highest prevalence levels in the world, ranging from 87–113/100 000 in the Channel Islands in the south to 309/100 000 (257 'probable' category) in the Orkneys in the north in the 1970s.[1,2] Prevalence is patchy, with studies in adjoining areas performed by the same team giving quite different levels: for example, 119/100 000 and 152/100 000 in north and south Cambridgeshire, respectively, in 1996.[3,4] More recently levels of 230.6/100 000 (200.5 standardized to 1961 population demographics) have been recorded in Northern Ireland.[5] This compares with 51/100 000 in 1951, rising through 80, 138 and 168/100 000 in 1961, 1986 and 1996 studies, respectively.[5]

Although France has a lower prevalence than Britain and Ireland of around 50–65/100 000,[6] a more recent study reported prevalence as high as 120/100 000 in Loraine[6] and suggests an increased incidence in women and more aggressive disease in those of North African origin.[7] A difference in the prevalence among women largely explains the difference in overall prevalence between Guernsey and Jersey in the Channel islands.[1] In the United States there is also an increasing incidence of MS, especially in women, the ratio changing from 1.4 female to 1.0 male in 1955 to 2.3:1 in 2000.[8]

While the original migration studies of people of West Indian origin in London found a lower prevalence of MS than among locally born residents of north European origin, recent studies suggest parity in the children of UK-born children of immigrants,[9] supporting an environmental agent triggering the disease, probably at an early age.

A huge variety of potential environmental factors have been explored over the years. An infective aetiology may be suggested by apparent outbreaks. The clearest was in the Faroe Islands after British troops had been based there during the Second World War. Here the prevalence rose from zero in 1939 to 3/100 000 in 1945 and 63.6/100 000 in 1972.[10] Putative infective agents have included canine distemper virus, measles virus, Epstein-Barr virus and HHV6 virus.[11–14] Vitamin D

deficiency and increased smoking are being suggested as possible contributors to susceptibility.[15]

The prevalence of MS is increasing in many parts of the world, perhaps due to better case ascertainment and technology in recent decades. The finding of increased prevalence with latitude remains but is lessening.[15] MS remains more common in northern Europe and in countries with a high rate of northern European migration such as North America and Australasia, suggesting genetic susceptibility.[15] A strong case for a genetic susceptibility is made by the 10- to 50-fold increased risk of the disease (2–5%) in first degree relatives and the lack of increased risk in adopted children.[15–17] Although about 25% of monozygotic twins are concordant for MS, the majority are not, meaning an additional factor is required to trigger the condition.[15,17–19] The presence of the HLA DRB1 allele, polymorphisms of the gamma-interferon gene and apoprotein E allele may all be involved in disease expression.[20]

Certain racial groups seem relatively resistant to MS, such as the New Zealand Maoris, Australian Aborigines, the Sámi population in Norway and the Hutterite community in Canada. All have unexpectedly low prevalence rates in geographic locations where MS is common.[19] This genetic predisposition has been investigated in two ways. In the first, candidate genes such as those coding myelin proteins and genes of the immune system, such as T-cell receptor genes, have been studied.[20] However, initial exciting suggestions of an association of MS with gene polymorphism in one population are often contradicted by other studies. For example, for myelin basic protein (MBP) polymorphisms and other myelin genes[21,22] it is possible that the associations are true only in certain populations: for example MBP in Finland but not the United Kingdom.[21,22]

The second method uses huge population studies to look for genes linked to MS. Screening the entire human genome via the use of polymorphic microsatellite markers has produced a whole new set of potential candidates to pursue. However, apart from major histocompatibility locus on chromosome 6p, meta-analysis of six major studies demonstrated inconsistent results between different populations.[23] Nevertheless, larger recent studies have refined further genetic associations with MS and are providing insight into disease susceptibility and clinical pattern.[24,25] Meanwhile other studies have investigated how genetic differences may modify the course of the disease.[20]

The epidemiological picture is important as many health services underestimate the numbers of people with MS. For example, the National Health Service (NHS) in England and Wales often assumes a prevalence rate of 100/100 000 possibly 120/100 000 at most, while some now think that the rate is 160/100 000 in the south and 180/100 000 in the north of the British Isles.[26,27] Resources clearly have a major impact on both diagnosis and disease management, with government estimates on costs of disease-modifying therapy based on a total of 50 000–60 000 people with MS in England and Wales.[26,28]

## Clinical features of multiple sclerosis and diagnostic tests

MS is clinically complex, as symptoms can affect any part of the central nervous system (CNS). MS can be mimicked by numerous clinical conditions and can mimic many others.[29–31] The progression of the disease is highly unpredictable in any single individual. However, the risk of accruing disability is high. The cardinal features are that lesions producing symptoms are separated in both space (location within the CNS) and the time they occur. The majority of people with MS (85% or more) have a relapsing-remitting pattern of disease (RRMS) at onset, while 10–15% present with a gradually progressing syndrome (primary progressive MS, or PPMS).[29] Around half of those with RRMS develop a progressive disability, called secondary progressive MS (SPMS). Some of those who seem to have the progressive form of the disease at onset will develop relapses (relapsing progressive MS), although this group is still ill defined.[29]

Although the diagnosis of MS has essentially been a clinical one since the nineteenth century, accurate diagnosis and exclusion of other diseases that can produce similar symptoms is increasingly important, as therapeutic intervention has become a realistic prospect. The first set of diagnostic criteria to be widely adopted in epidemiology studies was that of Allison and Millar in 1954.[32] Their entirely clinical criteria divided cases into ‘early disseminated sclerosis’, comprising people with few or no clinical signs but a history of relapsing-remitting symptoms typical of MS (including clinically isolated syndromes and early RRMS); ‘probable disseminated sclerosis’, comprising those with a classical history and physical signs (equating to RRMS with clinical signs and SPMS), usually with some disability; and a ‘possible disseminated sclerosis’ group with static or chronically progressive symptoms for which no other explanation had been found (essentially those that could have PPMS).[32]

The criteria proposed by Poser *et al.* in 1983[33] were widely adopted for clinical trials, and defined relapses and allowed inclusion of information from clinical investigations, such as imaging data from magnetic resonance imaging (MRI), evoked potential studies, objective urological tests and cerebrospinal fluid examination, to support a diagnosis of MS where purely clinical data were insufficient. The Poser *et al*. criteria defined groups with clinically definite RRMS, with or without laboratory support from the presence of cerebrospinal fluid oligoclonal bands, roughly equivalent to the Allison and Millar ‘probable’ group. Also clinical and laboratory supported probable MS, similar to the Allison and Millar ‘early’ group, but tend to miss the progressive spinal cord cases.

Much work has gone into defining the disease clinically; this has been particularly helpful in allowing clear groups of patients to be identified for clinical trials.[32–34] All of these have included clinically isolated syndromes, such as optic neuritis, as a group with potential MS in some way. The more recent international panel consensus of 2001, the ‘McDonald criteria’, and its revised version in 2005 (Table 1), have been more reliant

**Table 1.** Revised McDonald criteria for the diagnosis of multiple sclerosis, combining clinical, MRI and other supportive evidence

| Clinical picture suggesting MS | MRI and other supportive evidence required for MS diagnosis |
|---|---|
| At least two attacks with objective clinical evidence of at least two lesions | None |
| At least two attacks with objective clinical evidence of one lesion | Dissemination in space shown on MRI or two or more MRI lesions consistent with MS, plus positive CSF findings[a] |
| One attack with objective evidence of at least two lesions | Dissemination in time on MRI or second clinical attack |
| One attack with objective evidence of one lesion | Plus dissemination in space shown on MRI or two or more lesions consistent with MS, plus positive CSF findings[a] and dissemination in time shown on MRI or second clinical attack |
| Insidious neurological progression suggestive of MS plus 1 year of disease progression (prospective or retrospectively determined), plus MRI and supportive evidence | Or prospectively, plus two positive brain MRI (nine T2 lesions or at least four T2 lesions with positive visual evoked potential), positive spinal cord MRI result with at least two T2 lesions, and positive CSF findings[a] |

MRI, magnetic resonance imaging.
[a]Positive cerebrospinal fluid (CSF) oligoclonal bands.

on the use of MRI in making the diagnosis.[34,35] MS can now be diagnosed based on a combination of symptoms and signs and evidence from investigations. MRI is now also used to show progression over time.[34,35]

## Role of imaging in the diagnosis and management

Imaging has been used to help in the diagnosis of MS for decades. Initially it was used as a proof of lack of other causes for symptoms – for example a negative myelogram in progressive spinal cord syndromes. In the 1970s and 1980s, cranial computerised tomography excluded other causes of neurological deficit and began to be able to demonstrate the plaques, especially with the use of high-dose contrast.

Since the 1980s MRI has become the most important investigation in supporting a diagnosis of MS. MRI utilises the spin properties of the atomic nuclei of hydrogen ions, aligned in a strong magnetic field displaced by radio waves. Images produced distinguish between solid and liquid states and produce fine anatomical detail. T2-weighted images (which reflect the time taken for nuclei to decay) demonstrate the plaques of inflammation/demyelination. Typically, in MS these plaques aggregate in periventricular, posterior fossa and deep subcortical and juxtacortical white matter, but also in optic nerve and spinal cord. Atrophic change and areas of permanent damage called 'black holes' can be seen on the T1-weighted sequences, while gadolinium can be used to identify active lesions where the blood-brain barrier is disrupted (Fig. 1).[36,37]

Other specialised techniques can demonstrate abnormalities in normal-appearing white matter, or may be better at demonstrating some abnormalities – for example Short Tau Inversion Recovery (STIR) sequences in acute optic neuritis (Fig. 2).[38,39] Even when there has been only a single clinical episode, such as optic neuritis, the risk of developing MS can be estimated from cranial MRI. The presence of brain lesions can indicate multifocal onset or previous subclinical events. A normal brain MRI scan confers a low risk (10–15%) over 10 years while one showing numerous (9+) plaques indicates an 85–90% risk.[40–43]. The number of lesions after optic neuritis predicts the 5-year (51% with 3 or

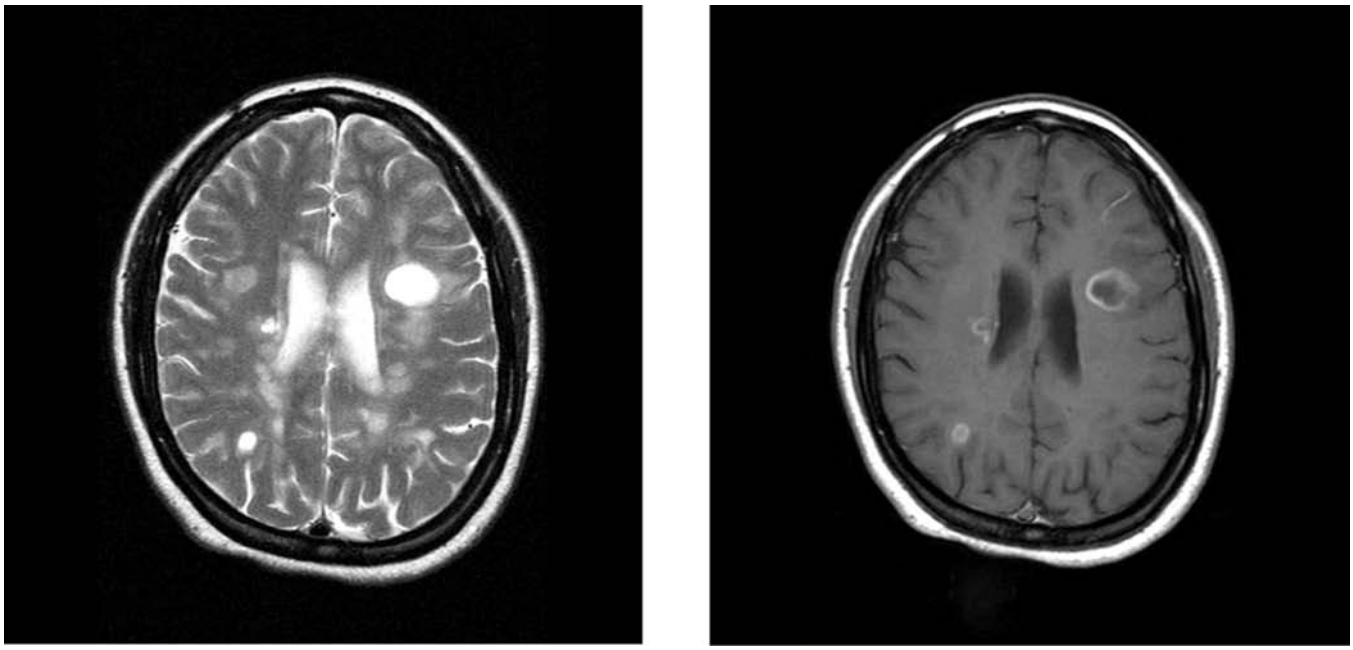

**Fig. 1.** T2-weighted and gadolinium-enhanced T1-weighted magnetic resonance images demonstrating multiple sclerosis plaques in typical periventricular, deep white matter. The juxtacortical location and enhancement are suggestive of active lesions.

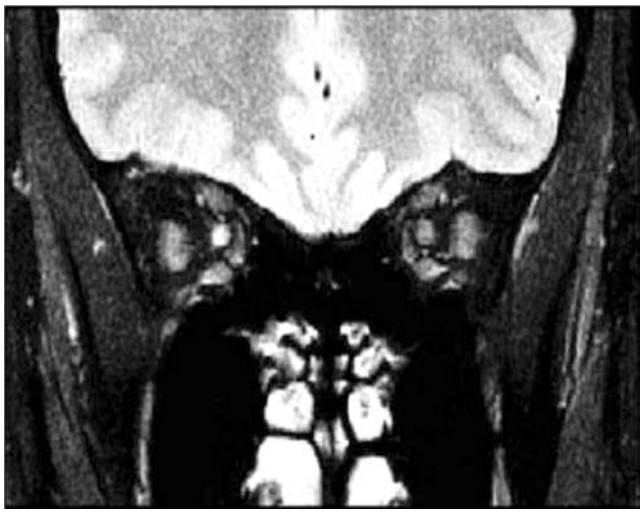

**Fig. 2.** Magnetic resonance image (fat-saturated, coronal oblique, proton density weighted, fast spin echo sequence) demonstrating increased signal in the right optic nerve in acute optic neuritis. (Courtesy of Dr S. J. Hickman.)

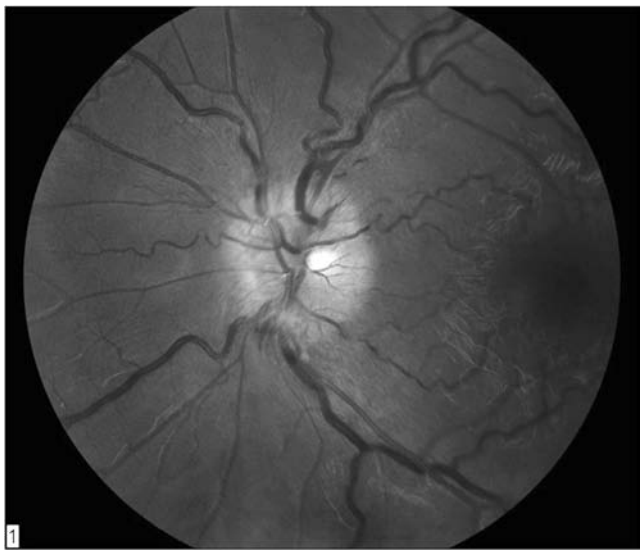

**Fig. 3.** Fundal photograph of a swollen optic nerve head in acute optic neuritis. (Courtesy of Mrs I. Pepper and Dr S. J. Hickman.)

more) or 10-year risk of developing MS; even a single brain lesion indicates a higher risk than a normal scan.

## Other investigations

Visual, somatosensory and auditory evoked potential studies have been in use since the 1970s.[44–47] Visual evoked potentials (VEPs) are the most often used. The principle is simple: a visual stimulus, such as a pattern reversing chequerboard at a set distance, is given and the time for a response on the relevant cortical electroencephalogram is recorded. VEPs are of particular value in the differential diagnosis of MS, as they give a physiologically relevant result. A delayed response is seen due to demyelination causing loss of fast saltatory conduction in the pathway tested.[44,45] The normal response obtained in the pattern-reversal-induced VEP is the large positive wave at approximately 100 milliseconds, the P100. Where acuity is more than 6/24 there is usually an obvious delay with a preserved waveform, although it can be absent in severe forms. The recovery of this delay mirrors clinical recovery of visual acuity and colour vision, but delays persist in 90% of adults. Somatosensory evoked responses (SSEP) and auditory evoked responses, developed in the 1970s, are used less frequently.[46,47]

Demonstration of inflammation in the cerebrospinal fluid (CSF), from lumbar puncture specimens, has been used in the diagnosis of MS since the 1920s. The essential point is that where there is inflammation just in the CNS and not systemically, more inflammatory proteins will be found in CSF than in blood serum. These spinal fluid proteins are subjected to electrophoresis and separated into different IgG immunoglobulins called oligoclonal bands.

There have been technological improvements over the years. Now the presence of intrathecal IgG in CSF – either in CSF only and not serum, or with more bands present than in serum – together with isoelectric focusing (where proteins are separated according to their overall charge, not just size) is highly sensitive. These oligoclonal bands are found in more than 95% of patients with clinically definite disease. They are particularly useful where MRI has shown non-specific, possibly vascular lesions, where symptoms and signs are typical but MRI uninformative, or in progressive syndromes such as PPMS presenting with a progressive spastic paraparesis.[48,49]

## Symptoms and signs in MS

Ophthalmic symptoms are common in MS. Optic neuritis is one of the most common acute optic neuropathies in the under-forties.[50] This classically presents with acute visual loss over days, pain (in 90% of cases, often on eye movement), loss of colour vision and evidence of field defects (classically central, but can be any); about one-third of cases will have disc swelling (Fig. 3).[50,51] Severity is often reflected in the length of the optic nerve lesion seen on MRI.

Recovery is often good (95% 20/40, i.e. 6/12 or better), occurring over weeks, but improvement can continue for up to a year. An Uhthoff's phenomenon of worsening vision while hot or after exercise may persist and a Pulfrich phenomenon of pendular movements of objects seeming elliptical can occasionally occur, due to the delay secondary to demyelination of the optic nerve. The affected eye almost universally exhibits a relative afferent pupillary defect. Optic atrophy and disc pallor, especially temporal, occur after 6–8 weeks and correlate with the optic nerve atrophy seen on MRI.[52–54] High-dose methylprednisolone improves the speed of visual recovery but not the extent, so is often not required.[50–55]

MS plaques have a predilection for the brain stem and cerebellum, so virtually any eye movement disorder and form of nystagmus can be seen. However, the classical pattern, commonly seen and highly predictive of MS, is internuclear ophthalmoplegia (INO). Clinical examination reveals reduced adduction or a subtle lag of

**Table 2.** Differential diagnosis in MS

| Condition | Method of diagnosis |
|---|---|
| Structural lesions such as tumours, cervical disc or syringomyelia | MRI and other imaging techniques |
| Neuromyelitis optica | Cranial MRI usually normal, spinal lesions are long, CSF oligoclonal bands negative, NMO (aquaporin-4) antibodies positive |
| Leber's plus MS | Mitochondrial genetics |
| Anterior ischaemic optic neuropathy | Older group with vascular risk factors, altitudinal field defect |
| Hereditary ataxias | Friedreich's and SCA genetics |
| Progressive spastic paraparesis | Imaging, HTLV1, HIV, VLCFA, white cell enzymes, $B_{12}$ deficiency, syphilis serology, genetics |
| Acute disseminated encephalomyelitis | Usually more severe, MRI lesions same age (enhance together), longer spinal lesions, higher CSF pleocytosis, delayed oligoclonal bands usually negative. Tests cannot fully rule out first attack of MS |
| Vasculitis | Imaging and serology. Matched bands in CSF and serum |
| Antiphospholipid syndrome | Positive serology and negative oligoclonal bands. VEPs often not typical of MS |
| Infective causes of white matter lesions on MRI | Lyme's serology, syphilis, HIV, matched CSF and serum oligoclonal bands |

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; NMO, neuromyelitis optica; SCA, spinocerebellar ataxia; HTLV1, human T-cell leukaemia virus 1; HIV, human immunodeficiency virus; VLCFA, very long chain fatty acids; VEP, visual evoked potentials.

adduction of one eye and nystagmus in the abducting eye. Careful examination of pursuit and saccadic eye movements is required. An INO can be unilateral or bilateral and may be seen in 25% of MS patients.[56,57] If it is bilateral and severe there can be an exotropia (the so-called wall-eyed INO). The causative lesion is in the medial longitudinal fasciculus in the caudal midbrain and rostral pons. An INO may be asymptomatic, cause diplopia or oscillopsia. Other visual symptoms can occur, including field defects and visual distortions due to involvement of the optic radiations and juxtacortical areas.[57]

Other brain stem syndromes that involve sensation, including paroxysmal symptoms, can occur, such as trigeminal neuralgia, facial weakness, speech (often cerebella) and swallowing problems. Other common presenting symptoms are disturbances of sensation and stiffness and weakness of the limbs due to partial spinal cord lesions. In PPMS, progressive spastic paraparesis is most common. However, cortical syndromes such as dysphasia, mood and cognitive dysfunction, bladder and bowel problems and pain and fatigue are also common.[48,58,59] All these syndromes can either be part of a relapse or form part of ongoing symptoms.

## Differential diagnosis

The differential diagnosis of MS symptoms is wide and includes both common and rare conditions (Table 2).[58] In the first episode, acute disseminated encephalomyelitis is always a concern if clinically multifocal. This is more akin to the experimental model of MS – experimental autoimmune encephalomyelitis; it is an acute autoimmune response to infection, possibly triggered by molecular mimicry. It is severe and may relapse. Cord lesions tend to be several vertebrae in length and the CSF is more cellular with polymorphs more likely and transient oligoclonal bands.

Structural problems need to be excluded, and these range from degenerative cervical discs to Chiari malformations with syringomyelia, cavernomas, dural fistula and tumours.[58] In progressive spastic paraparesis and ataxic syndromes the differential diagnosis includes the rare spinocerebellar ataxias, hereditary spastic paraparesis, neurodegenerative disorders such as the primary lateral sclerosis form of motor neuron disease, and metabolic and dysmyelinating disorders. The latter range from Pelizeaus-Merzbacher dysmyelinating disease in young boys, to genetic leucodystrophies, such as adrenoleucodystrophy, metachromatic leucodystrophy and Krabbe disease.[60–63]

Other potential differential diagnoses include relapsing Sjögren's disease, stroke syndromes, and autoimmune diseases such as systemic lupus erythematosus, Behçet's and the other vasculitides.[58] Differential infective conditions include tropical spastic paraparesis, human immunodeficiency virus (HIV), borreliosis (Lyme disease), Whipple's disease and syphilis,[64–66] and the primary CNS oligodendrocyte infection, progressive multifocal leucoencephalopathy. Vitamin $B_{12}$ deficiency can cause subacute combined degeneration of the cord.

In autoimmune conditions such as antiphospholipid syndrome (Hughes' syndrome), the MRI and clinical findings can be very like MS.[67–69] Similarly, white matter lesions are seen on the MRI in gluten ataxia.

Especially relevant in neuro-ophthalmology is neuromyelitis optica (NMO), with episodes of optic neuritis and spinal cord syndromes, usually without cranial MRI changes. The clinical recovery tends to be poorer and initial symptoms more severe. However, immunosuppression may prevent further events. Recently the finding of NMO (aquaporin-4) antibodies has become a relatively sensitive and specific test for NMO.[70–72]

The combination of bilateral severe optic nerve problems and MS has led to the recognition of a Leber's plus MS syndrome (Harding's disease) with the mitochondrial mutations of Leber's but MRI findings typical of MS.[73]

How far one searches for these conditions depends on the degree of suspicion, and depends on type of presentation, recovery pattern, progression, gender, age and other genetic and environmental factors. Some MS specialists will check for vasculitis and antiphospholipid syndromes in all patients; others check only if there have been suggestive symptoms. One would be more likely to check for borreliosis (Lyme disease) in patients from the New Forest than London, and one might check Leber's genetics and aquaporin antibodies in those with poor recovery and bilateral severe optic neuritis.

## Defining relapses and disability in MS

The definition of what constitutes an acute MS relapse is important in determining suitability for treatment with disease-modifying agents.[26,28,74–75] An MS relapse is usually defined as a period of neurological dysfunction (of the type seen in MS) lasting more than 24 hours (sometimes 48 hours) separated from any other symptoms by 1 month (30 days) and not occurring in the context of a febrile illness (pseudo-relapse). In practice, relapses usually develop over days and take many weeks to recover.

Disability is equally difficult to define, with many different ways of assessing its severity. Although open to criticism for its non-linear nature and dependence on the grading and interpretation of clinical signs by clinicians, the Expanded Disability Status Scale (EDSS),[76] developed by Kurtzke, remains the most commonly used method. This is possibly because it only requires a clinician with neurological skills and the Snellen chart, ophthalmoscope, tendon hammer, tuning fork and neurotip pin. The EDSS has been made more consistent by widespread use of a standardised version, available on line or on CD-ROM.[77] The EDSS scale runs from 0 (normal) to 10 (dead); scores up to 4 are determined by clinical signs, from 4 to 8 by the ability to walk, and from 8 to 10 by increasing dependency. Of the other scales available, the Guy's Neurological Disability Scale is more balanced and the MS Functional Composite Scale includes an objective test of hand function, a more sensitive visual test of contrast sensitivity and tests of cognition.[78,79]

## Pathogenesis

The clinical features of all types of MS are linked with the pathological processes occurring. The formation of inflammatory, demyelinated plaques is a hallmark of the disease. Relapses are linked with acute flare-ups of inflammation, breakdown of the blood-brain barrier and the formation of demyelinated plaques, classically in the white matter of the CNS. Blood-brain barrier breakdown can be demonstrated on MRI as a very early feature in plaque formation.[80,81] Plaques have been noted macroscopically since the time of Carswell (1838) and Cruveilier (1841), and microscopically since Rindfleisch (1861) and Charcot (1868).[81]

The plaques contain active T and B lymphocytes and microglia and a myriad of different cytokines, inflammatory mediators and nitric oxide,[82–84] contributing to nerve conduction block. There is also demyelination where the nerve axons have been stripped of the lipid- and protein-rich myelin membrane wrapping the axon.[81–84] Myelin is produced in the CNS by oligodendrocytes and allows more rapid signalling along the axons via saltatory conduction; the demyelinated axons have their sodium channels spread out rather than at internodes and conduct less well.[84] Although clear from the original pathological descriptions, the acute loss of axons in early acute lesions has now been recognised.[85]

Thus, inflammation, demyelination and axonal loss all occur, but not necessarily in a simple sequential pattern. The inflammatory plaques do repair, at least in part, forming shadow plaques. However, the axonal loss is irreparable and gliosis or scar tissue formation a permanent feature. The time course of a relapse seems to follow this inflammatory event, while disability accrual is believed to follow the axonal loss and inadequate remyelination.[84]

The current prevailing view is that there are four types of plaque pathology identified from brain biopsy specimens, which may have therapeutic implications.[86] These are:

- Type I: macrophage-associated demyelination,
- Type II: macrophage-associated demyelination with immunoglobulin precipitation and complement activation that seems antibody mediated,
- Type III: a distal dying back oligodendrogliopathy-associated demyelination,
- Type IV: primary oligodendrocyte degeneration with secondary myelin loss.

Type I is the typical MS plaque, type II is associated with B cells, type III resembles the effects of hypoxia, and type IV is rare (2%) and possibly linked to a genetic susceptibility to immune-mediated injury.

## Treatment in multiple sclerosis

Treatment of MS can be divided into the treatment of the acute symptomatic relapse, treatment to alter the course of the disease, and symptomatic management.

The mainstay of treatment of a disabling acute relapse is the use of corticosteroids. Much information has come from the optic neuritis treatment trials.[41,42,55] Very high dose steroids are now used to treat relapses, as methylprednisolone 1 g intravenously (equivalent to 800 mg prednisolone) for 3 days was found to be more effective than milligram/kilogram doses of prednisolone, which seemed to increase the risk of further episodes.[41] However, the route may not matter and either methylprednisolone 1 g for 3 days or 500 mg for 5 days orally or intravenously are now the conventional steroid regimens in the United Kingdom and Ireland.[26,55,87,88]

The optic neuritis trial showed that steroids speed recovery but do not affect eventual outcome. If there is little recovery, in a severe disabling relapse plasma exchange can be helpful.[90] The small Mayo Clinic study of 7 exchanges over 2 weeks demonstrated moderate or marked improvement in 5 of 11 of those in the treatment wing, compared with 1 of 11 who were placebo-exchanged. Later Mayo Clinic experience reported 44% of 59 patients with significant benefit.[91] There is speculation that these responders have more type II antibody-mediated pathology (more like neuromyelitis optica). However, intravenous immunoglobulin, also used effectively in many antibody-mediated disorders, seems no better than steroids.[92] Mild relapses can be managed conservatively. It is also important to rule out infective pseudo-relapses, where symptoms re-occur due to infections and steroids are contraindicated.

Disease-modifying therapies for MS are at an exciting time in their evolution. Several drugs alter the risk of getting MS after a single demyelinating episode and reduce the risk of further relapses and progression. Increasingly neurologists and neuroscientists are of the view that early intervention may reduce the chance of

**Table 3.** Symptomatic treatment in multiple sclerosis

| Symptom | Treatment |
|---|---|
| Spasticity and spasms | Physiotherapy, baclofen, tizanidine, dantrolene, benzodiazepines, gabapentin, botulinum toxin, intrathecal baclofen |
| Neuropathic pain | Amitriptyline especially for burning and allodynia, gabapentin and carbamazepine for lancinating pain, non-steroidal anti-inflammatory drugs for musculoskeletal pain |
| Bladder urgency | Anticholinergics such as oxybutynin, tolterodine, solifenacin, desmopressin, botulinum toxin |
| Bladder retention | Training, self intermittent and permanent catheterisation |
| Bowel dysfunction | Dietary measures, enemas, anticholinergics |
| Impotence | Sildenafil, alprostadil and other measures |
| Nystagmus | Baclofen, gabapentin and memantine |
| Diplopia | Orthoptic advice, prisms, occlusion |
| Fatigue | Amantadine and modafanil |
| Depression | Counselling, psychotherapy, antidepressants |
| Tremor | Beta blockers, buspirone, trihexphenidyl, cooling, deep brain stimulation |

future disability. The CHAMPS, ETOMS and BENEFIT studies have all convincingly shown that systemic interferon beta-1a or -1b reduce the chance of developing MS, and the PRECISE trial has shown that glatiramer acetate does also.[93–96]

Use of these drugs after a single demyelinating episode is not currently funded by the NHS in the United Kingdom although it is recommended by the Association of British (and Irish) Neurologists (ABN) in those whose clinical presentation or MRI results suggest a higher risk of MS. This is controversial as overall half of such patients will not suffer a further attack.[75] However, the treatment of RRMS with beta-interferon and glatiramer acetate is now standard. It is recommended in the National Institute of Clinical Excellence (NICE) guidelines for those who have had two clinically significant relapses over 2 years and are still mobile. Interferon beta-1a (at either a lower dose of 30 μg intramuscularly once a week or a higher dose of 22 or 44 μg subcutaneously three times per week), interferon beta-1b (8 IU/250 μg) subcutaneously on alternate days and glatiramer acetate (Copolymer 1, 20 mg) subcutaneously daily all reduce relapses by about a third, and tend to make relapses milder.[96–100]

There may be an interferon dose effect and neutralising antibodies may reduce effectiveness.[98,101,102] These beta-interferons may also slow a tendency of MS to progress.

In secondary progressive disease, the only trial showing delayed progression was the European interferon beta-1b study, but interferons do reduce relapses in SPMS.[103,104] Hence, the ABN (2001 and 2007) recommended beta-interferon in those with SPMS who continue to have disabling relapses.[73,74] Unfortunately these drugs have no effect in PPMS.

The interferon drugs, just like natural interferons, which are normally produced in the body to aid the fight against infection, commonly cause influenza-like side effects and injection-site reactions and can affect the liver, cause blood dyscrasias and depression. Glatiramer acetate (said to mimic myelin basic protein) can cause injection-site problems and occasional episodes of chest pain.

For those with more aggressive disease there are now more options. Natalizumab, a humanised monoclonal antibody that blocks integrin-mediated transport of white cells into the CNS, is now available. It is given as a 300 mg 4-weekly infusion. Natalizumab reduces relapses by 66% and slows progression of disability for up to 2 years.[104,105] It is, however, also potentially more toxic. Three cases of the potentially fatal infection progressive multifocal leucoencephalopathy (PML) have occurred with natalizumab during clinical trials. Two of the MS patients were also on interferon beta-1a; one patient with inflammatory bowel disease was on other immunosuppression. Natalizumab is no longer used with an interferon, but there have now been a few reported cases of PML in patients on natalizumab alone. The estimated risk is about 1 in 1000. Additionally there is an increase in mild infections and allergic reactions, and a theoretical risk of cancers. NICE therefore recommends its use only in those with rapidly evolving severe MS who have had two disabling relapses in the previous year and activity or progression shown on MRI, whether or not they are already on an interferon.[106]

For even more aggressive MS the cytotoxic agent mitoxantrone (12 mg/m$^2$ intravenously 3 monthly, or 20 mg/month with 1 g methylprednisolone for 6 months) is the most commonly used. Licensed in the United States, it seems to be highly effective but is potentially extremely toxic, with side effects including cardiotoxicity and bone marrow suppression.[107,108] Occasionally autologous bone marrow transplant or cyclophosphamide is used, but these carry even more safety concerns.[104]

Alemtuzumab (formerly known as Campath) is another monoclonal antibody, which appears to be highly effective in preventing relapses in early disease and may hold promise in preventing progression.[109] It is now going into wider trials, but side effects of thyroid disease and occasional immune thrombocytopenia may preclude its widespread use. Other biologicals such as ritixumab, immune modulators such as fingolimod, and older drugs such as cladribine and novel oral agents are being studied in clinical trials.[104] Many hold promise and it is hoped that some will encourage repair. Azathioprine is still in use and has some effect on progression and relapses in MS.[110]

Symptoms in MS are extremely diverse and may respond to an equally diverse range of treatments (Table 3). A multidisciplinary team is essential and neurorehabilitation is needed for both acute relapses and ongoing disability.[111] At diagnosis the main problems may be anxiety and fear, which are best dealt with by education and counselling by specialist MS nurses. Pain and fatigue are very common. Pain can be of any type and was found to be a problem in 40% of patients in a community-based study.[59,111,112] Lancinating pain such

as neuralgia often responds to anticonvulsants such as carbamazepine and gabapentin.[112] More diffuse, burning pains may respond to amitriptyline, but the evidence base is poor.[112]

Musculoskeletal and postural problems, secondary to weakness and spasticity, may be treated best by physiotherapy. Spasticity can be associated with painful spasms treatable with baclofen, tizanidine, dantrolene and gabapentin.[26,111] Severe spasticity can be treated with focal botulinum toxin or intrathecal baclofen.[110,111,113] Foot drop can be treated with splinting and functional electrical stimulation.[114] Attention to seating and occupational therapy assessments of activities of daily living is essential in the more disabled. Treatments for tremor are not very effective, but severe tremor can be treated by deep brain stimulation.[115]

Depression is common and is treated with conventional drugs or psychological intervention.[111] Cognitive problems can be assessed and helped by psychologists or occupational therapists. Fatigue can be helped by lifestyle alteration, amantadine and modafinil.[111,116]

Bladder urgency can be treated with anticholinergics, desmopressin and intravesical botulinum toxin;[111,113] retention by intermittent self-catheterisation; impotence by sildenafil, alprostadil and physical measures.[111]

Problematic nystagmus may respond to gabapentin, memantine or baclofen. Improvement has been reported in congenital nystagmus.[117] In a small trial of 16 on gabapentin, 16 on memantine and 15 on a placebo, subjects showed improvement in visual acuity foveation, and nystagmus intensity.[117] There is an ongoing trial to examine the effects of gabapentin and memantine in MS.[118] In a survey of current practice treating acquired nystagmus in 2006, 850 ophthalmologists and 434 neurologists were sent questionnaires, a third of whom replied. Gabapentin and baclofen were the commonest drugs used; 11 ophthalmologists and 44 neurologists reported improved nystagmus and vision.[118]

Diplopia can be relieved by the use of prisms or occlusion. Occasionally botulinum toxin is used to freeze an eye to relieve the symptoms of severe diplopia and nystagmus.[113]

Patients may wish to treat themselves with a variety of alternative remedies, often against the evidence of their utility.[111] For example, cannabinoids failed to improve spasticity in the large Medical Research Council trial but possibly do have some effect.[119] Hyperbaric oxygen and vitamin injections have been shown to be ineffective in objectively relieving symptom in MS but remain popular. Acupuncture may help pain but objective evidence in MS is lacking.[111] Of concern are spurious press reports of near-miraculous responses to non-autologous stem cell treatment. One's duty as a clinician is to inform patients of the evidence and the risks involved.

## Conclusions

MS is a common disease. It is aetiologically and clinically complex. The disease course is unpredictable. However, new and better disease-modifying therapies are emerging. Rehabilitation and symptom management remain essential in improving the life of those with MS.

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