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Review article

Understanding the impact of relapses in the overall course of MS; refinement of the 2 stage natural history model

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ABSTRACT

Recent studies suggest a need for refinement of the traditional two phase model of relapse onset multiple sclerosis (RMS) to include dynamically changing subgroups within the broad category of secondary progressive MS (SPMS). These studies challenge the traditional notion that relapses play a minor role in comparison to a secondary progressive (perhaps degenerative) process. Patients fulfilling the broad definition for SPMS may take several courses, including variable rates and patterns of overall worsening. New paradigms or models for mapping the trajectory of disability in RMS and SPMS (clinical phenotyping), including periods of remission, may impact our understanding of the underlying pathology, and will be important in assessing treatments.

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1. Introduction

Since initial symptoms of RMS usually resolve without disabling residua, and many patients eventually develop slow progressive decline, the long-term relevance of clinical relapses has been questioned (Lublin, 2011; Casserly and Ebers, 2011). The possibility of modifying disease course, through reduction of relapses, suggests that relapses may be important in the overall course of MS. Many epidemiologists lean towards the null hypothesis, namely that relapses are of limited relevance in understanding MS progression (Leray et al., 2010; Hutchinson, 2015). Even though carefully collected data have shown predictiveness of relapse phenotyping (severity, frequency, etc.), these data must be reconciled with other studies showing either minimal impact or no predictive value of relapses. Differences in study design are a

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likely explanation for disparate conclusions. Controversy centers on whether or not a secondary progressive phase (SPMS) is primarily inflammatory (Scalfari et al., 2010). Disability may largely result from clearly definable relapses (which are inflammatory events) which either produce disabling lesions or set the stage for secondary degenerative processes. However, elimination of relapses may have minimal long term benefit if the driving force of most disability is not pathologically connected to these clinical events.

2. Do relapses involve acute inflammatory injury and have permanent consequences?

There is consensus that lesions causing acute classical symptoms are inflammatory and are often correlated with an evolving MRI lesion. The number of acute MRI lesions is strongly associated with clinical events and with long term outcomes (Sormani et al., 2011; Fisniku et al., 2008). White matter lesions seen on MRI correlate with demyelination, axonal transections, and gliotic scarring found during multiple phases of lesion formation, suggesting inflammatory rather than degenerative processes may be the strongest driver of disability in MS (Bermel et al., 2013).

The disability accrued in a stepwise fashion in the setting of acute relapses does not appear to be trivial. A study of early MS patients found that by 5 years 8% of patients were severely disabled. These patients exhibited a relapsing stepwise decline suggesting attack related disability (Gholipour et al., 2011). Attacks with incomplete recovery in the first decade of the disease tend to be followed by similar disabling attacks and rapid accumulation of disability (Mowry et al., 2009; Scott and Schramke, 2010; Novotna et al., 2015). Even with new MS treatments 10–15 years after onset roughly one third of patients are disabled, and those with the most aggressive disease are still tending to have attacks (Scott et al., 2016). Even if poor recovery from attacks simply marks a transition to a more progressive form of disease, the inflammatory event of the attack itself seems important (Lublin et al., 2003).

3. Does the known pathology of MS support a 2 phase process?

A recent autopsy study showed that on average the presumed white matter pathology correlating with this transition occurs over many years, changing from a predominance of acute inflammatory plaques to either inactive or "smoldering plaques" (Frischer et al., 2015). Another type of transition to SPMS seems to occur in cortical gray matter, as sub-pial inflammation at or near the site of "B cell follicle-like structures" occurs (Magliozzi et al., 2010). Is it thus possible to stop progression through stopping inflammatory events, or do other treatment refractory processes mediated by microglia or monocytes then predominate?

We recently demonstrated that the stepwise accumulation of disability related to clinical relapses contributes to the phenotypic profile of most patients who become disabled in the first 15 years of RMS, with about 35% of patients reaching EDSS 3.0 or more, and 20–25% reaching EDSS 4.0 or more (Scott et al., 2016). By autopsy study acute appearing MS plaques decline from over 90% of all plaques in year 1 to about 25% in years 5–20. The number of inactive plaques equals active plus smoldering plaques by year 15. The development of progressive MS may be viewed as a many year transitional process rather than an "all or none" phenomenon occurring in distinct phases.

4. Do the newest natural history studies continue to suggest a 2 phase process?

A two phase model would ideally encompass the extreme variability seen in terms of the length of a benign phase (Scott et al., 2014). Given that only about half of patients attain moderate or severe disability in the first 30 years of MS, a 2 phase model is not appropriate for many patients (Novotna et al., 2015). Studies finding a steady worsening and then severe disability (EDSS 6.0 or more) among multiple patient phenotypes once a moderate level of disability has been reached (EDSS 3.0 or 4.0) provide some support for the 2 phase theory (Leray et al., 2010; Confavreux et al., 2000). This suggests a more degenerative process determines disability once a threshold of inflammatory injury is reached.

In treated patients during the first decade after onset, complete stability is rare, and our studies indicate worsening is roughly evenly distributed among three phenotypes: stepwise worsening due solely to relapses with sequelae, slow progression (which may or may not be associated with mild relapses without sequelae), and slow progression with additional worsening due to relapses with sequelae (see Fig. 1). Entry into a transitional type of clinical picture may not be needed to produce a moderate or severe disability.

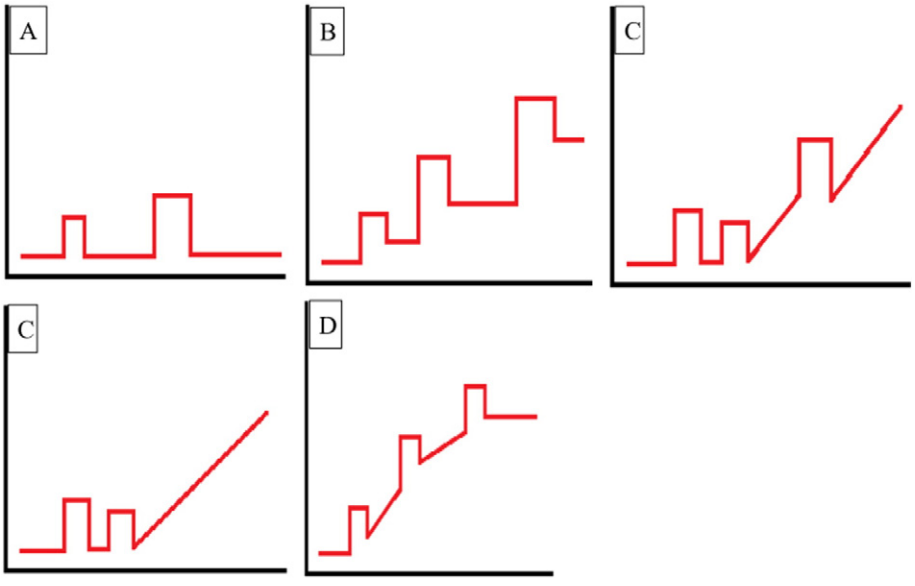

Fig. 1. Potential course of RMS over months or years. Over the course of months or years, the course of RMS may be categorized by the presence or absence of relapses and worsening (with worsening due to either relapse or slow progression). Type A = no worsening, with or without relapses. Type B = at least one relapse with sequela/worsening. Type C = worsening only by slow progression. Type D = at least one relapse with sequela/worsening and at least one year of slow progression (Lizak et al., 2016).