Primary-progressive multiple sclerosis

David H Miller, Siobhan M Leary

About 10–15% of patients with multiple sclerosis (MS) present with gradually increasing neurological disability, a disorder known as primary-progressive multiple sclerosis (PPMS). Compared with relapse-onset multiple sclerosis, people with PPMS are older at onset and a higher proportion are men. Inflammatory white-matter lesions are less evident but diffuse axonal loss and microglial activation are seen in healthy-looking white matter, in addition to cortical demyelination, and quantitative MRI shows atrophy and intrinsic abnormalities in the grey matter and the white matter. Spinal cord atrophy corresponds to the usual clinical presentation of progressive spastic paraplegia. Although neuroaxonal degeneration seems to underlie PPMS, the pathogenesis and the extent to which immune-mediated mechanisms operate is unclear. MRI of the brain and spinal cord, and examination of the CSF, are important investigations for diagnosis; conventional immunomodulatory therapies, such as interferon beta and glatiramer acetate, are ineffective. Future research should focus on the clarification of the mechanisms of axonal loss, improvements to the design of clinical trials, and the development of effective neuroprotective treatments.

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Department of Neuroinflammation, Institute of Neurology, University College London, London, UK (DH Miller MD, SM Leary MD); **National Hospital for Neurology and Neurosurgery, University College Hospital, London, UK** (SM Leary MD)

Correspondence to:
DH Miller, Department of Neuroinflammation, Institute of Neurology, University College London, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK
d.miller@ion.ucl.ac.uk

Introduction

Multiple sclerosis (MS) is a common, chronic neurological disease of young adults, with a prevalence of between 1 in 500 and 1 in 1500 of the population in Europe, North America, and Australasia. The clinical course is variable, although most patients develop significant locomotor disability 15–30 years after onset. In the past decade, disease-modifying treatments that reduce the frequency of acute relapses and the white-matter lesions seen on MRI have been made available, although their long-term effects are not known. The ability to modify beneficially at least a part of the disease pathology is important to define patient groups that might or might not benefit from therapeutic interventions.

The main clinical subtypes of MS were defined 20 years ago as relapsing-remitting MS (RRMS) and chronic progressive MS. The former is characterised by episodes of acute neurological deterioration (relapses), followed by partial or complete recovery (remission); the latter is characterised by steady progressive deterioration in neurological function over months or years. Although most cases of chronic progressive MS start as RRMS, in some patients there is a steady progression from onset, without relapses. The recognition that there are notable differences in MRI findings in the brain between these two progressive forms of MS[1] preceded the more general use of the terms primary-progressive MS (PPMS) and secondary-progressive MS (SPMS), to distinguish these forms of progressive disease. In 1996, a formal classification of MS clinical subgroups was proposed that included both PPMS and SPMS,[2] and this classification has become widely accepted (panel 1).

The classification of disease subtype—relapsing-remitting, secondary progressive, or primary-progressive—is highly relevant because of differences in prognosis and because disease-modifying treatments are effective only in predominantly relapsing MS. The diagnosis and differential diagnosis of PPMS can be a challenge, with a spectrum of disorders that differ from those considered in the diagnosis of relapse-onset MS. Although most of the major clinical subgroups fall within the framework of a single disease (MS), there is, nevertheless, evidence for differences in their pathology and pathogenic mechanisms. This Review of PPMS will survey recent literature on epidemiology, natural history, genetics, pathology, pathogenesis, and MRI findings, and consider the clinical manifestations, diagnosis, and management of this disorder (table 1).

Epidemiology and natural history

A presentation of PPMS is seen in 10–15% of patients. Although most patients come from regions where MS is common, such as North America and Europe,[3–5] patients with PPMS have also been reported in other parts of the world.[6,7] The age at onset is about 10 years older than that seen in RRMS (mean 40 years *vs* 30 years) but similar to the age of onset of SPMS. RRMS is between two and three times more common in men than women; however, there is no gender predominance in PPMS. A progressive disease course, from onset, is virtually unheard of in children.

Tremlett and co-workers[5] described the natural history of PPMS in a subgroup of 2837 patients from British

***Panel 1*: Definitions of subgroups of multiple sclerosis according to clinical course[2]**

Relapsing-remitting multiple sclerosis
Clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterised by a lack of disease progression.

Primary-progressive multiple sclerosis
Disease progression from onset with occasional plateaus and temporary minor improvements allowed.

Secondary-progressive multiple sclerosis
Initial RR [relapsing remitting] disease course followed by progression with or without occasional relapses, minor remissions, and plateaus.

Progressive-relapsing multiple sclerosis
Progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterised by continuing progression.

	Relapsing-remitting multiple sclerosis	Primary-progressive multiple sclerosis
Prevalence of onset type	85–90%	10–15%
Mean age of onset	30 years	40 years
Female:male ratio	2–3:1	1:1
Presenting syndrome	Optic nerve (25%), brainstem (20%), and spinal cord (45%, sensory >motor)	Spinal cord (80%, motor>>sensory), brainstem, and cerebellum (15%)
Brain lesions on MRI	Moderate	Small
Gadolinium-enhancing lesions	Common	Infrequent
Spinal cord lesions	Often	Usual
CSF oligoclonal bands	Usual (~90%)	Usual (~80%)
Early spinal cord atrophy	No	Yes
Healthy-looking white-matter injury (late)	Mild	Prominent
Cortical demyelination (late)	Mild	Prominent
Response to interferon beta	Yes (fewer relapses)	No (disability not affected)
Response to glatiramer acetate	Yes (fewer relapses)	No (disability not affected)

Table 1: **Features of relapsing-remitting and primary-progressive multiple sclerosis**

Columbia, Canada, who had a definite diagnosis of MS and were followed-up longitudinally: 352 (12·4%) were diagnosed with PPMS; the mean age at disease onset was 40 years; 53% (187) were female; and mean disease duration was 17 years. Much variation was seen in the rate of disability accrual: a quarter had a Kurtzke expanded disability status scale (EDSS) score of 6 (ie, they required assistance to walk) 7·3 years from onset, and a quarter were walking independently 25 years after onset.

In a series of papers that report the natural history of MS in patients from London, Ontario, Kremenchutzky and colleagues[8] describe the disease course of patients with PPMS and SPMS. The researchers found that the rate and character of the progressive phase was similar in both groups. They noted a high prevalence of corticospinal tract dysfunction, and postulated that dying-back axonopathy is a contributory mechanism for PPMS.

A study of 1844 patients in Lyon noted that the age of onset of the progressive phases of PPMS and SPMS were similar (~40 years, on average), and the course of the disorder in both progressive phases was similar: the disability landmarks reached were related to age and independent of previous relapses.[9,10] These data support the notion that the progressive phase of MS falls within a single disease entity, regardless of whether it occurs from onset or after a relapsing-remitting phase.

The investigators of a large, placebo-controlled trial of glatiramer acetate reported on short-term changes in disability.[11] Progression of accumulated disability was defined as a one point increase in the EDSS that was sustained for 3 months in those patients with a lower level of disability (EDSS 3·0–5·0) at baseline, and a 0·5 point increase in the EDSS that was sustained for 3 months in those with a higher baseline disability (EDSS 5·5–6·5). The yearly hazard ratios of progression in the placebo group, overall, were 0·21, 0·22, and 0·31 for the first, second, and third years of the study, respectively. At the first scheduled interim analysis, progression rates in the patients with at least 12 months follow-up were 16·1% in the subgroup with less disability and 19·3% in the subgroup with more disability.

Smoking might be a risk factor for MS. Hernan and co-workers[12] investigated this on the basis of general practice records in a group of patients from the UK. They found a 1·3-times increased risk of developing MS in people who have smoked, compared with controls. Although the number of patients with PPMS was small (n=22), the same trend was seen for all patients with MS. Hernan and co-authors[12] postulate that smoking can increase nitric oxide concentrations in CNS lesions, which, in turn, can accelerate axonal loss and the progression of disability. However, current data with regard to the effects of smoking on PPMS are sparse. Koch and co-workers[13] investigated whether differences in saturated and unsaturated fatty acids might influence disease course in MS. They found no significant differences between the MS and control groups or between MS subgroups and concentrations of saturated and unsaturated fatty acids, omega-3, and omega-6 polyunsaturated fatty acids in erythrocyte membranes.

Genetics

Similar HLA associations have been reported in both PPMS and RRMS, and both subtypes are associated with the DR2 haplotype *DRB1*1501* in the class II region of the MHC on chromosome 6,[14–16] which was recently confirmed in a large multicenter study of 1339 families.[17] Different associations with other HLA antigens have been seen,[14,18] but no consistent profile has been established. No clear associations have been found between haplotype and disease severity, although the authors of a large study of familial MS (two first-degree relatives with MS) reported that familial factors that are more probably genetic than environmental increase the

probability of a progressive clinical course, either from onset or after a phase of relapsing-remitting disease.[19] However, this effect was significant only between siblings, and with a kappa statistic of 0·12, and is a weak predictor at the level of the individual. Other gene associations have been reported in patients with PPMS, but such reports are usually isolated, and any consistent genetic association outside the MHC region has not been reported. Underexpression of the T-cell proliferation gene (*IL7R*) was reported in patients with PPMS,[20] which warrants further investigation. A patient with Pelizaeus–Merchbacher disease, with a novel mutation in *PLP1*, the gene encoding proteolipid protein 1, and who presented in adulthood with the clinical and laboratory phenotype of PPMS[21] highlights the challenges for differential diagnosis.

Pathology and pathogenesis

Revesz and colleagues[22] investigated demyelinated lesions in PPMS and reported that they contained fewer inflammatory cells than the lesions in SPMS. This finding, combined with early MRI studies that showed fewer focal white-matter lesions in PPMS[1], led to the notion that pathological features additional to classic inflammatory, demyelinating, white-matter lesions might be important for the disability in PPMS.

The lesions seen in patients with PPMS can show a loss of oligodendrocytes and, in a small subgroup, a unique pattern of oligodendrocyte degeneration has been reported;[23,24] furthermore, less acute axonal injury was seen in the lesions.[25] Patrikios and colleagues[26] reported extensive remyelination of more than 60% of the total lesion area sampled post mortem in the brains of three of 11 patients with a prior diagnosis of PPMS. This paradoxical finding is unexplained, but the authors did not investigate the spinal cords where, in most patients with PPMS, the functionally relevant pathology is found.

The authors of a recent pathological study reported extensive cortical demyelination and diffuse damage with microglial activation and axonal injury in the healthy-looking white matter of patients with PPMS and SPMS.[27] The investigators also noted in patients with acute MS or RRMS that multifocal and active focal demyelinating white-matter abnormalities were the more prominent features, and they noted little association between focal white-matter lesions and diffuse white-matter injury. They postulated that although focal inflammatory lesions are the main feature of relapse-onset MS, the progressive form of the disease is characterised by a global inflammatory process, with diffuse axonal injury in white matter and cortical demyelination.

Leech and colleagues[28] investigated lesions, healthy-looking white matter, and healthy-looking grey matter in patients with PPMS and SPMS for evidence of leakage at the endothelial tight junctions of the blood–brain barrier. Abnormal tight junctions were most evident in active lesions but were also seen in chronic inactive lesions and healthy-looking grey matter and white matter, which indicates a widespread and persistent leakage of the blood–brain barrier in progressive forms of MS.

The evidence for diffuse pathology, with demyelination and axonal loss but less overt inflammation, is consistent with an antibody-mediated pathogenesis.[29] No significant differences in the concentrations of antibodies to myelin oligodendrocyte glycoprotein were found in the serum or CSF between patients with RRMS and patients with PPMS and other non-inflammatory neurological controls.[30]

In a post-mortem study of the pathology of the spinal cord in patients with MS, the main finding in six patients with a primary progressive course was a mild increase in signal on T2-weighted MRI that was associated with partial demyelination on histology.[31] In another post mortem study, one patient with PPMS had a 45% loss of axons in the cervical and lumbar spinal cord.[32]

There is strong evidence that axonal loss underlies irreversible and progressive disability, which has led to the search for potential biomarkers of axonal damage for use in in-vivo studies. Tau is a microtubule protein that is expressed in axons, and increased tau concentrations in the CSF are seen in patients with either relapse-onset or progressive-onset MS early in the clinical course.[33] Wilczak and co-authors[34] reported an association between the serum concentrations of insulin growth factor-binding protein 3 and rate of disability progression in a group of patients with PPMS, and concluded that insulin growth factor-binding protein 3 might be an endogenous factor that influences the rate of neuroaxonal loss and hence disability.

Differences in immunological characteristics have been reported but no distinct profile has been defined for PPMS.[35] To investigate prospective immunological markers of the subtypes of MS, Furlan and colleagues[36] used multivariate analysis to quantify the concentrations of mRNA for 25 molecules in 198 patients with MS. A combined decrease in CXCR5, CCL5, and CCR3 mRNA concentrations was seen in patients with PPMS compared with patients with RRMS, which might mean that there are fewer inflammatory immunopathological events in the PPMS subgroup. The combinations of molecular abnormalities to identify subgroups might strengthen the case for the analysis of peripheral blood samples, although there is likely to be much variability because of non-disease-related factors in an isolated CNS disorder such as MS.

Abnormalities seen with MRI

Brain

To study MS in vivo, the findings of direct neuropathological observations have been supplemented with the indirect pathological inferences from MRI. The first MRI studies showed smaller lesion loads and a lower frequency of gadolinium-enhancing lesions in PPMS compared with SPMS.[1,37] The differences in inflammation and enhancement are quantitative rather than qualitative;

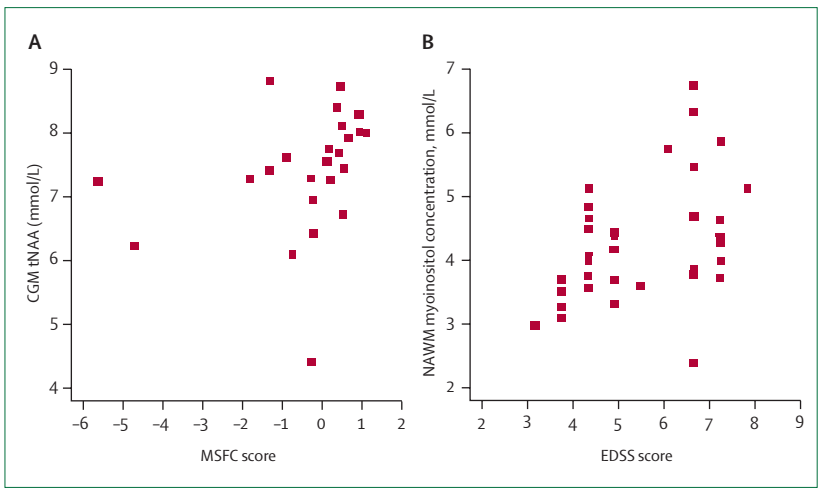

***Figure 1*: MR spectroscopy study of a group of 43 patients with PPMS**
A: Correlation between decreased cortical grey matter (CGM) N-acetyl aspartic acid (NAA) concentrations and decreased clinical function measured on the MS functional composite (MSFC) scale. B: Correlation between increased white matter myoinositol concentration and increased disability measured using the EDSS scale. CGM=cortical grety matter. NAWM=normal-appearing white matter. Reproduced with permission from the American Medical Association.[52]

studies with triple-dose gadolinium show more gadolinium-enhancing lesions in PPMS than single-dose studies.[38] Inflammation is more commonly seen early in the course of the disease: Ingle and co-workers[39] reported gadolinium-enhancing brain lesions in 42% of patients with PPMS whose disease duration was less than 5 years, and these patients had greater disability and brain atrophy.

Quantitative MRI-based techniques show structural abnormalities in the healthy-looking brain tissue of patients with PPMS,[40] although some of the changes are similar to those seen in SPMS.[41] Measurement of the magnetisation transfer ratio shows subtle abnormalities in the healthy-looking white matter and grey matter of patients with PPMS.[42,43] Khaleeli and co-workers[44] followed up 30 patients with early-stage PPMS for 1 year and reported that a lower mean baseline magnetisation transfer ratio in healthy-looking white matter was associated with greater deterioration in EDSS scores and the ability to walk.

Increasing diffusivity was reported over 1 year in the healthy-looking grey matter of patients with PPMS, which suggests that pathological changes accumulate in the grey matter over time.[45] In a 5 year clinical follow-up study of 52 patients with PPMS, baseline EDSS values and grey matter mean diffusivity were independent predictors of clinical deterioration.[46] An increase in diffusion abnormalities has also been seen in the healthy-looking white matter of patients with PPMS.[47]

Manfredonia and colleagues[48] used histogram analysis of T1 relaxation time maps to investigate abnormalities that are seen within 5 years of the onset of symptoms in healthy-looking white matter and grey matter in patients with PPMS. The authors reported evidence for abnormalities in the white matter and grey matter that increased during 2 years of follow-up. Furthermore, the mean and peak height of T1 relaxation time maps in healthy-looking white matter at baseline was predictive of disability, as measured by the MS functional composite scale 2 years later.

Atrophy of both grey matter and white matter takes place in early PPMS, and increases in global atrophy and in grey matter atrophy were detected over 1 year.[49] Regional analysis showed that atrophy was most pronounced in the deep grey-matter.[50] A 5 year follow-up study of 41 patients with PPMS, who had several MRI scans over the study period, showed progressive brain atrophy that tended to be constant within individuals but varied considerably between patients.[51]

Reduced concentrations of N-acetyl aspartate is seen on MR spectroscopic analysis of healthy-looking white matter and grey matter, which indicates neuroaxonal loss or dysfunction because N-acetyl aspartate is contained almost exclusively in neurons. The decrease in cortical grey matter N-acetyl aspartate concentration was associated with clinical impairment (figure 1).[52] Myoinositol is increased in the healthy-looking white matter of patients with PPMS, and the increase is associated with disability (figure 1):[52] myoinositol is expressed in glial cells, and the increase might indicate increased astrocytosis. Brain atrophy and a reduction in concentrations of N-acetyl aspartate in the whole brain were seen in another group of patients with PPMS,[53] although these two measures of neuroaxonal loss were not associated, which suggests that they provide complementary information on the total extent of neuroaxonal damage.

The authors of two studies have investigated cerebral perfusion in the grey matter of patients with PPMS. One group used arterial spin tagging and showed decreased perfusion compared with healthy controls, particularly in deep grey-matter nuclei (figure 2).[54] The other used bolus gadolinium-enhanced MRI and reported decreased cerebral blood flow and blood volume in deep grey-matter, which was associated with the extent of fatigue reported by patients.[55]

The responses to passive and active ankle movements in patients with PPMS have been seen with functional MRI.[56] Increased activity was seen with passive movements in regions that participate in sensorimotor integration, such as the putamen; this probably indicates true functional reorganisation because passive movements induce brain activation only through sensory afferents. There was an inverse association between the functional MRI response and clinical or MRI measures of disease progression in the regions associated with motor control, which is consistent with a loss of distributed activation in patients with more disability.

Spinal cord

Multifocal, T2-hyperintense lesions that are less than one vertebral segment in length and cover only part of the

cross-section of the cord are typical in all subtypes of MS.[57] Diffuse mild hyperintensity is seen on T2-weighted images in about 50% of patients with PPMS,[58] which suggests that many of these patients have a diffuse pathological abnormality.

Cervical cord atrophy is seen in patients with PPMS and is associated with disability.[59] A 5 year follow-up of patients with PPMS reported a significant correlation between the decrease in cord area and the increase in EDSS score (r=0·31).[51] Bieniek and co-workers[60] investigated atrophy in the brain grey matter, brain white matter, upper cervical cord white matter, and the magnetisation transfer ratio in healthy-looking grey matter and white matter in the brains of patients with early RRMS and PPMS. Although diffuse brain abnormalities were seen in both groups, atrophy of the cord was seen only in PPMS. In a multivariate regression analysis, cord atrophy was the only feature seen with MRI that distinguished between the two groups.

Agosta and co-workers[61] applied diffusion tensor imaging in the cervical spinal cord of patients with PPMS and reported a decrease in fractional anisotropy and an increase in diffusivity that was unrelated to the abnormalities of diffusion measured in the brain. Diffusion tensor imaging therefore has the potential to detect diffuse, pathological cord damage.

Clinical presentation and course

Typical presentation

The clinical feature that distinguishes progressive-onset MS from relapsing-onset MS is the time course over which symptoms develop. In relapsing-onset MS, relapses typically develop rapidly, with symptoms worsening over hours to days, and the symptoms take days to weeks to recede. Progressive-onset MS develops much more slowly: functional impairments increase steadily over months to years and—apart from minor fluctuations—do not reverse.

The most common presentation (80% of patients) is progressive spastic paraparesis, mainly in the legs. Loss of motor and sphincter control is more apparent than sensory manifestations, although many patients will have abnormal sensory responses on examination (eg, loss of vibration sense). The main symptoms are impaired mobility, with weakness, stiffness, clumsiness, and dragging of the legs, which is commonly asymmetrical. A common feature is exercise-related fatigable weakness: the further patients walk, the more difficult it becomes, and they might need to rest. Urgency of micturition is common and can be accompanied by urge incontinence, whereas hesitancy occurs less frequently. Erectile dysfunction is common. Constipation can occur, and faecal incontinence is an occasional but distressing symptom. Sensory symptoms can include pins and needles, numbness, and dysaesthesia. Examination shows an asymmetrical spastic paraparesis or quadriparesis, with weakness of the pyramidal-type, hyper-reflexia and spastic increase in tone. Sensory findings, when present, are rarely striking, and a sharp sensory level is not expected. The presence of sensory findings suggests a focal structural lesion that compresses the spinal cord.

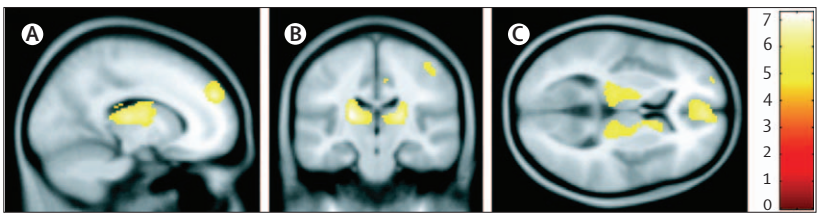

Figure 2: **Regions of perfusion decrease in patients with primary-progressive multiple sclerosis**
A: Sagittal plane. B: Coronal plane. C: Axial plane. Colour bar indicates the T score. Reproduced with permission from the BMJ Publishing Group.[54]

Less common presentations

The second most common presentation is a progressive ataxic syndrome with prominent cerebellar features, which is the main feature in about 15% of patients. Signs of cerebellar or brainstem involvement can also be seen in patients who have a spastic paraplegia, which is evidence of dissemination in space.

A rare presentation is progressive visual failure due to optic neuropathy. Lower motor neuron features are occasionally seen owing to the involvement of the spinal cord grey matter (eg, focal wasting or areflexia); however, such motor findings should prompt the reconsideration of other potential diagnoses.

Cognitive function

Although dementia is rare in MS, some degree of cognitive impairment is common. Cognitive function was investigated in PPMS, and impairments were reported in attention, working memory, verbal memory, spatial reasoning, and verbal fluency.[62] Differences in cognitive function between patients with PPMS and SPMS can be subtle, and cognitive impairment is not fully explained by the inflammatory lesions.[63] Denney and colleagues[64,65] reported a slowing of information processing, although this was less profound in patients with PPMS compared with patients with either RRMS or SPMS. By contrast, Wachowius and colleagues[66] reported slightly more cognitive impairment in PPMS compared with SPMS, with particular abnormalities of verbal learning and fluency. The authors of another study found similar abnormalities when individual neuro-psychological tests were applied to patients with either PPMS or SPMS, although a statistical approach with discriminant analysis helped to differentiate the subgroups.[67] Longitudinal follow-up of 99 patients with PPMS over 2 years showed no change in mean cognitive scores, although a third of patients showed decline on individual test scores.[68]

Overlap with other subgroups of MS

Progressive-relapsing MS, which is characterised by a progressive course from onset with superimposed

relapses, is less common than PPMS. However, a significant minority (28% in one large study[3]) of patients with PPMS will report an apparent relapse at some time during the course of the disease.

Prognosis

The studies of the natural history of MS confirm that progression—compared with relapse and remission—is a poor prognostic feature, and there is considerable variation in the reported rates of progression among individuals and groups with different natural histories.[5,8] The average rate of deterioration is the same for PPMS and SPMS, and long periods of relative stability are seen in some patients. The more favourable spectrum should be recognised when counselling patients, to avoid undue pessimism at the time of diagnosis.

The authors of the Ontario Natural History study[3] reported that a shorter time from onset to an EDSS score of 3 and the involvement of three or more neurological systems at onset were adverse prognostic factors. Tremlett and co-workers[5] reported that neither gender, age, nor mode of onset were prognostic indicators, although the time taken to reach an EDSS score of 6 predicted the time it would take to reach an EDSS score of 8 (wheelchair bound). The authors of a multicentre study of 122 patients with PPMS who had clinical and MRI follow-up over 5 years reported that baseline disease duration, EDSS score, and brain volume were predictive of outcome; so too were changes in T2-weighted lesion volume, cord area, the number of new lesions, and EDSS score throughout the first 2 years.[69] Once the progressive stage of MS is established, the rate of disability accrual does not seem to be influenced by superimposed relapses.[4,9,10]

Investigations and diagnostic criteria

MRI is the most useful investigation in patients with suspected progressive-onset MS. In patients with progressive spastic paraplegia, both spinal cord MRI and brain MRI should be obtained. Lesions that are typical for demyelination are usually seen in both locations; however, when the MRI of the brain is negative, spinal cord lesions are of particular diagnostic value.[70] T2-weighted imaging, including FLAIR images of the brain, is most sensitive for depicting lesions. Although there are commonly fewer lesions in the brains of patients with progressive-onset MS than in patients with RRMS or SPMS, the appearance of the lesions is otherwise typical for demyelination. As in other forms of MS, common locations for lesions are periventricular, juxtacortical, and infratentorial. Patients with a cerebellar form of PPMS have larger brain lesion loads on MRI than those with a primary-progressive spinal cord syndrome.[71]

The CSF contains an increase in IgG or oligoclonal IgG bands, which are not found in the serum of about 80% of patients.[11] Visual evoked potentials in some patients show a delayed but well-formed response that is consistent with demyelination.

***Panel 2*: Differential diagnosis of progressive spastic paraplegia**

Primary-progressive multiple sclerosis

Cord compression
- Cervical spondylosis
- Intrinsic or extrinsic tumour

Hereditary
- Hereditary spastic paraplegia
- Friedreich's ataxia
- Leucodystrophies (adrenomyeloneuropathy, Krabbe's disease)

Metabolic
- B12 deficiency
- Phenylketonuria
- Copper deficiency

Inflammatory
- Neurosarcoidosis
- CNS vasculitis

Infection
- Human T-lymphotrophic virus 1 (HTLV-1)
- Schistosomiasis
- Syphilis
- HIV
- Brucellosis

Degenerative
- Motorneuron disease

Toxic
- Lathyrism
- Nitrous oxide

Vascular
- Dural arteriovenous malformation
- CADASIL

Paraneoplastic

Criteria for the diagnosis of PPMS were proposed several years ago,[72] with three categories of diagnostic certainty: definite, probable, and possible. The presence of oligoclonal bands in the CSF was needed to make a definite diagnosis, and various combinations of brain and cord MRI and visual evoked potential abnormalities were needed to fit within the different levels of diagnostic classification. A definite or probable diagnosis was made in 99% of 156 patients taking part in a multicentre study of the natural history of PPMS.[72] These findings were included in the McDonald 2001 criteria for MS diagnosis[73] but, perhaps because of their complexity, were not received with widespread enthusiasm.

The revised McDonald 2005 criteria for PPMS requires a compatible progressive neurological disorder for at least 1 year and two of the following: (1) nine MRI brain lesions or at least four brain lesions and abnormal visual evoked potentials; (2) at least two MRI spinal cord lesions; and (3) CSF oligoclonal IgG bands or increased IgG index (CSF IgG:serum IgG/CSF albumin:serum albumin), or both.[74] These criteria are simpler to apply in

practice and enable a diagnosis to be made in patients who do not have oligoclonal bands in the CSF. In the PROMiSe trial of the effects of treatment with glatiramer acetate, 78·4% (739) of patients had immunoglobulin abnormalities in the CSF. Although patients without CSF immunoglobulin abnormalities had fewer MRI lesions,[75] a review by a patient eligibility committee concluded that the diagnosis of PPMS was reliable.[11]

Differential diagnosis

The main differential diagnosis is progressive spastic paraplegia (panel 2). The differential diagnosis is broad, and includes consideration of the age of the patient (older adults are more likely to have cervical spondylosis), family history (a positive history might indicate hereditary spastic paraplegia, leukodystrophy, or CADASIL [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy]), and geographical location (human T-cell lymphotropic virus-related myelopathy is confined to certain parts of the world, such as the Caribbean and Latin America).

Progressive ataxic syndromes have different diagnostic spectrums, including hereditary spinocerebellar ataxias, structural abnormalities of the posterior fossa or foramen magnum (including Arnold–Chiari malformation), and paraneoplastic disease.

Management

Supportive management

The provision of accurate information and access to support is an essential part of the management of all types of MS. Information specific to disease type should be supplied; for example, information for patients about PPMS is available from the MS Society. Symptomatic treatments and rehabilitation are the same as those for MS in general and are well documented elsewhere.[76]

Disease-modifying treatment

A short course of high-dose, intravenous methylprednisolone is mainly used to shorten the duration of relapses in MS, although there is no controlled trial evidence that corticosteroids modify the long-term course of PPMS. If subacute deterioration with prominent motor involvement is present, a one-off course of intravenous methylprednisolone is sometimes given empirically (ie, in the absence of a controlled trial). Sudden deterioration after intravenous methylprednisolone was reported in advanced progressive MS.[77]

To date, there is no proven or licensed disease-modifying treatment to slow the course of progressive MS.[78] Two small, single-centre, placebo-controlled trials of interferon beta have been done for PPMS. In one trial, 50 people were studied for 2 years, and the authors reported no beneficial effects of intramuscular interferon beta-1a on the development of disability or brain and spinal cord atrophy seen on MRI, although an increase in the total volume of T2 lesions was mitigated by therapy.[79] In the second trial 73 patients were studied for 2 years. The authors reported a non-significant trend for less sustained disability accumulation (as assessed with the EDSS) in those patients treated with interferon beta-1b versus placebo (28% *vs* 38%) and a significant effect on the MS functional composite score.[80] The treatment group also accumulated fewer T2-hypointense and T1-hypointense lesions but there was no effect on measures of brain or spinal cord atrophy. Interferon beta treatment of RRMS and PPMS is associated with a sustained increase in concentrations of soluble vascular endothelial adhesion molecule-1 in the serum, which suggests a modification of the adhesion molecule cascade.[81]

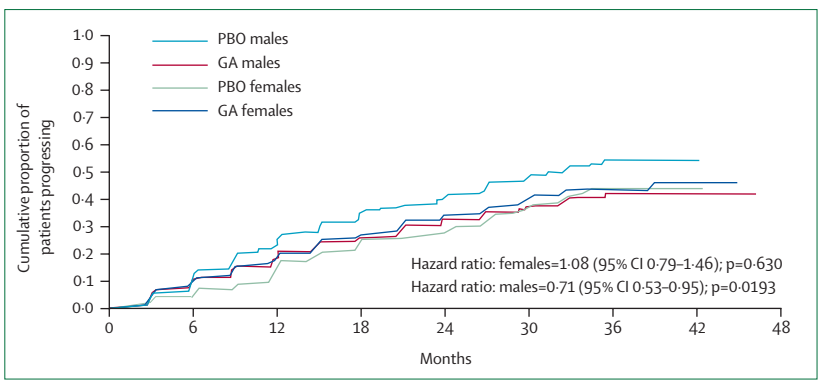

Figure 3: **Increase in the confirmed disability scores in the PROMiSe trial (placebo-controlled trial of glatiramer acetate in PPMS)**
PBO=placebo. GA=glatiramer acetate. Reproduced with permission from John Wiley and sons, Inc.[11]

A large, placebo-controlled, randomly assigned, 3 year trial of glatiramer acetate was done in 943 patients with PPMS.[11] The number of patients who had a sustained increase in disability was lower than expected, which meant that the power of the study to show an effect on disability was less than originally calculated. There was no substantial reduction in the proportion of patients who became disabled in the treatment arm, and the study was stopped on the basis of futility after a 2 year interim analysis. A post-hoc, subgroup analysis showed that the accrual of disability slowed in glatiramer-treated males, possibly because of the higher progression rate of the males in the placebo group (figure 3). The concentration of antibodies to glatiramer acetate were elevated during the treatment period,[82] although there is no evidence that they neutralise the effect of the drug.

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A small, placebo-controlled trial of mitoxantrone was done in patients with PPMS;[83] the preliminary results suggest no clinical benefit, although they have not been reported in detail. Treatment with mitoxantrone was associated with an increase in CD8 T cells over 9 months.[84] Several controlled trials of progressive MS have included patients with PPMS and SPMS. Cladribine had no effect on disability[85] but methotrexate (7·5 mg, once a week) had a small beneficial effect on arm dysfunction,

measured with the nine-hole peg test.[86] Provisional results from a study of intravenous immunoglobulin suggest a favourable effect in PPMS that was not seen in SPMS; however, the final results are still outstanding.[87]

In a baseline crossover trial of riluzole in 16 patients with PPMS who were monitored for 1 year before and during treatment, there was an apparent stabilisation of brain T1-hypointense lesion volume and cervical cord area.[88] A larger placebo-controlled trial is needed to investigate this therapy further.

The results of uncontrolled trials of autologous haematopoetic stem cell transplantation,[89] cyclophosphamide,[90] or perfenidone[91] have shown stabilisation in some patients with PPMS; however, the design of these studies prevents any meaningful interpretation.

Suppression of B-lymphocyte-mediated humoral immunity is another potential immunomodulatory strategy. The results of a preliminary investigation of four patients with PPMS treated with rituximab, an anti-CD20 monoclonal antibody, showed that although the number of B cells was depleted in peripheral blood, there was a temporary and limited effect on B cells in the CSF.[92] A double-blind, placebo-controlled trial of 435 patients with PPMS is underway.[93]

Future research priorities

There is a need for effective disease-modifying treatments for progressive forms of MS; the current focus is on strategies for neuroprotection, including sodium channel blockers, glutamate antagonists, and cannabinoids. The UK Medical Research Council is sponsoring a 3 year, placebo-controlled, phase III trial of oral cannabinoids for progressive MS, with disability as the primary outcome measure. Although there is less inflammation than is seen in RRMS, it is still possible that inflammatory or immunological pathogenic mechanisms contribute to the ongoing tissue damage and disability; therefore, the investigation of therapies directed at such inflammatory mechanisms is worthwhile. Strategies to promote remyelination or axonal regeneration should also be investigated, and current interest is focused on autologous stem cell transplantation.

Trial design is important. Studies that have disability measured with the EDSS as an endpoint typically need several hundred patients to be followed up for 2 years or longer.[94] More sensitive and reproducible clinical scales have been sought, such as the MS functional composite scale[95] and the MS impact scale;[96] however, no alternative scale has superseded the EDSS. MRI of neuroaxonal loss is used to support clinical outcome measures in trials of neuroprotection. Sensitive and reproducible registration-based methods enable small amounts of brain atrophy to be detected over 1 year or less. The sample sizes for proof-of-concept trials that use brain atrophy as a primary outcome measure might be less than those required for a disability endpoint.[97] Although spinal cord atrophy might seem a particularly appropriate outcome measure for trials of PPMS, it is a challenge to detect small changes in a small structure, and the sample sizes needed to show therapeutic effects are not known.

Despite an increase in interest in PPMS in recent years, the pathophysiology of this disorder is still poorly understood. Ultimately, the research priority is to better understand the mechanisms of tissue damage and axonal loss in PPMS before rational new therapeutic approaches can be made possible.

Search strategy and selection criteria

Material for this Review was selected by a PubMed search of English language publications from 2004 until early 2007 with the term "primary progressive multiple sclerosis". Abstracts were reviewed, and when novel or interesting findings were reported, the full article was reviewed.

Contributors

DHM drafted the first version of this Review, and SML made constructive comments and revisions.

Conflicts of interest

DHM has received honoraria from UCB Pharma, Schering, Biogen Idec, GSK, and Wyeth for consulting services, speaking, and serving on a scientific advisory board. He has received reimbursement for work as co-chief Editor of *Journal of Neurology* and research grant support from the MS Society of Great Britain and Northern Ireland, Wellcome Trust, Medical Research Council UK, Biogen Idec, GlaxoSmithKline, and Schering. SML has received funding from Biogen, Teva, and Schering to attend academic meetings.

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