Multiple Sclerosis Phenotypes as a Continuum
The Role of Neurologic Reserve

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Abstract

Purpose of Review
This review presents the hypothesis that loss of neurologic reserve explains onset of progressive multiple sclerosis (PrMS).

Recent Findings
Evidence supporting the separate classification of PrMS and relapsing multiple sclerosis (RMS) is limited and does not explain PrMS or the response of these patients to therapy.

Summary
We argue that multiple sclerosis (MS) progresses along a continuum from RMS to PrMS, with differing levels of neurologic reserve accounting for phenotypic differences. In early MS, inflammation causes brain atrophy with symptoms buffered by neurologic reserve. As brain loss from normal aging and MS continues, reserve is depleted and effects of subclinical MS disease activity and aging are unmasked, manifesting as PrMS. Most therapies show limited benefit in PrMS; patients are older, have fewer inflammatory events, and the effects of aging cause continued loss of neurologic function, even if inflammation is terminated. Loss of neurologic reserve means patients with PrMS cannot recover function, unlike patients with RMS.

Multiple sclerosis (MS) involves inflammatory processes (believed to be mediated by lymphocytes and astrocytes) that ultimately lead to oligodendrocyte and neuronal loss, as illustrated in figure 1.1-3,5-7 However, neuronal loss (evidenced by brain volume loss) is increasingly acknowledged as the primary driver of neurologic disability in patients with MS and correlates with declines in motor, cognitive, and sensory functions, as assessed by the Expanded Disability Status Scale.4 The first attempt to differentiate MS types was done by international expert consensus and was based on common clinical courses of the disease.3,3 This classification was revised in 2013 by Lublin et al.3 as our understanding of MS increased owing to new insights into clinical relapse rate and imaging data (table 1). Briefly, this update removed progressive-relapsing MS (PRMS), introduced clinically isolated syndrome (CIS), and the concept of active and nonactive MS subtypes to all stratifications.5,6,7 In addition, the terms “worsening” and “disease progression” were differentiated, the former to describe advancing symptoms for any reason and the latter reserved specifically for “true progression” rather than relapse.5,6,7

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Figure 1  Inflammatory Activation in Early MS Leads to Astrocyte Activation, Demyelination, and Neuronal Destruction

(A) The dura mater and subarachnoid space of the brain are well connected to the circulation, filled with blood vessels and lymphatic vessels across which immune cells, such as B and T lymphocytes, can enter and exit the CNS. (B) Autoreactive B cells and T cells mature in the lymph nodes, including the deep cervical lymph nodes, and enter the circulation, where (C) these cells cross the blood-brain barrier and enter the CNS. Effector functions of autoreactive B cells include antibody and cytokine production, and antigen presentation to T cells, which further drives CNS inflammation. The proinflammatory cytokines released by these cells drive the activation of CNS resident cells, including astrocytes. The inflammatory processes mediated by activated astrocytes include the release of TNF-α, production of reactive oxygen species including NO (via iNOS) and other toxic intermediates, leading to oligodendrocyte damage and apoptosis, neuronal/axonal damage, and the loss of astrocytes themselves. Oligodendrocyte damage may be compounded by the fact that some patients with MS can be predisposed to factors that inhibit oligodendrocyte maturation, and loss of normal astrocyte function may also affect the blood-brain barrier, microglial activation, and neuronal damage. Indeed, repair in lesions is accompanied not only by regeneration of oligodendrocytes but the reappearance and maturation of astrocytes. Of interest, the role of astrocytes was elucidated by studies with the S1PRm fingolimod. S1PRms are also thought to be potentially neuroprotective in the CNS through their direct effects on astrocytes, as well as neurons and oligodendrocytes. Autoreactive B cells are able to leave the CNS, crossing the blood-brain barrier by draining through the deep cervical lymph nodes and on into the peripheral lymphatic system, where further rounds of maturation and clonal expansion can occur before repopulating the CNS and driving pathologic process further. INOS = inducible nitric oxide synthase; NO = nitric oxide; S1PRm = sphingosine-1 phosphate receptor modulator; TNF = tumor necrosis factor.
Although the revised Lublin criteria were devised to help to diagnose progressive forms of MS and aimed to distinguish between clinical phenotypes, in our opinion some of the definitions are difficult to apply consistently in clinical practice, resulting in a lack of consensus on this method of differentiation. Furthermore, the phenotype definitions do not address a number of issues: most MS-related CNS inflammation occurs at the onset of MS; over 80% of new brain MRI lesion formation detected by 0.6 T MRI is subclinical; in patients with radiologically isolated syndrome (RIS), thalamic atrophy (neuronal loss or neurodegeneration) has been identified; and MS-related brain atrophy is already present at the CIS stage of MS. It should also be remembered that, after the age of 30–40 years, humans lose neurons at an increasing rate because of aging, a process which also consumes neurologic reserve. Once neurologic reserve is exhausted, aging will also contribute to slowly progressive neurologic disability.

As our understanding of the biology of MS has increased, it has become apparent that there are no confirmed genetic or immunologic differences between relapsing forms and progressive forms of MS, and that the reported pathologic and radiographic differences between primary and secondary progressive MS subtypes and between progressive and relapsing disease are quantitative rather than qualitative, supporting the view that these apparent subtypes are part of a spectrum of disease rather than different biological entities. What, then, causes the onset of progressive disability in patients with MS? We propose that applying the concept of brain or neurologic reserve (figure 2A) may help to address this question.

### Is There Evidence That Progressive and Relapsing MS Are Distinct Conditions?

#### Diagnostic Evidence

To date, no diagnostic tests have been discovered that can identify a patient with progressive vs relapsing disease. There may be some quantitative differences in markers of disease that correlate with and could possibly predict progressive disease; however, there is a lack of data to support the view that it is possible to distinguish the 2 states by genetic, immunologic, pathologic, or radiographic findings.

#### Are There Genetic Differences Between MS Phenotypes?

There is limited evidence to suggest that there are genetic differences between progressive and relapsing MS. The human leukocyte antigen (HLA) class II region has been identified as having a strong influence on the susceptibility to MS. As associations have been reported between genes in this region and both progressive and relapsing forms of MS, suggesting that HLA-related mechanisms contribute to both phenotypes. Furthermore, 2 large studies in patients with MS could not find an association between disease progression and various non-HLA disease-susceptibility genes.

Further evidence that there is no genetic difference between MS phenotypes comes from studies within families, in which the chance of having progressive disease has been shown to be the same as in the general population. A study of a family with 15 members affected with MS showed that the clinical characteristics of the affected individuals were indistinguishable from those seen in sporadic MS, and the frequency of primary progressive MS (PPMS) was approximately 13%, which is the same as in the overall population.

#### Are There Pathologic/Radiographic Differences Between MS Phenotypes?

There are no qualitative differences in brain pathology between relapsing and progressive forms of MS (table 2). Ultrahigh field MRI analysis of gray and white matter lesions demonstrated that lesion morphology does not differ in PPMS and relapsing-remitting MS (RRMS). Age-adjusted analyses of gadolinium-enhancing (Gd+) T1 lesion load and normalized total brain, gray, and white matter volumes showed no differences between RRMS and secondary progressive MS (SPMS). Likewise, no significant

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**Table 1** Phenotype Descriptions for RRMS and PrMS

| RRMS | MR evidence of dissemination in space, as well as gadolinium-enhancing and nonenhancing T2 lesions on a single MRI scan and/or a subsequent event |
|------|-----------------------------------------------------------------------------------------------------------------------------------|
| CIS  | Active* or Not active                                                                                                             |
| PPMS | Progressive accumulation of disability from onset with progression or progression without progression                            |
| SPMS | Progressive disease                                                                                                               |
| PrMS | Active, with progression or Not active, with progression                                                                            |
|     | Progression after initial relapsing course                                                                                         |

**Abbreviations:** CIS = clinically isolated syndrome; MS = multiple sclerosis; PPMS = primary progressive MS; PrMS = progressive MS; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.

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* Clinical relapses and/or MRI activity (gadolinium-enhancing MRI lesions or new/enlarged T2 lesions) assessed at least annually.

* Measured by clinical evaluation at least once yearly.
differences were found in MRI measures of lesion activity or brain volume loss between PPMS and SPMS. Rates of annualized brain volume change were not statistically different in patients with PPMS, RRMS, or SPMS when adjusted for baseline normalized brain volume. Indeed, what differences there appeared to be in relapsing and progressive MS can be explained by the longer disease duration that characterizes progressive forms of MS. Notably, 2 prominent neuropathologists specializing in MS were asked to write review papers, one arguing for different pathologies between relapsing and progressive disease.
Retinal changes are observed in patients with MS, with some studies suggesting differences between progressive and relapsing MS subtypes based on optical coherence tomography data. However, analyses are complicated by the effects of aging because thinning of the retinal layers is part of the normal aging process, and rates of thinning may increase with age, suggesting that much of the retinal atrophy observed in older patients with MS could be attributable to normal aging. A recent study showed that progressive MS was associated with faster retinal layer atrophy than RRMS, even after adjusting for age, disease duration, and severity; however, it is unclear whether this reflects differences in the pathobiological mechanisms between phenotypes or an increased susceptibility to neurodegeneration in individuals with progressive MS.

### Are There Immunologic Differences Between MS Phenotypes?

Inflammatory activation in early MS leads to demyelination and neuronal destruction (figure 1). However, the frequency of new inflammatory events decreases with age such that patients in their seventh decade have only approximately 30% of the disease activity of patients in their third decade. Although the cause of this decline in the frequency of new inflammatory events in the CNS of aging patients with MS is not known, it is important to keep this observation in mind when considering reports of immunologic differences between RRMS and progressive forms of MS. Tissue-resident memory T cells (TRM cells) have been observed invading the perivascular space in patients with progressive MS; however, TRM cells have also been detected in acute MS cases with short disease duration, suggesting that the population of the perivascular space may start in the early stages of MS. Chronic white matter lesion activity (smoldering lesions) has been shown to predict clinical progression in PPMS, but these lesions are also observed in RRMS.

Indeed, several studies report immunologic differences between relapsing and progressive forms of MS. However, none of these studies confirms the findings of any of the others. One potential explanation for this inconsistency is that all but one study did not control for age. Another is that all the studies were relatively small and made multiple comparisons without making Bonferroni-type corrections. This could mask any differences in early MS, and the differences could therefore have been a result of older patients having had MS longer and lower rates of immunologic activity. The immune system ages and goes into senescence, which could also explain differences within patient groups of different ages. It is noteworthy that to date, no immunologic or biomarker tests have been identified that can clearly distinguish between progressive and relapsing MS. Although neurofilament light chain (NFL) is considered a promising biomarker for MS, analysis suggests that it is useful as a marker of disease activity and does not clearly distinguish MS subtypes. NFL levels are known to increase as part of the normal aging process, even in healthy individuals, limiting its value as a marker of progression or progressive MS. Thus, the only way to distinguish between relapsing and progressive forms of MS is to interview the patient and/or examine the patient serially over time.
What Does Explain the Different MS Phenotypes?

Duration of disease and age are 2 factors that correlate with evolution to progressive disease.20,21,e27,e28

Reviewing the natural history of MS is necessary to help us to understand the cause of PrMS.21 MS tends to start in late adolescence or early adult life.22 Studies have demonstrated that most inflammatory lesions (approximately 80%) occurring in the CNS are clinically silent but are causing MS plaque formation8 and that lesion volume is associated with accelerated brain atrophy, representing loss of neurons.23,26 This phenomenon is seen at the CIS stage24 and even at the RIS stage.8 This pattern of preclinical and subclinical progression of neurologic injury before development of clinically apparent neurologic symptoms is seen in other CNS diseases, including Alzheimer disease25 and asymptomatic traumatic brain injury,26,27 as well as in normal aging.28 Most humans demonstrate the onset of brain atrophy owing to loss of neurons after the age of 20 years but maintain normal neurologic function into late life through brain and cognitive reserve.29 In healthy individuals, brain atrophy is slow at first but accelerates in the sixth and seventh decades (figure 2B).30 This process of cerebral atrophy is accelerated in Alzheimer disease29 and repetitive closed-head injury.26,27 Work in these fields has focused primarily on cognitive dysfunction and has developed the terms “brain reserve” and “cognitive reserve” as concepts to help to explain the ability of the brain to buffer for injury, at least in the early phase of disease.31,32,33 The brain reserve concept proposes that maximal lifetime brain volume protects against cognitive decline, with impairment occurring when this falls below a critical threshold; the cognitive reserve concept suggests that intellectual enrichment and activities and behaviors that keep the brain active also offer protection against cognitive decline.32 These concepts have been shown to extend to MS. Brain reserve can protect against disease-related declines in cognition in MS. A larger brain reserve, estimated from intracranial volume (ICV), reduced the impact of disease burden on cognition,32 while a longitudinal study showed that a larger ICV protected against the decline in cognitive efficiency seen in patients with MS.33 Similarly, higher lifetime intellectual enrichment (cognitive reserve) can attenuate the effects of brain atrophy on cognition in patients with MS.34,35 Furthermore, the protective effects of intellectual enrichment on cognition were shown to be independent of the beneficial effects of brain reserve against cognitive decline.32 We propose to use the term “neurologic reserve” in MS to expand the concepts as used in dementia, which focus on cognition, to include most other neurologic functions that are affected by MS, including motor and sensory function.

If we apply this same concept of the ability of the brain to buffer for injury to MS, then the onset of progressive disease represents the point at which neurologic reserve has been depleted or exhausted.32 At this point, 2 things happen: the brain can no longer compensate for subclinical MS disease activity and we have unmasked the effect of normal aging on the brain (figure 2B).35 In addition, as the biology underlying neurologic reserve (mostly related to cortical remodeling) and neurologic resilience (the ability of the brain to recover function after injury) has also declined, it would follow that progressive patients would be less able to recover function with exercise or other interventions than patients with RRMS.

Neurologic Reserve

The concept of neurologic reserve has been used to explain why similar levels of brain injury may lead to different degrees of clinical impact.31 Is it possible that level of neurologic reserve may explain why some patients with MS develop progressive disease earlier than others?

It is well established that brain volume correlates with age, MS duration, level of disability, and MRI markers.2,23 Diminishing functional/neurologic reserve is a potential biological explanation for what happens to patients when they transition to progressive disease from RMS. The inflammatory phase of MS tends to start early,35 when most manifestations of the disease are subclinical. The brain begins to shrink early in the disease owing to loss of neurons, regardless of MS phenotype, and it has been shown that rate of brain loss is a predictor of subsequent disability.2 In the early phase of MS, symptoms may be buffered if there is adequate neurologic reserve. Indeed, Schwartz et al.32 showed that patients with MS with high-active cognitive reserve had less symptom burden than those with low-active cognitive reserve and were more likely to have RRMS rather than progressive disease. Others have also shown that cognitive reserve and brain reserve (the latter measured by brain volume) protect against cognitive disability in MS.33 As brain loss continues, the neurologic reserve is used up and patients enter the progressive stage of the disease, in which the effects of subclinical inflammatory disease and the effect of normal aging are unmasked. Thus, the occurrence of progressive disease will be determined to some extent by the initial neurologic reserve of the patient (figure 2C). This is broadly in line with the topographical model of MS proposed by Krieger et al.34 which suggests that clinical signs and disability in MS are driven by the relationship between focal lesion formation and the loss of neurologic reserve.

We propose that MS phenotypes are part of a disease continuum. As described in figure 1, inflammation is initially the cause of brain atrophy in MS; however, as inflammation declines with age, brain loss due to normal aging becomes more important. There are data to indicate that, by the time patients are approximately 60 years old, over half of brain loss observed is due to normal aging, that is, not due to MS (figure 3, A–D).35 One group looked at the nature of lesions as a function of age in patients with MS at autopsy compared with age- and sex-matched controls and found that the frequency of acutely active lesions, chronically active lesions and burnt-out lesions is steadily shifting in the direction of the burnt-out lesions as patients age.6 Furthermore, when investigating the whole brain of postmortem patients with progressive disease, they could be divided into 2 categories: those with pathologically active disease, characterized by classical active or slowly expanding lesions, and those with pathologically
inactive disease, who only showed inactive, burnt-out lesions. Patients with inactive disease were older and had longer disease duration than those with active disease. Adding support to this concept of the impact of normal aging, markers of neuronal death such as amyloid precursor protein in patients with inactive disease indicated that the rate of neuronal death was the same as in age-matched controls, thereby contradicting the concept of progressive disease being a result of accelerated neuronal loss.6 MS prognosis is in part age-dependent, uninfluenced by an initial relapsing or progressive disease course.10 The brain shrinks at an accelerated rate in patients with young-onset MS,35 and at any given age patients with earlier onset have smaller brains and increased disability, adding strength to the hypothesis that neurologic reserve is a key element of defining MS phenotypes and that age-related changes affect cellular vulnerability.

The assessment of cognitive reserve and its effects on outcomes in patients with MS provides a good basis for considering how to evaluate neurologic reserve in MS. Several measures have been used to evaluate active and passive aspects of cognitive reserve.36 Passive reserve refers to factors that precede disease onset and typically relies on measures of education, occupation, and childhood activities to quantify intellectual enrichment. Active reserve relates to current activities and behaviors that keep the brain active and includes leisure activities and hobbies (table e-1, links.lww.com/CPJ/A248).e36 Schwartz et al.32 suggested a broader view of reserve extending beyond cognition to encompass factors such as physical activity, social/community participation, and spiritual/religious practices, as well as personal characteristics, such as attitudes, values, and socioemotional skills that may enhance a person’s resilience.

Figure 3 Rates of Brain Atrophy in MS and in Normal Aging and Rates of Disability Worsening in RRMS and SPMS35,38

Stacked histograms showing the trend of brain atrophy slopes by age in HCs (red) and MS-specific atrophy (blue). The total rate of atrophy in patients with MS is represented by the total height of each histogram bar (combining colors). For SIENA (A) and the thalamus (B), the contribution of MS-specific atrophy and normal aging to the total atrophy slope changed significantly across decades, whereas normal aging was stable across decades in the caudate (C) and the putamen (D). The rates of disability worsening in RRMS and SPMS are depicted in (E), in which mean annualized EDSS scores indicate that disability worsening is significantly higher in patients with SPMS in the first 3 years after initiating treatment than in those with RRMS. Data are annualized to allow comparison between time epochs of different duration. *p < 0.5, **p < 0.01, ***p < 0.001, Mann-Whitney U test. EDSS = Expanded Disability Status Scale; HC = healthy control; MS = multiple sclerosis; RRMS = relapsing-remitting MS; SIENA = structural image evaluation using normalization of atrophy; SPMS = secondary progressive MS. Adapted from (A–D) Azevedo et al., 2019,35 and (E) Coles et al., 2006.38

Figure 3 Rates of Brain Atrophy in MS and in Normal Aging and Rates of Disability Worsening in RRMS and SPMS35,38
Reducing MS Comorbidities and Protecting Neurologic Reserve Through Diet and Physical Activity

MS is associated with numerous comorbidities, which may lead to greater disability, increased mortality, and reduced quality of life. For example, registry analysis showed that vascular comorbidity (diabetes, hypertension, heart disease, hypercholesterolemia, and/or peripheral vascular disease) was associated with an increased risk of disability progression in patients with MS. As such, there is great interest in lifestyle choices that may help to reduce the burden of common comorbidities in patients with MS, such as hypertension, diabetes, hyperlipidemia, ischemic heart disease, and chronic lung disease, and so potentially benefit patients by helping to protect neurologic reserve. Physical activity has been associated with increased brain volume in patients with MS, and it has been suggested that physical activity provides an important reserve-building activity by expanding the synaptic network and ensuring that more areas of the brain and interconnections remain active and fit. Therefore, we suggest that physical activity may be able to develop an increased buffer against injury by expanding the synaptic network of the brain, as has been documented in Alzheimer disease.

Pharmacologic Treatment of PrMS: What Do Clinical Trial Results Suggest?

Several issues need to be considered in clinical trial design for disease-modifying therapy (DMT) interventions in progressive forms of MS. First, patients with progressive disease are on average 15 years older than those with RRMS. Thus, they are experiencing far fewer acute inflammatory events as measured by new T2 or Gd+ lesions or by relapse rate. Second, as we contend, these patients have exhausted neurologic reserve, which means they can no longer mask the effect of subclinical inflammatory disease due to MS or the effect of age-related neuronal loss that begins in the fourth decade of life in humans. Finally, unlike patients with RRMS, patients with PrMS have little ability to recover function when receiving highly effective DMTs, as was demonstrated in a study by Coles et al. When treated with alemtuzumab, patients with RRMS steadily recovered function over 3 years of observation, whereas patients with PrMS showed a slowing in the rate of disability progression but continued to progress slowly (figure 3E). We would propose that this is due to the unmasking of the effect of aging on the brain because of premature consumption of neurologic reserve by MS. Moreover, the neurobiology of neurologic reserve is primarily mediated through cortical remodeling, as is recovery of function or neurologic resilience. If we delay the use of highly effective therapies until patients have developed significant disability and are entering the progressive phase of MS, the best outcome (without reparative therapies) will be a slowdown in the decline in function. Early treatment of RRMS with highly effective DMTs is associated with better long-term outcomes than delayed treatment and it generally results in improvement, if not resolution, of MS-related disability.

To date, most therapies have shown limited benefit in patients with progressive forms of MS, with the exception of ocrelizumab (approved for the treatment of PPMS in Australia, Europe, and the United States), siponimod (approved for the treatment of active SPMS in Europe and the United States and SPMS in Australia and Japan), and cladribine (approved for the treatment of active SPMS in the United States). Although other potential therapies for the treatment of PrMS are still under investigation, our therapeutic goal in the management of MS is to treat as early as we can with the most effective DMT with an appropriate safety profile to minimize further neuronal loss and to preserve neurologic reserve both to avoid entry into the progressive phase of MS and to buffer against normal aging effects on the CNS in later life.

Conclusions

In summary, we believe that there is a lack of genetic, pathologic, and immunologic evidence to justify stratifying progressive and relapsing forms of MS as 2 separate entities. Furthermore, there appears to be no simple classification that can accurately distinguish between the 2 forms. Instead, we believe that MS progresses along a continuum from RMS to PrMS, with phenotypic differences along this spectrum accounted for by differing levels of neurologic reserve. This is a concept well developed in other fields, notably Alzheimer disease. When applied to MS, it explains the pattern of

TAKE-HOME POINTS

1. There are no confirmed genetic or immunologic differences between relapsing and progressive forms of MS.
2. The reported pathologic and radiographic differences between these apparent MS subtypes represent quantitative differences on a pathologic spectrum, influenced by patients with progressive disease generally being older, with longer disease duration rather than being pathognomonic to relapsing or progressive MS.
3. We propose that loss of neurologic reserve owing to MS-related inflammation explains the onset of PrMS, and the level of neurologic reserve may explain why some patients with MS develop progressive disease earlier than others.
4. We propose that reducing comorbidities, through strategies such as a healthy diet or active lifestyle, may help to protect neurologic reserve and could therefore prove beneficial in the care of patients with MS.

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treatment response seen when patients are treated with the various DMTs that cannot be accounted for by consideration of genetic, pathologic, or immunologic differentiators. It also provides the scientific rationale for early intervention with highly effective DMTs, helping patients with MS to adopt active and healthy lifestyles to build reserve and to improve their neurologic function over their lifetime.

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