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Mechanisms of neuronal dysfunction and degeneration in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. Due to its high prevalence, MS is the leading cause of non-traumatic neurological disability in young adults in the United States and Europe. The clinical disease course is variable and starts with reversible episodes of neurological disability in the third or fourth decade of life. This transforms into a disease of continuous and irreversible neurological decline by the sixth or seventh decade. Available therapies for MS patients have little benefit for patients who enter this irreversible phase of the disease. It is well established that irreversible loss of axons and neurons are the major cause of the irreversible and progressive neurological decline that most MS patients endure. This review discusses the etiology, mechanisms and progress made in determining the cause of axonal and neuronal loss in MS.

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1. Introduction

Multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system (CNS), is the leading cause of non-traumatic neurological disability in young adults in North America and Europe, affecting more than two million people worldwide (Hauser and Oksenberg, 2006; Noseworthy, 1999; Noseworthy et al., 2000; Trapp and Nave, 2008; Weinshenker, 1998). Although descriptions of putative MS date back as early as the middle ages, the first pathological report was published by Jean-Martin Charcot, Professor of Neurology at the University of Paris, in 1868 in the *Leçons du mardi* (Charcot, 1868). He documented characteristic 'plaques' thereby coining the definition of '*la sclerose en plaques*' upon examination of a young woman's brain. His diagnostic criteria based on nystagmus, intention tremor and scanning speech are still helpful in recognizing the disease. Although considerable scientific progress has been obtained through over a century of subsequent research, the underlying cause of MS is still unknown.

Pathologically, the diagnosis of MS is confirmed by the presence of multifocal inflammatory demyelinated plaques distributed over time and space within the CNS. Thus, identification of multiple foci of demyelination in the CNS of patients clinically diagnosed with MS is one of the cardinal pathological findings for confirming the MS diagnosis. The International Panel on diagnosis of MS presented several guidelines (McDonald et al., 2001) termed "McDonald Criteria" for detection of MS. The most recent recommendations of

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Table 1
Diagnostic criteria for MS (adapted from the "Revisions to McDonald Diagnostic criteria for Multiple Sclerosis" (Polman et al., 2005).

Clinical presentation	Additional data needed for MS diagnosis
• Two or more episode of neurological disturbance for which causative lesions are likely to be inflammatory or demyelinating in nature (attacks) • Objective clinical evidence of two or more lesions	No additional tests are recommended
• Two or more attacks • Objective clinical evidence of one lesion	Two or more MRI-detected lesions and positive CSF analysis (detection of oligoclonal bands) OR Dissemination in space demonstrated by MRI: Fulfilling at least three of following: - One gadolinium enhanced lesion - One infratenotorial lesion - One juxtacortical lesion - Three periventricular lesion OR Await further clinical attack
• One attack • Objective clinical evidence of two or more lesions	Dissemination in space demonstrated by MRI with previous criteria OR Await second clinical attack
• One attack • Objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space demonstrated by MRI with previous criteria OR Two or more MRI-detected lesions consistent with positive CSF analysis And Dissemination in space demonstrated by MRI with previous criteria OR Second clinical attack
• Insidious neurological progression	One year disease progression and any two of the following - positive brain MRI - positive spinal cord MRI (two focal T2 lesions) - positive CSF

the panel are listed in Table 1 (Polman et al., 2005). However, in the absence of standardized equipment, analysis and interpretation, diagnosis of MS can be made reliably a by a knowledgeable physician using clinical data.

The majority (~85%) of MS patients have a biphasic disease course, beginning with the primary phase termed relapsing-remitting MS (RR-MS). During this disease course, patients experience alternating episodes of neurological disability and recovery that can last for many years (Hauser and Oksenberg, 2006; Noseworthy, 1999; Noseworthy et al., 2000; Trapp and Nave, 2008). Within 25 years, ~90% of RR-MS patients transform into a secondary-progressive disease course (SP-MS) which is characterized by steady neurological decline (Noseworthy et al., 2000; Trapp and Nave, 2008; Weinshenker et al., 1989). About 10% of MS patients also exhibit a disease course with steady decline in neurological function without recovery and are classified as primary progressive MS (PPMS). A small minority of MS patients (~5%) suffer from a disease course with progressive neurological decline accompanied by well demarcated acute attacks with or without recovery. This disease course is classified as progressive-relapsing MS (PR-MS).

Typically, MS lesions include breakdown of the blood–brain barrier, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axonal degeneration (Dutta and Trapp, 2007; Prineas, 2001; Trapp and Nave, 2008). While immune-mediated destruction of CNS myelin and oligodendrocytes are considered the primary pathology of MS, it is well established that progressive axonal loss is the major cause of neurological disability in MS (Stadelmann et al., 2008; Trapp and Nave, 2008). Various approaches including magnetic resonance imaging (MRI) (Bakshi et al., 2008; Filippi et al., 2003; Filippi and Rocca, 2007), magnetic resonance spectroscopy (MRS) (De and Filippi, 2007; Narayana, 2005; Tartaglia and Arnold, 2006) functional magnetic resonance imaging (fMRI) (Bakshi et al., 2008; Filippi et al., 2003; Rocca et al., 2003; Rocca and Filippi, 2007; Tartaglia and Arnold, 2006), and morphological analysis of MS tissue (Anthony et al., 2000; Bruck, 2005; Stadelmann et al., 2008; Trapp et al., 1998; Trapp and Nave, 2008) have provided evidence for axonal loss as the major cause of irreversible neurological disability in MS.

2. Neurological disability in RRMS

The majority of RR-MS patients have alternating episodes of neurological disability and recovery with formation of new lesions. Brain imaging shows new lesion areas as enhanced with gadolinium (GAD), which reflects breakdown of the blood-brain barrier, infiltration of hematogeneous leukocytes, demyelination, and oligodendrocyte death. The edema associated with "MS lesions" is a major contributor to neurological relapses, blocking conduction of action potentials. Demyelination, which occurs throughout the CNS, is another contributor to the transient disability. The brain employs a number of adoptive mechanisms that restore function to demyelinated white matter. Recent fMRI studies have identified cortical areas which are activated after a white matter lesion which can be transient and may reflect recovery of function within the lesion. A classical example of such a phenomenon is the redistribution of Na^+ channels following demyelination (Waxman, 1982). The demyelinated axon responds to the loss of myelin by re-distributing its voltage-gated Na^+ channels along the demyelinated axolemma (Waxman, 2006). These axons slowly regain the ability to conduct action potentials, albeit at a reduced velocity. Subsequently, the edema resolves, leading to remyelination and the restoration of nerve conduction. Understanding the cellular and molecular mechanisms of axonal transection with disease progression is imperative for the development of neuroprotective therapies.

2.1. Axonal transection during inflammatory demyelination

A series of papers in the late 1990s described a variety of axonal changes in actively demyelinating lesions present in postmortem