Recent advances in the understanding, diagnosis and management of multiple sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) and a common cause of disability in young adults. This brief review will focus on recent advances in the pathogenesis, diagnosis and management of MS.

PATHOGENESIS

The characteristic lesions of MS consist of perivascular infiltration with T cells and macrophages, primary demyelination (loss of the myelin sheath with preservation of the axon), and astrocytic gliosis. Any part of the CNS may be affected but the optic nerves, spinal cord and periventricular cerebral white matter are particularly involved. Conduction block due to primary demyelination is a major cause of the neurological deficits in MS. It is likely that clinical recovery from attacks of MS is largely due to remyelination by oligodendrocytes; however, this requires further investigation. Some persistent neurological deficits may be due to a failure of remyelination, but axonal loss can also occur in MS[1] and is probably an important cause of persistent disability.

There is increasing evidence that MS is an autoimmune disease.[2,3] All of the pathological features of MS can be produced in laboratory animals by immunisation with myelin antigens and complete Freund's adjuvant. Such immunisation induces the disease, experimental autoimmune encephalomyelitis (EAE), which causes episodes of paralysis and serves as a useful animal model of MS.[4,5] At present it is not clear which CNS antigens are the targets of the immune attack in MS, but myelin proteolipid protein, myelin basic protein and myelin/ oligodendrocyte glycoprotein are potential candidates, as each of these proteins can induce EAE when injected into experimental animals.

Twin studies have indicated that there is a significant genetic susceptibility to MS. The concordance rate of clinical MS in monozygotic twins is 26% compared to 2% in dizygotic twins.[6] A recent study has shown that the familial aggregation of MS is genetically determined and has found no effect of shared environment.[7] Multiple genes appear to be involved in this genetic susceptibility, including class II human leukocyte antigen (HLA) genes. With genomic typing techniques, the HLA association has been specified to be with the DRB1*1501-DQA1*0102-DQB1*0602 (DR15, DQ6, Dw2) haplotype.[8] It is likely that the HLA-based susceptibility to MS is mediated through the effects of HLA molecules on antigen presentation to autoreactive T cells. At present it is unclear what other genes contribute to MS susceptibility. However, there is evidence of an increased occurrence of other autoimmune diseases in MS patients and in their relatives.[3] This suggests that MS occurs on a genetic background that predisposes to autoimmunity, perhaps mediated through immunoregulatory genes.

Environmental factors also appear to have a role in the pathogenesis of MS. The well-known North-South gradients of MS prevalence have been used to support the role for an environmental factor; however, it is possible that genetic factors contribute significantly to these gradients, particularly in Europe and North America, through the selective migration of genetically predisposed individuals. More convincing evidence for an environmental role comes from studies showing that exacerbations of MS can be

TABLE 1
Investigations for Multiple Sclerosis

Investigation	Diagnostic utility	Limitations
CSF immuno-electrophoresis	Oligoclonal IgG bands in CSF, but not in serum, indicate intrathecal B cell immune response consistent with MS.	These bands can be found in many other inflammatory CNS diseases. Such bands are sometimes absent in MS.
CSF cell count	Mononuclear pleocytosis indicates intrathecal T cell immune response consistent with MS.	Mononuclear pleocytosis can be found in many other inflammatory CNS diseases. Cell count may be normal in MS.
MRI brain and spinal cord scans	Exclude other pathology. Can demonstrate lesions typical of MS. Can demonstrate unsuspected additional lesions. Gadolinium enhancement indicates active disease.	MRI findings of MS can be mimicked by other diseases. MRI brain scan may be normal in MS, especially in primary progressive MS.
Evoked potential (visual, auditory, somatosensory, motor) studies	May demonstrate clinically unsuspected lesions.	The changes are non-specific and can be produced by many other CNS diseases.

triggered by viral upper respiratory tract infections.[9,10] It is unclear whether this triggering effect is mediated through general upregulation of the immune system or through the selective activation of autoreactive T cells by molecular mimicry or superantigens. There is no evidence that viral infection of the CNS itself is involved in the pathogenesis of MS.

DIAGNOSIS

The diagnosis of MS is based primarily on the clinical history and physical examination, but magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) examination and evoked potential studies are useful investigations that assist in diagnosis (Table 1). In about two-thirds of cases, the initial clinical course is a relapsing-remitting one, whereas in about one third of cases the course is progressive from onset (primary progressive MS). Relapsing-remitting MS may later follow a progressive course (secondary progressive MS). Common presentations of relapsing-remitting MS include optic neuritis, a brainstem lesion or a partial spinal cord lesion. It is often difficult to distinguish between acute disseminated encephalomyelitis (ADEM) and the first attack of MS. ADEM is an acute autoimmune inflammatory demyelinating disease of the CNS that can be triggered by a viral infection or vaccination and that generally does not recur.[11,12] In some instances one can be relatively sure of the diagnosis of ADEM on the basis of the triggering factor, a fulminant course and extensive lesions, such as a transverse myelitis instead of a partial

spinal cord lesion. However, usually one is uncertain as to whether the diagnosis is ADEM or MS. Although the presence of MRI lesions outside the site of clinical involvement and the presence of oligoclonal IgG bands in the CSF, but not in the serum, increase the likelihood of MS,[13] the diagnosis of MS cannot be made until a further attack occurs in a region of the CNS different from the site of clinical involvement in the first attack. Perhaps the single most important feature in diagnosing inflammatory demyelination of the CNS, whether it be due to ADEM or MS, is the temporal profile of the neurological deficit. Inflammatory demyelinating lesions typically produce symptoms and signs evolving over days or weeks, remaining stable for days or weeks, and resolving over days or weeks. This is in contrast to the more acute evolution of stroke or the slower and more progressive profile of a neoplasm. The presence of a CNS immune response typical of MS can be confirmed by the detection of a mild CSF mononuclear pleocytosis or the presence of oligoclonal IgG bands in the CSF but not the serum. MRI of the brain, spinal cord and optic nerves is useful in excluding other pathology and in demonstrating the typical lesions of MS. Enhancement of a lesion after the intravenous injection of gadolinium reflects breakdown of the blood-brain barrier and is a useful indicator of disease activity.[14] Clinical neurophysiological (evoked potential) studies may demonstrate clinically silent lesions in the visual, auditory, somatosensory or central motor pathways. It is important to note that connective tissue diseases

TABLE 2
Management of Multiple Sclerosis

Clinical problem	Recommended management
Mild relapse of relapsing-remitting MS	Nil
Moderate-severe relapse of relapsing-remitting MS	Intravenous high-dose methylprednisolone infusion
Recent accelerated deterioration in progressive MS	Intravenous high-dose methylprednisolone infusion
Sustained deterioration in severe progressive MS, refractory to intravenous high-dose methylprednisolone	Oral low-dose methotrexate
Troublesome spasticity	Baclofen and/or diazepam
Persistent (non-paroxysmal) neuralgia	Tricyclic antidepressants
Troublesome paroxysmal disturbance (such as paroxysmal dysarthria, tonic seizures or trigeminal neuralgia)	Carbamazepine or phenytoin
Persistent severe fatigue	Amantadine
Bladder dysfunction	Urological consultation

and vasculitides can produce MRI, CSF and evoked potential abnormalities similar to those found in MS. These diseases can be distinguished from MS by the involvement of organs outside the nervous system. The presence of anti-nuclear antibodies, in the absence of other organ involvement, does not militate against the diagnosis of MS, as these antibodies occur at an increased frequency in patients with MS.[15,16]

Primary progressive MS can pose a significant diagnostic challenge. This form of MS commonly presents with progressive spastic paraparesis but may present with other progressive syndromes such as progressive visual loss.[17] Neuroimaging, particularly with MRI, is necessary to exclude compressive lesions of the spinal cord or visual pathways and may also reveal other pathology such as leukodystrophy. It is important to note that the MRI brain scan findings in primary progressive MS tend to be much less prominent than in other forms of MS.[18] Evoked potential studies may be useful in demonstrating clinically silent lesions. The presence of mononuclear pleocytosis or oligoclonal IgG bands in the CSF provides important support for the diagnosis of MS and virtually excludes hereditary spinocere-

bellar ataxias. However, the diagnosis of primary progressive MS cannot be established until there has been progressive neurological deterioration over at least six months and until there is clinical, MRI or neurophysiological evidence of involvement of regions of the CNS not involved at the time of initial presentation.

MANAGEMENT
The prognosis of MS is notoriously difficult to predict. In a minority of patients the disease progresses rapidly over a few years, whereas at the other extreme there is minimal deterioration over decades. Multivariate analysis has shown that the following factors are significantly associated with an adverse outcome in MS: older age at onset; male sex; cerebellar involvement or insidious onset of a motor deficit as first symptom; persisting deficits in the brainstem, cerebellar or cerebral systems; a higher frequency of attacks in the first two years after onset of disease; a short first interattack interval; and higher levels of disability on the Kurtzke disability status scale at two years and five years from onset.[19] The therapy of MS can be subdivided into therapy of the disease process, and symptomatic therapy. Therapy of the disease process can in turn be divided into therapy of the acute attack and prevention of further deterioration. The management of MS is summarised in Table 2.

Therapy of Acute Attack
High-dose intravenous infusion of methylprednisolone (500 mg daily for five days) has been shown to accelerate recovery from attacks of MS.[20] This therapy is indicated for moderate to severe attacks that significantly interfere with the activities of daily living and that do not spontaneously improve within a short period (one to two weeks). At the present time, mild attacks are probably best left untreated. High-dose intravenous methylprednisolone therapy may also result in some improvement in patients with chronic progressive MS.[20] There is no evidence that standard-dose oral corticosteroid therapy has any beneficial effect on MS, and, in fact, there is one report that oral corticosteroid therapy may increase the risk of relapse of optic neuritis.[21]

Prevention of Further Deterioration
Interferon-β
Subcutaneous interferon-β has been shown to reduce the frequency of relapses and to reduce the accumulation of MRI lesions in relapsing-remitting MS.[22,23] However, even after five years of therapy, this agent has not been shown to have

any significant effect on disability,[24] which is the main problem for people with MS. The expense, inconvenience of administration, frequent occurrence of flu-like symptoms and lack of proven effect on disability are major factors limiting the usefulness of interferon-β.

Copolymer 1
Copolymer 1 is a synthetic basic random copolymer of four amino acids and has immunological cross-reactivity with myelin basic protein. As it inhibits EAE, it has been suggested as a possible therapy for MS. A recent study has shown that subcutaneous copolymer 1 reduces the relapse rate and improves disability in relapsing-remitting MS.[25] The effect on relapse rate was less marked in patients with greater disability at the time of entry to the study. The drug was well tolerated. Further studies are required to determine whether the effect on disability is maintained with treatment beyond two years, particularly as copolymer 1 has no significant effect on progressive MS. At present the usefulness of copolymer 1 is limited by its cost, inconvenience of administration and minimal efficacy in severe MS.

Immunosuppressants
Treatment with high-dose intravenous cyclophosphamide plus ACTH has been reported to stabilise or improve progressive MS,[26] although a randomised, placebo-controlled, single-masked trial found that therapy with intravenous cyclophosphamide plus oral prednisone had no such effect.[27] Long-term cyclosporin A therapy has been found to have a modest effect in delaying disease progression in patients with moderately severe progressive MS.[28] However, this therapy has a high incidence of severe adverse effects, particularly renal impairment and hypertension, and its use requires close supervision. As low-dose cyclosporin A therapy converts acute EAE into chronic relapsing EAE, the possibility that cyclosporin A may aggravate MS in some patients needs to be considered.[29] Long-term azathioprine therapy appears to have a small beneficial effect on MS, but the effect is so small that adverse effects preclude its routine use.[30] Cladribine (2-chlorodeoxyadenosine) is a specific antilymphocyte agent that is incorporated into DNA and induces lymphocyte apoptosis. Intravenous cladribine has been reported to result in improvement in patients with chronic progressive MS during a 12 month period of observation.[31] It was generally well tolerated although it caused lymphopenia in all patients and severe but reversible aplastic anaemia in one patient. Further trials are required to determine whether cladribine is safe and effective in the long-term treatment of MS and whether the more convenient subcutaneous route of administration is adequate.

A more promising immunosuppressant drug for the treatment of MS is methotrexate, which is widely used in the treatment of two other chronic autoimmune diseases, namely rheumatoid arthritis and psoriasis. A recent study has shown that low-dose (7.5 mg per week) oral methotrexate reduces progression of disability in chronic progressive MS.[32] This beneficial effect was observed in patients with secondary progressive MS, but too few patients with primary progressive MS were included to assess efficacy in the latter group. This treatment is well tolerated but requires regular monitoring of the full blood count and liver function. Currently, low-dose oral methotrexate appears to be the best therapy for slowing deterioration in chronic progressive MS. At present its use should probably be limited to patients with severe progressive MS not responding satisfactorily to high-dose intravenous methylprednisolone therapy.

Other therapies
Plasmapheresis and intravenous immunoglobulin therapy are beneficial in some autoimmune diseases but their efficacy in MS is unclear and requires further study. Specific immunotherapy, such as oral tolerisation with myelin antigens or vaccination with autoreactive T cells, has been shown to inhibit EAE and is currently being investigated in MS. However, specific immunotherapy in MS is unlikely to be successful until the specific target autoantigens have been determined.

Symptomatic Therapy
The symptomatic therapy of MS is also important and includes the use of baclofen or diazepam for spasticity, tricyclic antidepressants for persistent neuralgic pain, phenytoin or carbamazepine for paroxysmal symptoms, urological consultation for bladder problems and impotence, and physiotherapy and occupational therapy.[33] Amantadine can be useful for treating fatigue, a frequent and major symptom of MS.[34] ∎

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