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Review article

Relapses in multiple sclerosis: Relationship to disability

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ABSTRACT

Multiple sclerosis (MS) is a recurrent inflammatory disease of the central nervous system, which ultimately causes substantial disability in many patients. A key clinical feature of this disease is the occurrence of relapses, consisting of episodes of neurological dysfunction followed by periods of remission. This review considers in detail the importance of the occurrence of relapses to the ultimate course of MS and the impact of relap setreatment (both acutely and prophylactically) on the long-term outcome for individuals. The ultimate goal of therapy in MS is the reduction of long-term disability. Clinical trials in MS, however, typically only extend for a very short time period compared to the time it takes for disability to evolve. Consequently, short-term outcome measures that are associated with, and predict, future disability need to be identified. In this regard, not only are relapses a characteristic feature of MS, they have also been proven to be associated with the occurrence of long-term disability. Moreover, treatments that reduce the number and severity of these attacks improve the long-term prognosis.

Contents

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) (Bar-Or et al., 1999; Compston et al., 2006; Conlon et al., 1999; Hauser and Oksenberg, 2006), which ultimately causes substantial disability in many patients (Bar-Or et al., 1999; Compston et al., 2006; Conlon et al., 1999; Hauser and Oksenberg, 2006). About 90% of MS cases are characterized by the occurrence of clinical attacks, which consist of episodes of neurologic dysfunction lasting for some period of time (usually defined as more than a day), and then followed by a remission of symptoms (Cook et al., 2012; Lublin and Reingold, 1996). Indeed, the occurrence of such attacks has been an essential component of every diagnostic scheme for MS in the past 50 years – from the early, pre-magnetic resonance imaging (MRI) criteria of the Schumacker committee in 1965 (Schumacker et al., 1965) through the most recently revised International Panel criteria published in 2011 (Polman et al., 2011). Thus, clinical attacks are essential to the very definition of MS. Although the neurologic disability experienced during an attack can be quite marked, some neurological recovery from these attacks occurs in the majority of patients and is often seemingly complete. Therefore, the question naturally arises as to whether (or to what extent) these clinical attacks are responsible for, or contribute to, the ultimate disability experienced by individual MS patients.

2. Pathology of multiple sclerosis

In MS, there is pathological evidence of multi-focal injuries of varying ages to the myelin sheaths surrounding the axons, to the oligodendrocytes and, to a somewhat lesser extent, the nerve cells and their processes (Bar-Or et al., 1999; Compston et al., 2006; Conlon et al., 1999; Hauser and Oksenberg, 2006). Axonal injury within active lesions and gray matter demyelination also both occur (Bo et al., 2003; Ferguson et al., 1997; Lucchinetti et al., 2011; Peterson et al., 2001; Trapp et al., 1998). Within acute lesions, presumably under the influence of cellular adhesion molecules (CAMs) and pro-inflammatory cytokines, auto-reactive, cluster of differentiation (CD)4^+, thymic-derived lymphocytes (T cells), $CD8^+$ cytotoxic lymphocytes, $CD20^+$ bone marrow-derived lymphocytes (B cells), and $CD68^+$ macrophages cross the blood–brain barrier (BBB) to enter the CNS (Bar-Or et al., 1999; Compston et al., 2006; Conlon et al., 1999; Hauser and Oksenberg, 2006). These activated cells are thought to contribute to the CNS tissue damage that is seen in acute MS lesions.

MRI lesions characterized by only T2-hyperintensity (i.e., T2-only lesions), are much more likely to have preserved myelin than MRI lesions characterized by persistent T1-hypointensity and a reduced magnetization transfer ratio (MTR), in addition to T2-hyperintensity (i.e., T2/T1/MTR lesions) – in fact, only 20–45% of T2-only lesions are associated with demyelination on histopathological examination (Fig. 1) compared to 80–83% of the T2/T1/MTR lesions (Fisher et al., 2007; Moll et al., 2009). Nevertheless, regardless of the presence or absence of demyelination, most of the T2-only MRI lesions still contain activated microglia and evidence of BBB breakdown. Even in the so-called normal-appearing white matter, 30% of the regions sampled contain activated microglia. It remains to be determined whether activated microglia within myelinated T2-only lesions are causing new damage or are simply responding to a cytokine release associated with the breakdown of the BBB from Wallerian degeneration, or both. Indeed, it is possible that the microglia may actually be involved in cleaning up lesions (possibly even promoting repair), whereas the macrophages may be responsible for the actual tissue damage (Yamasaki et al., 2014).

Thus, MS lesions show considerable histopathological diversity, ranging from chronic gliotic demyelinated scars, to highly inflamed demyelinating lesions, to less inflamed regions in which the myelin is preserved (Fig. 1).

3. The blood–brain barrier

The endothelial cells in the CNS are non-fenestrated and have extraordinarily tight junctions between them. For a long time, these tight junctions were thought to be primarily responsible for creating the BBB, but it is now known that this barrier is actually the result of a very complex interface between the vascular system and the CNS, which is called, collectively, the neurovascular unit (Engelhardt et al., 2014; Holman et al., 2011; Muoio et al., 2014). This unit includes the endothelial cells, the extracellular matrix, the basement membrane, and also the cells surrounding the endothelial cells, notably pericytes and astrocytes. Together, this unit works to both provide mutual trophic support and to make the entry of hydrophilic molecules (by active transport or diffusion) and transcytosis into the CNS extremely selective. A focal breakdown of the BBB can be caused by any one of a variety of CNS insults including inflammation, toxic exposure, neoplasia, trauma, and ischemia.

In MS, the breakdown of the BBB is thought to represent a critical step in the development of a new MS lesion and the basis for an acute MS attack. Nevertheless, whether this BBB breakdown is the initial event in lesion formation is not entirely clear (Filippi et al., 1998; Goodkin et al., 1998). Thus, using the magnetization transfer ratio (MTR), focal changes in the relative concentrations of free and bound water can be detected in those otherwise normal-appearing CNS white matter regions that, months later, are destined to become a gadolinium (Gd)-enhancing lesion on MRI. Presumably, these MTR changes reflect biochemical alterations, which are the initial events in lesion formation. It is nonetheless possible that these early events represent a selective breakdown in the BBB not detectable by conventional MRI and, in this view, the more general breakdown of the BBB, which is reflected by the Gd-enhancement, would be a secondary phenomenon.