New Insights into Multiple Sclerosis Clinical Course from the Topographical Model and Functional Reserve

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KEYWORDS

• Multiple sclerosis • Clinical course • Prognosis • Topographical model • Reserve

KEY POINTS

- The topographical model of multiple sclerosis (MS) visually represents the dynamic nature of lesion patterns, functional reserve, and transient fluctuations owing to physiologic stressors, in the evolution of MS clinical course.
- The topographical model of MS may be used as a clinical tool for educating patients about the clinical expression of MS disease, and may aid in predicting future disability.
- An emphasis on reserve in the model encourages future research on sources of reserve against disability, and motivates patients to engage in lifestyle choices that may build reserve.

INTRODUCTION

Multiple sclerosis (MS) is distinct among neurologic diseases in that it is characterized by both acute relapses and incremental progression of disability. This is but one source of heterogeneity across people with MS, because the disease varies considerably in symptoms, severity, and course, and is notoriously difficult to prognosticate at the individual patient level. The topographical model of MS[1] was proposed as a clinical framework through which both archetypal features of the clinical course of MS, as well as essential factors driving interpersonal variability, can be visualized. This model reflects the growing recognition of the way that functional reserve influences MS phenotype and prognosis, and also acknowledges the need for inclusion of

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MS-related cognitive dysfunction in representations of the disease course. Indeed, this insidious but pervasive symptom has not been fully incorporated into longstanding approaches to disability assessment or conceptualizations of MS phenotypes. This paper reviews important concepts in the clinical course of MS, the novel contributions of the topographical model, and the crucial role of functional reserve in MS prognosis and outcomes.

BACKGROUND

Approximately 80% to 90% of MS cases begin as a relapsing disease characterized by acute neurologic events caused by focal inflammatory lesions.[2] Characteristic neurologic symptoms indicative of relapse—principally optic neuritis, partial myelitis, and brainstem syndromes—are essential to the international panel diagnostic criteria for MS.[3] The accepted clinical course phenotypes initially published in the 1990s divide MS into relapsing remitting MS, secondary progressive MS (SPMS), and primary progressive MS (PPMS) forms of the disease (**Fig. 1**). The updated phenotype descriptions include an emphasis on close observation for evidence of ongoing inflammatory relapsing disease activity, and the presence or absence of insidious worsening of neurologic function in the absence of relapses referred to as disease progression.[4] MS has thus often been conceptualized as a "2-phase" disease,[5] with the early inflammatory relapsing phase followed by progression characterized by neurodegeneration.

Although acute relapse is the diagnostic and phenotypic hallmark of MS, and approved disease-modifying therapies for MS have demonstrated their efficacy fundamentally through prevention of relapses, the long-term impact of relapses on the clinical course and the accumulation of disability continues to be a matter of debate.[6,7] Numerous studies have demonstrated that a substantial portion of relapses do not result in a full recovery; therefore, residual neurologic dysfunction may be observed.[8] An increased frequency and severity of relapses early in disease course may also confer an unfavorable prognosis and rapid development of disability.[9] In contrast, older studies of long-term outcomes in MS had identified a very limited impact of early relapses to the development of disability once the progressive phase of MS has become apparent.[10]

Recent work characterizing relapse symptomatology more precisely has shown that motor system relapses and those with incomplete recovery measured at several time points exert a more significant prognostic impact on disability accumulation.[11,12] These data provide an argument that the localization of relapse-causative lesions, their severity, and their degree of recovery are important drivers of subsequent disability. Acute lesions seen on MRI are strongly associated with the occurrence of clinical relapse, and serve as a surrogate marker for inflammatory disease activity.[13] Furthermore, MRI lesions accumulated early in disease course have been shown to be a strong predictor of disability accumulated 20 years later.[14] That the MRI burden of disease often seems to be more substantial than clinical symptoms apparent early in disease has been referred to as the "clinical–radiologic paradox," although the concept of reserve in the topographical model of MS may help to make this less paradoxical.

In addition to early clinical and MRI prognostic factors, the role of advancing age as a significant contributor to the clinical course of MS has more recently come into focus.[15] The likelihood of developing progressive disease increases with age, with more than one-half of the MS population older than 65 having a progressive course.[16] Those diagnosed at an older age are at higher risk of manifesting a PPMS course or