Progressive Forms of Multiple Sclerosis

Distinct Entity or Age-Dependent Phenomena

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KEYWORDS

• Aging • Multiple sclerosis • Progression • Smoldering plaque

KEY POINTS

- Multiple sclerosis (MS) disease course is defined by a subclinical or clinical relapsing-remitting phase, a progressive phase, and the overlapping phase in-between.
- Each phase can have intermittently active or inactive periods.
- The onset of progressive phase of MS is age-dependent but time and pre-progressive phase agnostic.
- Pathologic hallmarks of progressive MS onset are age-dependent but pre-progressive phase agnostic.
- Subclinical activity behavior in patients with radiologically isolated syndrome evolving to primary progressive MS are mostly indistinguishable from patients with relapsing-remitting MS evolving to secondary progressive MS.

DEFINITIONS OF PHENOMENOLOGY IN MULTIPLE SCLEROSIS

Disease course in multiple sclerosis (MS) is defined by the interaction of 2 distinct phenomena: relapses and progression. A "relapse" can present either clinically as new central nervous system (CNS)-related neurologic symptom(s) evolving over hours to days, or subclinically as new MRI lesions without symptoms. Pathologically, an MS relapse is an acute inflammatory demyelination with or without axonal injury. When symptomatic, a relapse is generally expected to plateau over days to weeks, followed by a partial or complete recovery period. In some patients, there may be no recovery at all.

"Clinical recovery" is the maximum improvement attained after the peak deficit related to a relapse. In our experience, stabilization of clinical recovery usually occurs within the first 3 months and rarely continues beyond 6 months following a relapse.[1]

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"Subclinical recovery" can be seen as resolution of enhancement, changes in diffusion characteristics, and/or shrinkage in size of the MS lesion(s) in MRI. The period through which recovery continues is referred to as the "remission" period, with the pathologic hallmark of remyelination with or without restoration of axonal integrity.

A "pseudo-relapse" is characterized by the emergence of symptoms in the setting of a previous clinical or subclinical relapse and is triggered by factors such as heat, infection, exercise, and fatigue. In our current understanding, this phenomenon appears when the symptomatic threshold is exceeded due to higher demand than the damaged nervous system can deliver. Symptomatic improvement follows swiftly with elimination of the specific trigger. When short-lived (<24 hours), it is easy to distinguish a pseudo-relapse from a relapse, but beyond that time point, it may be necessary to use imaging to rule out a new lesion as the cause of ongoing symptom(s).

"Progression" is the insidious and irreversible worsening of neurologic function due to MS with the pathologic hallmark of progressive axonal injury or loss. Progression can happen without ongoing clinical or subclinical relapses. To avoid confusion, the term "disability progression" should be changed to "disability worsening."[2] Disability worsening can be directly due to MS biology or can be due to other non–MS-related factors. MS-related disability worsening can result from stepwise accumulation of neurologic deficit from relapses, insidious accumulation of neurologic deficit from progressive disease course, or a combination of both. In our clinical practice, we also frequently use the term "pseudo-progression" to describe the disability worsening due to other non–MS-attributable factors, such as being deconditioned or degenerative hip disease.

MS activity is assessed both clinically and by MRI. "Active disease" is defined as new clinical or subclinical relapses (contrast-enhancing T1 hyperintense lesions or new T2 hyperintense lesions or enlarging T2 hyperintense lesions).[2] "Inactive disease" is defined as the absence of clinical events and MRI activity for $\geq$1 year[2] also known as "no evidence of disease activity."[3]

Based on these definitions, modern disease course classification in MS consists of 2 phases: the "relapsing-remitting phase" and the "progressive phase" (**Fig. 1**). Approximately 4 in 5 patients are expected to evolve from relapsing-remitting to progressive phase of the disease in their lifetime.[4] Each phase is then further defined as active or inactive at any given time.

RELAPSING-REMITTING PHASE OF MULTIPLE SCLEROSIS

Patients can present as asymptomatic or symptomatic during the relapsing-remitting phase of MS. The asymptomatic phase is incidentally discovered when MRIs are obtained in individuals due to reasons unrelated to typical MS symptoms. When the MRI findings fulfill $\geq$3 of the 4 imaging criteria,[5] a diagnosis of radiologically isolated syndrome (RIS) is established.[6–8] Many asymptomatic individuals also present with typical lesions suggestive of demyelinating disease, but fulfill fewer than 3 of the 4 imaging criteria. In our practice, we refer to these cases as pre-RIS. It is unclear how many of these individuals will evolve to RIS.

Clinically isolated syndrome (CIS) refers to the first symptomatic encounter in the relapsing-remitting phase of MS. This definition has evolved over time due to the changing dissemination in time and space criteria application in MS diagnosis. Originally defined as a single clinical relapse without any weight on MRI findings, CIS can evolve into clinically definite MS[9] when patients experience a second clinical relapse.[10] According to the most recent updates, subclinical relapses also fulfill dissemination in time and space criteria leading, therefore, to a diagnosis of MS