Multiple sclerosis

This article aims to give a brief overview of the epidemiology, diagnostic issues and treatment of multiple sclerosis (MS). The disease is common, especially in the UK. People are often diagnosed in their 20s and 30s but live for a median of 35 years with their disease. The degree of disability accrued is very variable. There are now increasing options for both disease modification and symptom management.

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Multiple sclerosis (MS) is the commonest cause of disability in younger adults in the UK. Onset is often in the third or fourth decade and median survival is 35 years from onset, and overall life expectancy is shortened by several years—especially in those who have accrued the most disability. Median age to reach wheelchair use is about 63 years for those with relapsing or progressive onset MS. The prevalence of late-onset MS (when the condition develops after the age of 50 years) is 4–9·6%, and the increased incidence of vascular disease in this subgroup makes the diagnosis of MS more difficult.[1-3]

An autoreactive immune system causes attacks of inflammation plus demyelination and axonal loss. The latter two processes are the main causes of the disability with MS. Treatment of acute relapses has been more recently accompanied by disease modifying therapies that reduce the frequency and severity of relapses and show genuine hope in reducing disability accrual, with several new medications on the horizon. Meanwhile there have been improvements in diagnostic tests and in medications to ameliorate symptoms.

Epidemiology

MS is common in the UK. The highest recorded prevalence in the world was in the Orkney Isles in the 1970s, reaching 309/100,000 (257 of which were in the "probable MS" category). There is a geographical gradient from North to South. For example, the prevalence of MS was recorded as being 87-113/100,000 in the Channel Islands in the 1990s,[4,5] and rates of 50/100,000 have been reported in France.[6,7] However, a recent study indicated that Lorraine has a MS rate of 120/100,000,[6,7] and this figure falls further in countries towards the equator.

Prevalence can also differ within the same area; for example, North Cambridge has a rate of 119/100,000 while South Cambridge has a rate of 152/100,000.[8,9] In some areas, it appears to be rising: in Northern Ireland, it increased from 51/100,000 in 1951 to 80/100,000 in 1961, to 138/100,000 in 1986, and to 168/100,000 in 1986.[10] This increase has cost implications for health and social care. MS has always been more common in women, and the female-to-male ratio has increased over time from 1·4 in 1955 to 2·3 in 2000 (in the USA).[11] Case ascertainment may well be a contributor to these changes.

Children of immigrants from low prevalence areas, such as the West Indies, now achieve parity with those of north European origin.[12] This, together with the apparent epidemics of MS, such as in the Faroe Islands after British forces were stationed there in the second world war,[13] supports the idea of an environmental factor, probably in childhood, triggering the disease. Numerous viral triggers have been put forward, but none have stood the test of time. More latterly, exposure to sunlight and low Vitamin D levels have been mooted. However, the 25% concordance rate in identical twins and familial risk of 2% in offspring and 4% in siblings of those with MS suggest a genetic susceptibility.[14,15] The finding that prevalence rates are high where those of North European origin have migrated also supports this. As does the relative resistance to MS of certain populations such as the New Zealand Maoris, Australian Aborigines, or Finnish Sami, who reside in areas of high prevalence.[16] Screening of candidate genes of myelin or the immune system have proved unfruitful and whole genome wide screening has only consistently shown a link to the HLA DR2 locus.[17]

It is possible that many factors (ie, a "multi-hit"), such as a genetic susceptibility made up of several genes and environmental insult, cause the development of MS.

Pathogenesis

The pathognomonic lesion of MS is the inflammatory plaque. There is an infiltrate of lymphocytes and macrophages, with many lymphocytes migrating from the general circulation. There are a whole host of interacting inflammatory cytokines and complex interactions between the cell types. As well as a stripping of the myelin, preventing saltatory conduction, axonal loss occurs even at early stages of the disease. Sodium channels spread along the axons and they become vulnerable to excitatory damage. Nitric oxide increases conduction block. Plaques are capable of partial repair, with a degree of remyelination, reflecting clinical recovery.

Brain biopsy specimens show four pathological subtypes, which may reflect different disease subtypes and has lead to different targets for therapeutic action. These subtypes are: macrophage associated demyelination, the typical plaque (Type I); macrophage associated demyelination, with immunoglobulin precipitation and complement activation that seems antibody B cell mediated (Type II); Distal dying back oligodendongliopathy associated demyelination, resembling hypoxia (Type III); and primary oligodendrocyte degeneration with secondary myelin loss, possibly a genetic immune susceptibility (Type IV).[18–20]

Clinical features and diagnosis

Ninety percent of MS patients have the relapsing-remitting onset form of the disease, which is when the patient has an episode of new or worsening symptoms (a relapse) that may later improve (remission). About half of these patients will eventually develop secondary-progressive MS (the condition becomes worse over time, with permanent symptoms). The remaining 10% will have primary-progressive MS (symptoms become gradually worse with no remittance).

A relapse is defined as a new or worsening symptom or sign attributable to the central nervous system (CNS), lasting more than 24 hours, occurring a month or more apart from another relapse, in the absence of a febrile illness. Diagnosis is still essentially clinical. There must be symptoms and signs of CNS dysfunction separated in space and time. However most relapses develop over days to weeks and improve over weeks to months, often incompletely. Typical symptoms include optic neuritis (painful loss of central vision), sensory and motor partial spinal cord syndromes, diplopia, ataxia and other brainstem syndromes and abnormalities of the bladder and bowel. Cognitive and psychiatric symptoms can also occur. The sheer variety of MS symptoms can make diagnosis difficult. As the condition is multifocal, there may be no clear single location to explain them. Detailed clinical examination is paramount. More patients have mild-to-moderate disability than severe disability. Life is shortened (directly) only in the small group of the very disabled.[21]

No diagnostic test is a 100% predictive but useful investigations include: magnetic resonance imaging, conventionally T2 weighted sequences. The examination of cerebrospinal fluid (CSF) and blood for the presence of CSF only oligoclonal bands, which indicate central nervous system directed inflammation. Also evoked potential studies, especially visual, where slowing of the response reflects loss of myelin and saltatory conduction, can help to confirm diagnosis.[22] The revised McDonald criteria allow the use of interval MRI imaging to demonstrate new lesions and confirm the diagnosis before another episode is clinically apparent (Table 1).[23,24] A time interval is allowed to differentiate MS from acute disseminated encephalomyelitis.

The risk of developing MS is higher in those with clinically isolated syndromes, such as optic neuritis, that have multiple lesions on MRI. The Optic Neuritis Treatment Trials suggest that the risk of developing MS over 10 years rises from 10-15% in those with normal cranial MRI to 90% in those with nine or more spots on T2 weighted MRI. The location of lesions on MRI is also helpful with periventricular, juxtacortical and posterior fossa lesions being much more typical of MS.[25, 26]

The differential diagnosis of MS is large.[24] The aim is to find other treatable conditions and increase prognostic accuracy. There are numerous other causes of white matter lesions on MRI,[25] including the vascular lesions of small vessel disease (a particular problem in patients older than 50 years), vasculitis, antiphospholipid (Hughes') syndrome, and the genetic condition CADASIL. There are other autoimmune causes of optic neuritis and transverse myelitis aside from MS, and they can be identified by certain factors. Neuromyelitis optica (Devic's) usually has more severe episodes, longer cord lesions and poorer recovery than MS, and NMO/aquaporin 4 antibodies are often present. If the patient is found to have neuromyelitis optica (Devic's) rather than MS, immunosupression should be considered.[28] NMO/aquaporin 4 antibodies also may be present in Sjogren's syndrome. Sarcoidosis, Lyme's disease, HIV, HTLV 1 infections and B12 deficiency need to be considered, where appropriate. Antigliadin antibodies can be associated with ataxia and there are numerous

Table 1: Revised McDonald criteria for the diagnosis of multiple sclerosis[23,24]

Clinical picture suggesting multiple sclerosis	Magnetic resonance imaging (MRI) and other supportive evidence required for 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 cerebrospinal fluid (CSF) oligoclonal bands; or await further clinical attack, implicating a different site
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 at least one lesion	Plus dissemination in space shown on MRI or two or more lesions consistent with MS plus positive CSF oligoclonal bands and dissemination of time shown on MRI or second clinical attack
Insidious neurological progression suggestive of MS plus one year of disease progression (prospective or retrospectively determined)	Two out of: 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 oligoclonal bands

rare genetic conditions, including the hereditary ataxias, hereditary spastic paraparesis and leukodystrophies that can look like progressive MS clinically.[27, 29] Genetic testing and counselling may be required.

Treatment

The National Institute for Health and Clinical Excellence (NICE)[30] published its guidance for MS in 2003. The guidance covers specialised services, rapid diagnosis, seamless and responsive services, sensitive and thorough assessment and self referral after discharge. The aims of treatment are to treat relapses, modify disease progression, ease symptoms (table 2), and minimise disability.

Relapses

The treatment of an acute relapse depends on its functional impact. Corticosteroids shorten attacks, but do not improve eventual outcome. A tingling hand may not require treatment in a retired person but might in someone needing sensitivity of hand function such as a hairdresser. Intravenous or oral methylprednisolone 1 g for three days or 500 mg for five days are most commonly used, with steroid tails in severe cases.

Therapy interventions and symptomatic treatments are equally important. For severe, poorly recovering relapse, plasma exchange may improve outcome in 42%.[31] This group of patients possibly have Type II antibody mediated pathology.

Disease progression

Unfortunately no current treatments are effective at slowing progression in primary progressive, but there are an increasing number of therapies to treat those with relapsing disease.

β–interferon Ib and 1a subcutaneously three to four times a week, β–interferon 1a intramuscularly once weekly and glatiramer acetate subcutaneously daily are the conventional drugs used. These all reduce relapses by about a third and tend to reduce their severity. They may also have a very slight effect on progression. The β–interferons are also of limited benefit to those with relapses in secondary progressive disease.[32–36] For relapsing remitting MS, treatment with an interferon or glatiramer acetate is recommended for those who can walk 100 meters who have had two or more clinically significant relapses in the previous two years and who have no contraindiations to the treatment. They are recommended less strongly for those walking between 10 and 100 metres. For secondary

Table 2: Management of symptoms associated with MS

Symptom	Management
Spasticity and spasms	Physiotherapy, baclofen, tizanidine, dantrolene, benzodiazepines, gabapentin, botulinum toxin, intrathecal baclofen
Neuropathic pain	Amitriptyline especially for burning and allodynia, gabapentin, pregabalin and carbamazepine for lancinating pain. Non-steroidal anti-inflammatory for musculoskeletal pain
Fatigue	Amantadine, modafinil, diaminopyridine for motor fatigue
Nystagmus	Gabapentin, memantine and baclofen
Diplopia	Orthoptic advice, prisms, occlusion
Tremor	β–blockers, buspirone, trihexyphenidyl (none very effective). Occupational therapy, cooling, deep brain stimulation
Bladder urgency	Anticholinergics like 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
Depression	Counselling, psychotherapy, antidepressants

progressive MS, treatment with a β–interferon is only recommended for those walking 10 M or more (with or without aids) who have had two or more disabling relapses in the prior two years and in whom relapses are the major cause of disability progression. Glatiramer acetate is not recommended for secondary progressive MS. All conventional therapies are provided under the "risk sharing scheme" in which the NHS share the cost of the drug with the drug company, receiving a cost reduction if the drugs are not as effective as claimed. The criteria follows recommendations of the 2001 Association of British Neurology guidelines and Health Service Circular 2002/04.[37,38]

More powerful and expensive drugs are becoming available. Natalizumab reduces the rate of relapses by two thirds and also slows progression. Its cost and potential toxicity of 1/1000 of progressive multifocal leukoencephalopathy mean that NICE has restricted its use to those with rapidly evolving MS, defined as two or more disabling relapses in a year.[39] Mitoxantrone, a cytotoxic agent, is also used in rapidly progressing aggressive MS. Cardiac and immunosuppressive toxicity limit its dosage, and about 1/200 develop secondary leukaemia. Allogenic bone marrow transplant is also occasionally used in this hyper aggressive group.[40]

There are several promising agents on the horizon including alemtuzumab, which reduces relapse by 90% but has a significant risk of Grave's disease and idiopathic thrombocytopenia.[41] Several oral treatments look promising: cladribine reduces relapses by 55%; and fingolimod reduces relapses by up to 60%, but there are concerns about disseminated infections and melanoma. Teriflunomide, laquinimod and fumarate are also all in Phase III trials. Non-bone marrow stem cell treatment is still a long way from becoming a viable treatment.[42–44]

Symptom management

MS specialist nurses are vital in reassuring patients and educating them about common issues. The newly diagnosed or those with high-risk clinically isolated syndrome are often in a state of panic and need accurate information

as well as support. Attention to detail is essential, and it is useful to have a standard set of questions to cover common problems to make it easier to discuss more sensitive issues. It is important to ask about pressure areas, mobility, transfers and wheelchair issues with patients with severe disabilities. Involvement of neurophysiotherapists, speech and occupational therapists is vital, and access to neuropyschology is important. Fatigue should be managed with lifestyle changes, reducing sedative drugs and ensuring sleep is not disrupted by pain or bladder problems before the use of medications such as amantadine or modafinil.

Musculoskeletal pains due to imbalance of neurological function are common and best treated by simple analgesics and physiotherapy. Neuropathic pain can be dysaesthetic, burning, tight or lancinating. Several drugs can be used to relieve pain, but amitriptyline is perhaps best for dysaesthetic pain and anticonvulsants (such as gabapentin, pregabalin and carbamazepine) for more lancinating types of pain. Spasticity can be painful, physiotherapy input with stretches is used but baclofen, tizanidine, dantrolene and occasionally benzodiazepines can be helpful. Botulinum toxin is helpful for focal muscle problems. For severe spasticity, baclofen may given intrathecally. Bladder urgency can often be helped by lifestyle changes, such as less caffeine, but also by anticholinergics or intravesical botulinum toxin in difficult cases. Desmopressin can be used to treat nocturnal incontinence, and an atonic bladder can be managed with a self-intermittent catheterisation before resorting to an indwelling catheter. Regular toileting, fibre, stool softeners or enema can be used for constipation.[45]

Conclusion

Multiple sclerosis is common and can be disabling but there is now much we can do to treat relapses and symptoms and will likely be able to reduce disability accrual in the future.

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