REVIEW ARTICLE

Primary progressive multiple sclerosis

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Summary

Patients with multiple sclerosis who develop progressive disability from onset without relapses or remissions pose difficulties in diagnosis, monitoring of disease activity and treatment. There is a need to define the diagnostic criteria for this group more precisely and, in particular, to describe a comprehensive battery of investigations to exclude other conditions. The mechanisms underlying the development of disability and the role of MRI in monitoring disease activity in this clinical subgroup require elucidation, particularly in view of the lack of change on conventional imaging in the presence of continuing clinical deterioration. The prognosis is poor and there are currently no treatment trials for this form of the disease.

Keywords: multiple sclerosis; primary progressive; diagnosis

Abbreviation: HLA = human lymphocyte antigen

Introduction

Multiple sclerosis is classically characterized by a relapsing/remitting course due to lesions in many parts of the CNS, with the majority of patients developing progressive disability at some stage. There is, however, a small group of patients in whom the course of the illness is progressive from onset and whose condition tends to involve predominantly one part of the CNS, most often the spinal cord. This atypical clinical course frequently causes diagnostic difficulty, and clarity has not been well served by the array of labels which has been applied to it or by the unsatisfactory way it has been described in Poser's Criteria (Poser *et al.*, 1983).

It is particularly important now to attempt to clarify the situation for a number of reasons. (i) There is considerable evidence to suggest that, quite apart from the unusual clinical course of the disease it may differ from relapsing/remitting disease both immunologically and pathologically. Indeed the question arises as to whether this may be a separate disease entity or part of the broad spectrum of multiple sclerosis. (ii) With the advent of MRI, there is the potential to increase our understanding of the mechanisms of disability and, in particular, to evaluate the respective contribution of failure to recover after relapse and insidious progression; studying the group which is characterized by insidious progression only may help to resolve this important question. (iii) There is now the opportunity to consider a therapeutic trial for these patients, who have never been studied specifically, and who tend to be excluded because of their atypical clinical and MRI activity.

The issues of definition, diagnosis, frequency, clinical characteristics, immunological abnormalities, pathology and

Table 1 *Consensus definitions of subgroups of multiple sclerosis**

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

Secondary progressive multiple sclerosis
Initial relapsing/remitting disease course followed by progression with or without occasional relapses, minor remissions or plateaus.

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

Progressive-relapsing multiple sclerosis
Progressive disease from onset, with clear acute relapses, with or without full recovery.

*From Lublin and Reingold, 1996.

treatment, in this relatively rare but important subpopulation of multiple sclerosis patients, are addressed in this review.

Definition

One of the major confounding factors has been the variety of terms applied to these patients, the most common of which has been 'chronic progressive multiple sclerosis'. This term has, in turn, had a number of definitions, some of which included patients who had relapses. In a recent international survey, Lublin and Reingold (1996) found that there was no common agreement in relation to the term 'chronic progressive multiple sclerosis' and suggested that it should be abandoned. The term 'primary progressive multiple sclerosis' initially used in the Scandinavian and Italian literature has now become well established with a clear and consistent definition (Lublin and Reingold, 1996). There is, however, a further group of patients whose disease is essentially progressive from onset, but who have had a single relapse and/or remission. This sometimes occurs many years before the onset of the progressive phase, but may occur immediately prior to progressive deterioration or on a single occasion during the progressive phase. This group could be usefully labelled as 'transitional' because their clinical activity lies between primary and secondary progressive multiple sclerosis, but it appears more similar to the former (Filippi *et al.*, 1994). In their recent paper Reingold and Lublin (1996) describe patients who are initially progressive but subsequently have definite relapses from which they may or may not make a complete recovery as 'progressive-relapsing' (*see* Table 1).

While optimized nomenclature regarding disease classification will be of great value in future studies, there remains the concern that patients may move from one disease group to another during their lifetime as described by Goodkin *et al.* (1989) who quoted a figure of ≥40%. In their study the old nomenclature was used and it is not clear how many patients with primary progressive multiple sclerosis were involved.

Diagnostic criteria

The Poser Committee (Poser *et al.*, 1983) accepted the established view that to make a definite diagnosis of multiple

sclerosis it is necessary to demonstrate multiplicity of lesions in time and space. The Poser criteria differ from others in incorporating the results of investigations, including evoked potentials, MRI and CSF analysis, in particular to look for evidence of intrathecal synthesis of IgG.

Primary progressive multiple sclerosis was not discussed as such by Poser *et al.* (1983), but they did require, in patients with a progressive course from onset, that evidence of new lesions had to be obtained before a case could be classified, either as clinically definite multiple sclerosis or (when there was evidence of intrathecal IgG synthesis) as laboratory-supported definite multiple sclerosis.

In this group of patients, multiplicity of lesions may be demonstrated by evoked potentials or MRI. Two points in relation to the latter deserve emphasis. First, cerebral MRI may be normal in primary progressive multiple sclerosis when there are multiple lesions visible in the spinal cord (Thorpe *et al.*, 1996). Secondly, many patients with primary progressive syndromes suggestive of multiple sclerosis are in the older age group, in which non-specific abnormalities in the cerebral hemispheres is common. Again spinal MRI may be invaluable because incidental white-matter abnormalities are rare in healthy individuals at all ages (Kidd *et al.*, 1993).

The demonstration that new lesions have developed over time may be achieved by clinical examination or, more often, by investigation. For example, an evoked potential which is normal at presentation but delayed at follow-up provides useful evidence. Serial MRI may also be useful, but it may need to include the spinal cord because of the infrequency of lesions in the cerebral hemispheres.

A further important issue is the duration of symptoms considered necessary before a definite diagnosis should be made. The Poser criteria suggest a minimum of 6 months but, in our view, this is rather a short period of time in which to evaluate the disease course and to ensure that it is exclusively progressive. A period of 2 years is more appropriate, both to demonstrate dissemination and to exclude the occurrence of relapses. In practice, most patients have a history going back several years at initial presentation, though in such instances retrospective clinical information must be treated with some caution.

Table 2 *Differential diagnosis of primary progressive multiple sclerosis*

Diagnosis	Investigation
Compressive lesions	MRI
Systemic disorders, including SLE, Sjogren's syndrome	Angiography, ESR, autoantibodies anti-Ro, anti-La
Sarcoidosis	Calcium, chest X-ray, Kveim Test
CNS infections	Borrelia, brucella, syphilis
Tropical spastic paraparesis	HTLV-1
Anterior horn cell disease	EMG
Subacute combined degeneration	Serum vitamin B_{12}
X-linked adrenoleucomyeloneuropathy	Very long chain fatty acids in serum
Leber's optic neuropathy	Mitochondrial DNA evaluation

ESR = erythrocyte sedimentation rate; HTLV-1 = human T-cell lymphoma virus-1; SLE = systemic lupus erythematosus.

Criteria for excluding other conditions

The other essential component in establishing a diagnosis of multiple sclerosis is the exclusion of other conditions which can produce a similar clinical picture (*see* Table 2). This is of paramount importance in the primary progressive group. In view of the progressive nature of the syndrome, the first requirement is to exclude any compressive pathology. MRI is the investigation of choice, particularly to exclude compression of the spinal cord at the foramen magnum (including Arnold Chiari malformations) or elsewhere. Intrinsic lesions of the cord, such as angiomas, can usually be identified using modern MRI equipment (Thorpe *et al.*, 1994), although arteriography may occasionally be necessary to confirm the diagnosis, and it is, of course, required when therapeutic embolization is planned. Inflammatory cord lesions may result from a wide range of systemic disorders such as systemic lupus erythematosus, primary Sjogrens syndrome (Marzo *et al.*, 1997) and sarcoidosis. Infective causes include borrelia, brucella and syphilis, and in Afro-Caribbean and Japanese patients human T-cell lymphoma virus-1 must be excluded. Motor neuron disease may occasionally cause diagnostic difficulty if there are no lower motor neuron signs (anterior horn cell disease). A detailed family history should be taken to exclude hereditary spastic paraparesis though there may still be some difficulties with sporadic cases. Serum vitamin B_{12} should be measured to exclude subacute combined degeneration of the cord. Rarer causes include X-linked adrenoleucomyeloneuropathy; serum should be checked for very long chain fatty acids, particularly in the event of two male family members being affected (though a family history is not essential). Finally, in male patients presenting with severe visual deterioration Leber's optic neuropathy should be considered. A study of 23 cases with bilateral subacute optic neuropathy of uncertain cause revealed mitochondrial DNA mutations allowing a diagnosis of Leber's optic atrophy in four cases (Morrissey *et al.*, 1995).

Chronic progressive myelopathy

Progressive paraparesis (arising from chronic progressive myelopathy) is the most common presenting symptom of primary progressive multiple sclerosis and it is therefore appropriate to give further consideration to patients with this condition, particularly as a proportion of them may continue to cause diagnostic difficulty, despite comprehensive investigation and lengthy follow-up (Weinshenker *et al.*, 1990). In a study of 72 patients with progressive myelopathy carried out in the pre-MRI era, Paty *et al.* (1979) concluded that 44% had multiple sclerosis when neurophysiology, CT and CSF examination were taken into account. A figure of 85% was found in a study of myelopathy which included MRI (Miska *et al.*, 1987). A study of non-compressive spinal cord syndromes by Miller *et al.* (1987) included 50 patients with a chronic progressive myelopathy; multiple cerebral lesions were found in all 21 (100%) of the patients who were aged ≥50 years and in 18 of the other 29 patients (61%) who were aged <50 years, i.e. in 74% of the whole group of 50 patients. Oligoclonal bands were seen in 38%, delayed visual evoked potentials in 29% and delayed brain auditory evoked potentials in 24%. Intrinsic cervical cord lesions were detected in 61% of patients (19/31). It is, of course, possible that the cerebral MRI abnormalities in some of these patients were not due to demyelination, especially in the older age group where incidental white matter changes due to small vessel disease are commonly found. The increased liklihood of progressive non-compressive myelopathies demonstrating dissemination in space by MRI when compared with acute myelopathies was also stressed by Filippi *et al.* (1990). Multiple abnormalities on cranial MRI were seen in only 20% of acute myelopathies but they were found in 78% of the progressive cases with motor and sensory disturbances.

There is a small group of patients in whom it is not possible to demonstrate dissemination in space even after long periods of follow-up. Weinshenker *et al.* (1990) described a 25-year follow-up of one patient prior to post-mortem when the diagnosis was confirmed. Such patients should not be included in research studies. Furthermore, there are well-documented cases which have evidence of demyelination limited to one anatomical region, e.g. the spinal cord, at post-mortem (Allen *et al.*, 1981). In a recent study of 20 patients with suspected multiple sclerosis and negative brain MRI, 11 had primary progressive disease (Thorpe *et al.*, 1996).

All had MRI abnormalities of the spinal cord, seven out of eight investigated had oligoclonal bands in the CSF and six of 10 had abnormal visual evoked potentials. Occasionally evidence of other pathological processes may be seen in patients with undiagnosed progressive myelopathy such as leucodystrophy (Eldridge *et al.*, 1984) and encephalitis (Yamamoto *et al.*, 1984).

Frequency

Patients with multiple sclerosis whose disease course is progressive from onset and who have no periods of relapse or remission are relatively rare. The precise proportion varies among studies and is probably influenced by the criteria set and the strictness to which they are adhered. In the study of Confavreux *et al.* (1980) of 349 patients (including definite, probable and possible multiple sclerosis) 64 (18%) were progressive from onset while in the study of Minderhoud *et al.* (1988) it was as high as 37%. In the 25-year follow-up study of Runmarker and Andersen (1993), 36 of 308 patients had primary progressive multiple sclerosis (11%). A slightly higher percentage (18%) was quoted in the retrospective component of Weinshenker's Canadian study (Weinshenker *et al.*, 1989). However, when patients were seen from their initial presentation the percentage fell to 7.7%. The effect of data collection (retrospective versus prospective) on the presumed prevalence of primary progressive multiple sclerosis has already been highlighted, particularly in relation to the ease with which an initial relapse may be forgotten with time (Mathews, 1991). An average figure of 10% would suggest that there are ~35 000 patients with primary progressive multiple sclerosis in Europe.

An increase in the incidence of multiple sclerosis has been reported in Western Norway over a 30-year period (Larsen *et al.*,1985) and it has subsequently been suggested that this relates to an increase in relapsing/remitting and secondary progressive multiple sclerosis, but not in the primary progressive type (Midgard *et al.*, 1991). Although this study includes patients with possible multiple sclerosis, and the definition of chronic progressive multiple sclerosis allows superimposed relapses, there is a suggestion that the progressive and relapsing forms of multiple sclerosis behave in different ways.

Clinical characteristics

There is a general consensus that patients whose disease is progressive from onset present at a later age than those in the relapsing/remitting group. The mean age of presentation in the Lyon study was 37.3 years (compared with 29.2 years in the relapsing/remitting group of Confavreux *et al.* (1980) and 43.6 years in the probable progressive group in Thompson's study (Thompson *et al.*, 1986). Leibowitz reported that 57% of patients with primary progressive multiple sclerosis were 40 years or over when they presented

initially (Leibowitz *et al.*, 1964), and Weinshenker *et al.* (1989) commented on the increasing incidence with increasing age (75% of those presenting at ⩾50 years had primary progressive multiple sclerosis).

It has been suggested that primary progressive multiple sclerosis may affect a higher proportion of men than in the relapsing/remitting disease group, resulting in an equal male to female sex ratio or even a slight male preponderance. Of the 36 patients in the Runmarker and Andersen (1993) study 23 were male (63%), while in the study of Van Lambalgen *et al.* (1986) 16 of 23 were male (58%). Of 104 patients with primary progressive multiple sclerosis currently being studied at the National Hospital for Neurology and Neurosurgery, 55 (52%) are male (V. Stevenson and A. Thompson, unpublished observations). In contrast, of 65 patients with primary progressive multiple sclerosis in a study from Northern Ireland 68% were female (McDonnell *et al.*, 1996). It has been suggested that this overall lack of female predominance may suggest processes other than inflammatory/immune mediated ones, as most auto-immune conditions tend to affect women more than men.

The most common mode of presentation in primary progressive multiple sclerosis is with a progressive paraparesis rather than with visual and sensory disturbances which are the most frequent initial presentations in relapsing/remitting disease. However, the concomitant presence of slowly evolving sensory and motor symptoms is highly suggestive of multiple sclerosis (Filippi *et al.*, 1990). Other less frequent presentations include progressive visual loss (Ormerod and McDonald, 1984), progressive hemiplegia (Cowan *et al.*, 1990) and progressive cerebellar/brain stem disturbance. Progressive cognitive deficit has been described only rarely; however, cognitive dysfunction is not a prominent feature in this group. Comi *et al.* (1995) have described an incidence of 7% of cognitive deficit cases in primary progressive multiple sclerosis as compared with 53% in patients with secondary progressive multiple sclerosis of similar physical disability. They suggest that this relates to the smaller cerebral MRI lesion load, particularly in a non-periventricular distribution, in this group. In a recent study, the psychological functioning of the two progressive groups was compared; it was found that primary progressive patients appeared to show overall better psychological functioning and were less depressed (Vleugels *et al.*, 1997). The authors suggested that this may relate to patients not having to cope with the unpredictability of relapses, though it could also relate to the relative lack of abnormality on cerebral MRI.

Genetic profile (Compston *et al.*, 1995)

The association between multiple sclerosis and certain human lymphocyte-antigen (HLA) haplotypes has been described since the early seventies (Jersild *et al.*, 1972) and, although there is some inconsistency, a link between an extended haplotype of DR2 (also called DR15), DQw6, at least in the Nordic countries, has been established. Madigand

et al. (1982) suggested that the HLA profile was different in patients whose illness was progressive from onset, from those with relapsing/remitting multiple sclerosis. In a French population, 61 patients with progressive multiple sclerosis (not subdivided) showed increased A1-B8-DR3. Both relapsing and progressive groups also showed increased B7 but only the relapsing group showed increased DR2. The authors postulated the existence of two forms of multiple sclerosis with different HLA profiles. A further study (Van Lambalgen *et al.*, 1986) also suggested differences between 23 patients with progressive multiple sclerosis from onset and 31 with relapsing disease. HLA B8 and B35 were significantly associated with males having progressive multiple sclerosis (16/23) while females with relapsing disease (23/31) had an increased incidence of HLA DR2. A subsequent study in north-east Scotland, which found a high incidence of HLA DR2 in both multiple sclerosis patients and controls but a significant increase in the frequency of DQw1 in the multiple sclerosis population, also looked at progressive (42 patients) and relapsing/remitting (136 patients) subgroups (Francis *et al.*, 1987). It was found that HLA DR2 was more frequent in the relapsing group as was HLA DQw1. In the progressive group HLA DRw6 was over represented while DR4 was under represented. However, this group included patients with both primary and secondary multiple sclerosis.

This issue was taken a step further by a Swedish group, who compared 26 patients with primarily chronic progressive multiple sclerosis and 74 patients with the relapsing/remitting form (including those with secondary progressive multiple sclerosis) using RFLP (restriction fragment length polymorphism) analysis of HLA-DR and DQ genes (Olerup *et al.*, 1989). Both groups were associated with the DRw15 (DR2), DQw6 haplotype, while the progressive group were positively associated with the DQB1 restriction fragment pattern seen in DR4, DQw8, DR7, DQw9 and DRw8 haplotypes and negatively associated with the Taq 1 DQB1 allelic pattern corresponding to the serological specificity DQw7. This group then published a collaborative study with the Norwegian group (Hillert *et al.*, 1992), of 20 primary progressive patients and 42 relapsing/remitting patients from Norway in which the association between primary progressive multiple sclerosis and HLA-DQB1 gene was not verified. However, both studies found the haplotype DRw17, DQw2 to be five times more common in the relapsing/remitting group compared with the primary progressive patients. Recently, Weinshenker *et al.* (1995) presented preliminary evidence that primary progressive disease may be associated with DR4.

In summary, while multiple sclerosis is associated with the haplotype A3-B7-DR2(15)-DQw6, this is predominantly with the relapsing/remitting form of the disease. Any relationship with primary progressive multiple sclerosis is inconsistent. However, the numbers studied are small and a large systematic study is clearly needed to establish whether there is an association between the HLA system and primary progressive multiple sclerosis.

Immunological abnormalities

There is but limited information about the immunological findings in primary progressive multiple sclerosis compared with the other forms of the disease. This is mainly due to the fact that in most published studies patients with chronic progressive multiple sclerosis have not been subdivided into primary or secondary progressive subgroups.

The most consistently reported immunological abnormality in multiple sclerosis as a whole is the increased intrathecal synthesis of IgG that is detected in discrete oligoclonal bands in the CSF. Magalhàes and de Sá (1993) studied 15 patients with primary progressive multiple sclerosis and 30 with relapsing/remitting or secondary progressive multiple sclerosis and found a higher frequency of intrathecal IgG production, but less evidence of blood–brain barrier breakdown in the primary progressive group. In a recent study from Finland it was observed that in patients with multiple sclerosis absence of oligoclonal bands mainly occurs in male patients who had experienced their first symptoms at a relatively late age and who suffered more often from the chronic progressive form of the disease (Pirttila *et al.*, 1995). Given these characteristics, it is likely, though not explicitly stated by the authors, that many of the patients had primary progressive disease. In older studies the prevalence of oligoclonal bands was the same in relapsing/remitting and chronic progressive multiple sclerosis (Thompson *et al.*, 1985; Tourtelotte *et al.*, 1988). Warren and Catz, (1994) studied the relative frequency of auto-antibodies in optic neuritis and multiple sclerosis CSF and their findings suggested two immunologically different forms of multiple sclerosis: a common form with autoantibodies directed against MBP (myelin basic protein) and a less common form associated with anti-PLP (proteolipid protein) antibodies. From the descriptions of the five patients with anti-PLP antibodies, it is likely that three of them had primary progressive multiple sclerosis. Remarkably, none of the three patients had signs of intrathecal IgG-synthesis and all were oligoclonal band negative. Differences between relapsing/remitting and primary progressive multiple sclerosis in the frequency of other autoantibodies, notably anti ganglioside antibodies, have also been reported (Acarin *et al.*, 1996)

Recent evidence suggests that disease activity in multiple sclerosis is determined by the balance between pro- and anti-inflammatory cytokines. Sharief and Hentges (1991) found evidence that intrathecal synthesis of the pro-inflammatory factor TNF-α (tumour necrosis factor-alpha) in CSF correlated with the severity and progression of the disease, though others have not been able to confirm this finding (Peter *et al.*, 1991). Chalon *et al.* (1993) demonstrated that serum and CSF levels of soluble IL-2R (interleukin-2 receptor), which can be used as a measure of *in vivo* immune system activation, were elevated in patients with chronic progressive multiple sclerosis compared with those with relapsing/remitting multiple sclerosis and non-inflammatory neurological disorders. In this study there were no differences

between primary progressive and secondary progressive disease.

A role for adhesion molecules in the pathogenesis of multiple sclerosis, and in particular penetration of inflammatory cells through the blood–brain barrier has recently been suggested. Matsuda *et al.* (1995) showed that both serum and CSF levels of soluble VCAM-1 (vascular cell adhesion molecule-1) were significantly increased in 17 patients during an acute exacerbation as well as in 11 patients with chronic progressive multiple sclerosis (seven of whom had primary progressive disease). The potential immunological differences between primary progressive and other forms of multiple sclerosis have been further highlighted by Giovannoni *et al.* (1996), who showed that serum levels of soluble E-selectin, an endothelial adhesion molecule, are only increased in patients with primary progressive disease. A correlation was found between concentrations of soluble E-selectin and TNF-α in the same study.

Neurophysiology

A small study by de Sá and Malalhaes (1993) of 13 patients with primary progressive disease found that they had fewer abnormalities in visual evoked potentials when compared with 27 relapsing/remitting patients. There was no difference between the two groups in either brainstem auditory evoked potentials or somatosensory evoked potentials. In an earlier study it was suggested that there was a higher incidence of symmetrically delayed visual evoked potentials in patients with primary progressive multiple sclerosis when compared with relapsing/remitting multiple sclerosis (Robinson *et al.*, 1984).

Pathology

There has only been one paper in which investigators sought to compare primary progressive multiple sclerosis with the relapsing form (Revesz *et al.*, 1994). This was a retrospective study of nine cases of multiple sclerosis, four primary and five secondary progressive. A total of 578 lesions was analysed without knowledge of the disease type. Inflammation, as judged by perivascular cuffing and increased cellularity of the parenchyma, was seen in both groups, but was significantly more marked in the patients with secondary progressive disease. Pathological studies have been carried out on other cases of chronic progressive myelopathy (Marshall, 1955) and 'spinal' multiple sclerosis (Allen *et al.*, 1981), but the paucity of the data makes it difficult to interpret in relation to the primary progressive group.

MRI

The first MRI study in which primary progressive multiple sclerosis was investigated specifically was a cross-sectional analysis of T_2-weighted cranial MRI in three clinical subgroups; secondary progressive and benign multiple sclerosis

were also evaluated (Thompson *et al.*, 1990). The surprising finding in this study was that patients with primary progressive multiple sclerosis, despite marked disability, had the least cerebral MRI abnormalities and those that were present tended to be small. This finding has been confirmed by Filippi *et al.* (1994) who also showed that brain abnormalities in 'transitional' progressive multiple sclerosis were of a similar extent to those of primary progressive multiple sclerosis. This obvious discrepancy between disability and abnormality on conventional MRI was a clear indication of the complexity of the relationship between these two parameters. The relative lack of brain lesions is consistent with the relative sparing of cognitive function described earlier.

A subsequent serial study confirmed the paucity of abnormality on cranial MRI in primary progressive multiple sclerosis and also showed that few new lesions occurred over time despite a clear increase in disability (3.3 per patient per year as against 18.2 in the secondary progressive group) (Thompson *et al.*, 1989). A further feature which distinguished primary progressive multiple sclerosis from secondary progressive disease was that few if any of the new lesions showed enhancement with the contrast agent Gd-DTPA (gadolinium–diethylenetriamine penta-acetic acid), 5% as against ~90% in the secondary progressive group (Kappos *et al.*, 1988; Thompson *et al.*, 1989; Thompson *et al.*, 1991). It is possible that there is a greater frequency of more subtle enhancement, since in a group of 10 patients Filippi *et al.* (1995*a*) found four lesions using the standard dose of Gd-DTPA and 13 using triple dose. However, Silver *et al.* (1996) did not observe an increase in the number of lesions identified by increasing the dose, and more data are clearly needed.

These results suggest that primary progressive multiple sclerosis may be a less inflammatory form of multiple sclerosis, an interpretation supported by the pathological studies referred to already. They also raise the issue of the nature of the mechanism underlying progressive disability in these patients, which was clearly only distantly related to the visible abnormalities on cranial MRI. One possible explanation is involvement of the spinal cord. However, subsequent cord imaging with phased array coils failed to demonstrate significantly more focal cord lesions on T_2-weighted images in the primary progressive group than in any other form of multiple sclerosis, either on cross-sectional (Kidd *et al.*, 1993) or serial evaluation (Kidd *et al.*, 1996). This observation is in keeping with the well-established discrepancy between chronic MRI lesions and impairment in the visual system (Miller *et al.*, 1988; Youl *et al.*, 1991). In contrast to these results a new technique for quantifying spinal cord atrophy at the C2 level has shown a good correlation with disability; despite this there is no difference between primary and secondary progressive multiple sclerosis (Losseff *et al.*, 1996*b*) (Table 3). A recent report describes a diffuse change in the cervical cord which is seen predominantly, though not exclusively, in primary progressive multiple sclerosis and which correlates with atrophy

Table 3 *Data from a range of more 'pathologically specific' MR techniques applied to four subgroups of multiple sclerosis*

Parameter	Primary/ progressive	Secondary/ progressive	Relapsing/ remitting	Benign
Cord area (Losseff *et al.*, 1996) at C2 (mm^2)	73.1	61.2	85.6	78.2
Magnetization transfer ratio (Gass *et al.*, 1994)				
NAWM	31.4	30.9	31.0	30.8
Lesion	24.2	23.7	24.8	25.4
Spectroscopy (Davie *et al.*, 1996)				
NAA NAWM (mm^2)	8.78	NA	NA	10.74
NAA lesion (mm^2)	8.83	7.82	8.73	10.5
Transverse magnetization decay curve (Kidd *et al.*, 1997)				
Biexponential lesion (%)	50%	29%	30%	23%
Biexponential large lesion (%)	47%	25%	20%	19%

NA = not available; NAA = *N*-acetyl aspartate; NAWM = normal-appearing white matter. Cord area: significant differences between controls and benign ($P < 0.05$), primary progressive ($P < 0.05$) and secondary progressive ($P < 0.001$)groups. Magnetization transfer ratio: NAWM values for multiple sclerosis subgroups were not significantly different from controls and there were no differences between subgroups. The magnetization transfer ratio of lesions in secondary progressive multiple sclerosis was significantly lower than in the benign group. Spectroscopy: NAA values in normal appearing white matter were significantly reduced in primary progressive multiple sclerosis ($P < 0.025$) but not in the benign groups, compared with controls. The NAA of the lesions was significantly lower than controls in relapsing/remitting multiple sclerosis ($P = 0.0008$), primary progressive multiple sclerosis ($P < 0.002$), secondary progressive multiple sclerosis ($P = 0.0003$) but not in the benign group. Transverse magnetization decay: patients with primary progressive multiple sclerosis had a significantly higher proportion of biexponential lesions than any of the other groups ($P < 0.05$). There was no significant difference between the groups in the frequency of biexponential large lesions.

(Lycklama a Nijeholt *et al.*, 1997). This finding supports the suggestion that disability in primary progressive multiple sclerosis may relate to diffuse pathology in normal appearing white matter. Initial studies quantifying T_1 and T_2 values in normal appearing tissue did not, however, show significant changes in primary progressive multiple sclerosis when compared with patients with secondary progressive multiple sclerosis (Thompson *et al.*, 1991). Recent studies using MR spectroscopy of the brain suggest that patients with primary progressive multiple sclerosis have lower levels of *N*-acetyl aspartate, a marker for axonal dysfunction, in the normal appearing white matter than patients with the benign form of the disease (Davie *et al.*, 1996) (Table 3).

Other MR techniques which give a more accurate indication of tissue destruction, such as magnetization transfer imaging, have been applied to both lesions and normal appearing white matter in the four clinical sub-groups of multiple sclerosis (Gass *et al.*, 1994) (Table 3). The magnetization transfer ratio of lesions was significantly lower in the multiple sclerosis patients than in the controls and correlated inversely with disability. Lower ratios were seen in the two progressive groups when compared with the benign and relapsing/remitting patients, though in this small cohort of patients, this was not significant. In other studies the magnetization transfer ratio of normal appearing white matter in patients with 'chronic' progressive multiple sclerosis (possibly including both primary and secondary progressive patients) was found to be significantly lower than those of patients with relapsing/remitting multiple sclerosis (Dousset *et al.*, 1992), particularly around lesions (Filippi *et al.*, 1995*c*), perhaps indicating an underestimation of disease burden in patients with progressive disease.

Another technique which indicates tissue destruction, and in particular an expanded extracellular space, is T_2 magnetization decay-curve analysis. When applied to lesions in the four clinical sub-groups a higher percentage of lesions (50%) and normal appearing white matter (47%) in the primary progressive group showed biexponential decay compared with the other groups (23–30%) suggesting greater tissue destruction (Kidd *et al.*, 1997) (Table 3).

In summary, while the mechanism of disability in primary progressive multiple sclerosis is not yet fully elucidated the development of new MR techniques, particularly those focusing on intrinsic change in the normal appearing white matter and the assessment of atrophy, suggest that axonal loss plays an important part.

Prognosis

There is general agreement that patients with primary progressive multiple sclerosis have a poor prognosis both in relation to the development of disability over time and mortality. Runmarker and Andersen (1993) showed that the median time to reach 6 on the Disability Status Scale (Kurtzke, 1965) was 6 years in patients with primary progressive multiple sclerosis, which was similar to the time for those who had entered the secondary progressive phase to reach the same level. Similar findings have been demonstrated in many other studies including that of Weinshenker *et al.* (1989).

Within the primary progressive group, few investigators have evaluated variables with the potential to predict outcome. Losseff *et al.* (1996*a*) followed up 22 patients with primary and secondary progressive multiple sclerosis 5 years after a

6-month frequent-MRI study and showed that, while in secondary progressive multiple sclerosis three factors (the number of enhancing lesions, relapse frequency and the development of disability over the 6-month period) predicted outcome, in the primary progressive group only the development of disability was of predictive value.

Treatment

There is a paucity of treatment trials in primary progressive multiple sclerosis, though some preliminary observations with regard to therapeutic options have been made. Although it is generally recognized that a short course of high-dose intravenous methylprednisolone is especially effective for patients with acute relapses, some studies suggest that this treatment can also be beneficial in some patients with chronic progressive disease, though not specifically primary progressive multiple sclerosis (Milligan *et al.*, 1987). Cazzato *et al.* (1995) reported on a double-blind, placebo-controlled, randomized, cross-over trial of high-dose methylprednisolone in patients with primary progressive multiple sclerosis; a statistically significant improvement of EDSS (Expanded Disability Status Scale) score (Kurtzke, 1983) was recorded in methylprednisolone-treated patients. Short-term improvements in patients with primary progressive multiple sclerosis after treatment with high-dose intravenous methylprednisolone were also reported by Frequin *et al.* (1994); however, these authors stressed their observation that even repeated courses did not seem to decrease the long-term clinical deterioration in comparison with the natural course in these patients. In two trials with immunosuppressive drug regimens it was found that patients with primary progressive multiple sclerosis were less likely to respond to the treatment and had poorer prognosis (Weiner *et al.*, 1993; Goodkin *et al.*, 1995).

Discussion

The data presented in this review may be used to address three central questions in relation to primary progressive multiple sclerosis. (i) Is it a different disease from relapsing/remitting and secondary progressive multiple sclerosis? (ii) What has the study of primary progressive multiple sclerosis taught us of the mechanisms of disability in demyelinating disease? (iii) How might treatment strategies be modified to be made more relevant to the primary progressive disease?

Is primary progressive multiple sclerosis a different disease?

The data presented establishes without doubt that patients with primary progressive multiple sclerosis are not only different clinically; there are also pathological and imaging differences between them and the relapsing/remitting groups. The immunological and genetic findings are much less clear cut at present. Are these differences so fundamental as to

suggest a different disease or do they merely represent a question of degree? We suggest that the latter is more likely to be the case, and that there is a broad spectrum of disease activity in multiple sclerosis with the relapsing/remitting group at one end and the primary progressive group at the other. Patients with secondary progressive multiple sclerosis lie between these two groups and it is of interest that patients with secondary progressive disease who progress without having relapses tend to behave in a similar fashion to patients with primary progressive multiple sclerosis with respect to the paucity of MR activity and gadolinium enhancement in the context of increasing disability (Kidd *et al.*, 1996). The concept of a spectrum is supported by the limited pathological data available which demonstrates that inflammation is present in the primary progressive group, albeit to a lesser degree than that seen in patients with the secondary progressive disease (Revesz *et al.*, 1994). A more recent pathological study carried out on a large number of biopsies (44) from patients with early multiple sclerosis has suggested that a broad range of pathological processes may occur, all of which include demyelination, but with variable involvement of oligodendrocytes and axons (Lucchinetti *et al.*, 1996). This work, which was carried out using immunocytochemical markers, indicated at least three pathologically distinct patterns: (i) minor reductions in numbers of oligodendrocytes in regions of active myelin breakdown; (ii) extensive oligodendrocyte destruction and loss within the lesion and occasionally within the periplaque white matter; (iii) demyelination in parallel with destruction of oligodendrocytes, astrocytes and axons. The authors postulated that the primary progressive group may fall into the third pathological pattern.

Recent genetic studies are also of relevance. Intra-familial comparisons of the clinical course have been reported in 166 families containing sibling pairs with multiple sclerosis (Robertson *et al.*, 1996); the authors obtained an overall significant kappa value of 0.150 ($P \leqslant 0.023$) for both primary progressive disease and relapsing/remitting disease, indicating significant intra familial concordance for disease course. However, by inference, there was a considerable number of families (38 in all) in whom one sibling had relapsing/remitting multiple sclerosis while the other had primary progressive disease. This would again support the view that we are dealing with a spectrum of disease activity rather than separate disease entities.

Mechanism of disability in primary progressive multiple sclerosis

Patients with primary progressive multiple sclerosis develop disability as a result of slow, steady deterioration and there is, by definition, no contribution from incomplete recovery after relapse, as seen in the other sub-groups of multiple sclerosis. The mechanisms underlying this slow progression remain uncertain. In the relapsing/remitting forms of multiple

sclerosis there is good evidence that the clinical features of acute relapse are due to conduction block to which both demyeination and inflammation contribute, and that remission depends, to an important extent, on the development of new sodium channels in the demyelinated internodal segments (*see* review by McDonald, 1994). Incomplete recovery from relapse is likely to occur when the lesion is more destructive and there is significant axonal loss. The factors determining axonal loss are unknown, but recurrent inflammation at the same or different levels in the same tract are likely to increase the risk of critical damage. Perhaps similar mechanisms underlie progression in both the primary and secondary progressive forms of the disease. This would imply the presence of chronic persistent inflammation which in primary progressive disease we conjecture to be present from early in the course of the disease, given that there is evidence of axonal loss in the white matter of the cerebral hemispheres at a time when they are otherwise normal on MRI (Davie *et al.*, 1996). The finding of a low level increase in permeability of the blood brain barrier, seen from gadolinium enhancement, even when focal enhancement after standard procedures is not visible, is consistent with such a postulate (Barnes *et al.*, 1991; Filippi *et al.*, 1995*b*).

Future treatment strategies

Treatment strategies are hampered by the lack of a clear understanding of the factors underlying progressive disability. Current approaches are heavily focused on interfering with immune mechanisms, either in a global or more focused way, so as to prevent inflammation and demyelination (Hughes and Sharrack 1996; Thompson and Noseworthy, 1996; Hohlfeld, 1997). The value of such an approach in primary progressive multiple sclerosis is unclear. However, given that inflammation does occur in this condition such an approach may have a role, though, because inflammation is less marked, it may be less effective than in the secondary progressive disease and may require a different therapeutic regimen.

Other treatment modalities warrant consideration. Drugs such as intravenous immunoglobulin which are thought to encourage remyelination in animal models of multiple sclerosis (Rodriguez and Lennon, 1990) may be of benefit and warrant exploratory studies.

Conclusion

It is clear that the lack of information on this less common form of multiple sclerosis needs to be rectified. Because of the low prevalence of primary progressive multiple sclerosis, collecting such information requires a multicentre study. Such a study has now been established in Europe within a scientific and technical network, the European Magnetic Resonance Networks in Multiple Sclerosis (MAGNIMS, EC contract No ERBCHRXCT94–0684) (Stevenson *et al.*, 1996). The programme will enable the study of a minimum of 200 patients serially for 2 years, involving the collection of clinical, cognitive and MRI data over that time. This should form a comprehensive database which would be useful in subsequent therapeutic trials.

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