Primary Progressive Multiple Sclerosis

What term do you use to refer to someone with MS?

MSer (noun) – someone with MS, MSers (plural) – group of people with MS.

To the best of my knowledge the term MSer was first used on the social network site shift.m.s, for young people with MS. A subsequent survey conducted on our multiple sclerosis research blog (www.msr-es.org) amongst people with MS revealed that MSer is the preferred term that people with MS would like to be referred to when addressed either as individuals (MSer) or as a collective group (MSers). MSer was preferred to the terms MSer, which is the abbreviation for MS sufferer, patient, client or person with MS.

Introduction
MS is the commonest non-traumatic disabling disease to affect young adults in the UK. Although current dogma states that it is an organ-specific autoimmune disease of the central nervous system the antigenic targets of the autoimmune attack have yet to be identified. Despite the cause of MS remaining undefined there is an increasing understanding of the causal pathways that underlie the disease. MS is considered by most to be a complex disease due to an interaction between genetic and environmental factors.

Clinical course
The clinical phenotype of MS is heterogeneous and determines the clinical classification of the disease. Approximately 85% of MSers in the UK present with attack onset disease that follows a relapsing-remitting (RRMS) course that in the pre-DMT era became secondary progressive (SPMS) in the majority of MSers (65-80%). Whether this latter figure remains as high as this in the post-DMT era is unknown at present; it is unclear whether or not DMTs delay or in some cases prevent the onset of the secondary progressive phase of MS. A minority of patients (15%) have a progressive course from onset and are referred to as having primary progressive MS (PPMS). The average age of onset of relapsing MS is between 28 and 31 years of age with a median time to the onset of SPMS of approximately 10 years. Interestingly the average age of onset of PPMS coincides with the age of onset of the secondary progressive phase of ~38-40 years of age. Importantly, the clinical courses of MS in the SP and PP phases are indistinguishable. When followed longitudinally anything from 5-25% of PPMSers go on to have superimposed relapses and are referred to as having progressive-relapsing MS (PRMS). Often MSers presenting with a PPMS-type course are found on detailed enquiry to have had a prior sentinel event compatible with a demyelinating attack; this typically occurs decades before the onset of disease progression. These MSers have been referred to in the past as having transitional MS; however, the current Lublin and Reingold classification categorises these MSers as having SPMS. Why bother with a detailed clinical classification? It turns out that relapses, and the presence of gadolinium(Gd)-enhancing lesions on MRI, predict a therapeutic

Figure 1: Although MS is a clinically heterogeneous disease it can be viewed as an inflammatory neurodegenerative disease with the clinical spectrum or phenotype determined by the presence or absence of focal inflammation, similar to that which occurs in infectious diseases, e.g. leprosy. The underlying neurodegenerative component of the disease may or may not be ongoing but it is modified by superimposed focal inflammatory events. The focal inflammation may be an appropriate host response directed at an unidentified aetiological agent or an inappropriate autoimmune response. These focal inflammatory events are responsible for clinical attacks and MRI disease activity. Although damaging in itself the focal inflammation provides the biological substrate in the form of trophic and growth factors which promote repair and clinical recovery. Inhibiting the focal inflammatory events, e.g. with generalised immunosuppression, would reduce the relapse rate and MRI activity and remove the important trophic and growth factor support provided by the inflammatory infiltrates, but it may not affect the underlying primary neurodegenerative processes. This strategy would simply convert relapsing remitting disease into non-relapsing progressive disease (Adapted from *)

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response to currently licensed disease-modifying therapies, or more broadly anti-inflammatory drugs. MSers with relapses and/or focal Gd-enhancing MRI activity indicative of focal inflammation respond to DMTs and this probably applies to PPMsers.  

**Differential diagnosis**

The majority of PPMsers present with a progressive spastic paraparesis. However, several other well-defined primary progressive phenotypes have been described including a progressive cerebellar syndrome, progressive optic atrophy and progressive hemispheric or well-circumscribed areas of focal inflammation, being referred to as lepromatous MS and Sjögren’s myelopathy. Sjögren’s myelopathy is not a well-defined clinicopathological entity and may simply represent an association between Sjögren’s syndrome and PPMs.  

**Pathogenesis**

Is PPM a different disease to relapse onset disease? This is unlikely for several reasons. Firstly, PPMsers are as likely to be positive for major at risk HLA-DRB1 *1501 as MSers with relapse-onset disease. Secondly, in sibling pairs concordant for MS only 50% are concordant for clinical course (see Table 1). If RR and PPM were different diseases you would expect the disease course to be concordant between siblings. Finally, pathological studies have not been able to differentiate relapse-onset from a primary progressive MS. Although there are a smattering of publications suggesting quantitative immunological differences between PPMs and relapse-onset MS; however, none of the findings are robust enough to make definitive claims. I therefore believe that PPMs and relapse-onset disease are part of the same spectrum and what determines whether or not someone has relapses depends on quantitative differences in the type of inflammatory response that occurs within the central nervous system in response to whatever is causing or triggering the disease. I have previously proposed that the MS spectrum is not dissimilar to what is seen with regard to the clinical course or phenotype in leprosy[11], with relapsing MS, characterised by well circumscribed areas of focal inflammation, being referred to as tuberculoid MS and PPMs, with more low grade chronic inflammation, being referred to as lepromatous MS and a spectrum between them (Figure 1). To test this hypothesis the inciting antigens, be they autoimmune or not, need to be defined.  

**Epidemiology of PPMs**

The epidemiology of PPMs is not dissimilar to that of relapse-onset disease with the exception that PPMs is very rare in children, occurs more frequently in males and its incidence seems to be relatively static. The female to male ratio is generally 1:1 with regard to PPMs and 2 or even 3:1 for relapse onset disease. The increasing female preponderance of MS, as seen by changes in the sex ratio, seems to be driven by relapse-onset disease, with the incidence of PPMs remaining relatively constant.  

**Diagnostic criteria**

PPMs is diagnosed using the same principles as relapse-onset disease; you have to demonstrate dissemination in time and space and exclude other potential causes. The original McDonald diagnostic criteria required an abnormal or positive CSF examination, as an absolute requirement, to make a diagnosis of PPM[9]; a positive CSF was defined as intrathecal oligoclonal IgG bands and/or a raised IgG index. These criteria were subsequently changed so that a diagnosis of PPM could be made with a normal CSF examination (Table 2). These changes were prompted by finding that 189/938 (20%) subjects in the glatiramer acetate in PPMs study (PROMiSe study) had a normal CSF study[10]. The PROMiSe study was subsequently terminated early due to a lack of efficacy; interestingly in this study the CSF negative group had a more benign course that the CSF positive cohort (Jerry Wolinsky, personal communication). This would imply that CSF negative PPMs is not the same disease as CSF positive PPMs and is a strong argument for reinstating the original McDonald criteria for PPMs. In fact, two contemporary clinical trials in PPMs require an abnormal CSF as an inclusion criteria[11,12] which is a vote of no confidence for the current criteria.  

**Treatment**

Unfortunately no clinical trials of licensed MS DMTs have shown an impact on the course of PPMs; both interferon beta[13,14] and glatiramer acetate[15] trials have been negative. Recently however, during the five-year period without treatment after termination of the two-year clinical trial of interferon beta-1b for the treatment of PPMs[16], the interferon beta-1b group had better 9-hole-peg-test, word list generation test scores and magnetisation transfer ratios in the normal-appearing white matter than subjects treated with placebo. The placebo group also showed a greater decrease in brain volume over the seven years of observation than the actively treated subjects. These observations led the investigators to suggest that drug-induced changes in the phase 2 rituximab in PPMs study[17] of PPMs, rituximab is a chimeric monoclonal antibody and ocrelizumab a humanised monoclonal antibody that both deplete B-cells by targeting CD20 on the surface of B cells. The ocrelizumab (anti-CD20) study was a follow-on of the phase 2 rituximab in PPMs study[18]; this was a 96 week study that randomised 439 PPMsers, in a 2:1 ratio, to receive either two 1,000 mg intravenous doses of rituximab or placebo infusions every 24 weeks. Although there were differences in time to confirmed disability progression on the EDSS between rituximab and placebo, subgroup analysis showed that the time to confirmed disability progression was delayed in rituximab-treated PPMsers less than 51 years of age, in those with Gd-enhancing lesions on MRI and in those aged less than 51 years with

### Table 1: Concordance rates for disease course within siblings (adapted from[9])

<table>
<thead>
<tr>
<th>Disease course</th>
<th>Frequency</th>
<th>Dichotomised disease course</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR vs. RR</td>
<td>84</td>
<td>RR* vs. RR</td>
<td>19.7</td>
</tr>
<tr>
<td>RR vs. RRSP</td>
<td>68.3</td>
<td>RR* vs. RR</td>
<td>19.7</td>
</tr>
<tr>
<td>RR vs. PP</td>
<td>33.7</td>
<td>PP vs. PP</td>
<td>97</td>
</tr>
<tr>
<td>RRSP vs. RRSP</td>
<td>39.3</td>
<td>RR* vs. RR</td>
<td>19.7</td>
</tr>
<tr>
<td>RRSP vs. PP</td>
<td>27</td>
<td>PP vs. PP</td>
<td>97</td>
</tr>
<tr>
<td>PP vs. PP</td>
<td>9.7</td>
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RR = relapsing remitting, RRSP = secondary progressive, PP = primary progressive

### Table 2. PPMs may be diagnosed in subjects with (adapted from[9]):

1. One year of disease progression (retrospectively or prospectively determined)
2. Plus 2 of the 3 following criteria:
   A. Evidence for dissemination in space in the brain based on ≥1 T2b lesions in at least one area characteristic for MS (periventricular, juxtacortical, or infratentorial)
   B. Evidence for dissemination in space in the spinal cord based on ≥2 T2b lesions in the cord
   C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

*If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the Criteria.
*Gadolinium enhancement of lesions is not required.
PMPs are subject to a similar array of symptoms that arise from MSers, though PMPs experience a more aggressive course of disease, typically progressive spastic paraparesis with increasing walking difficulties due to weakness and spasticity, sphincter involvement and myelopathic pain. There are recent developments regarding symptomatic treatments you should be aware of including the licensing of an oromucosal spray containing a fixed ratio of the cannabinoids, tetrahydrocannabinol and cannabidiol, for treating MS-related spasticity\(^2\) and lamotrigine, a slow-release formulation of lamotrigine, to improve walking speed in MSers.\(^28\) Both these drugs have yet to be reviewed by NICE, therefore their availability for PMPs under the NHS is limited at present.

**Conclusion**

Although PPMs is relatively uncommon it remains a significant clinical problem both diagnostically and therapeutically. PPMs is almost certainly part of the MS spectrum and there is no clinicopathological evidence to support PPMs as being a separate disease. Unfortunately, there are no licensed DMTs that are particularly prone to spastic cord disease. Despite this, there is some emerging evidence that PPMs may respond to immunomodulatory therapies. Two large phase 3 trials are currently underway to test this hypothesis.

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**References**


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**Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Teva Pharmaceuticals UK Ltd on telephone number: 01256 719768**

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**References**


By blocking the breakdown of natural dopamine, Azilect monotherapy enhances natural levels in the brain, helping you to hold on to what you've got.