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Pathophysiology 20 (2013) 71–84

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Immunopathological patterns from EAE and Theiler's virus infection: Is multiple sclerosis a homogenous 1-stage or heterogenous 2-stage disease?

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Abstract

Multiple sclerosis (MS) is a disease which can presents in different clinical courses. The most common form of MS is the relapsing-remitting (RR) course, which in many cases evolves into secondary progressive (SP) disease. Autoimmune models such as experimental autoimmune encephalomyelitis (EAE) have been developed to represent the various clinical forms of MS. These models along with clinico-pathological evidence obtained from MS patients have allowed us to propose '1-stage' and '2-stage' disease theories to explain the transition in the clinical course of MS from RR to SP. Relapses in MS are associated with pro-inflammatory T helper (Th) 1/Th17 immune responses, while remissions are associated with anti-inflammatory Th2/regulatory T (Treg) immune responses. Based on the '1-stage disease' theory, the transition from RR to SP disease occurs when the inflammatory immune response overwhelms the anti-inflammatory immune response. The '2-stage disease' theory proposes that the transition from RR to SP-MS occurs when the Th2 response or some other responses overwhelm the inflammatory response resulting in the sustained production of anti-myelin antibodies, which cause continuing demyelination, neurodegeneration, and axonal loss. The Theiler's virus model is also a 2-stage disease, where axonal degeneration precedes demyelination during the first stage, followed by inflammatory demyelination during the second stage.
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Keywords: Primary Progressive Multiple Sclerosis; Inside-Out Model; CpG oligonucleotides; Picornaviridae; Myelin Sheath; Wallerian Degeneration; Autoimmune Diseases of the Nervous System; Demyelinating Disease; Central Nervous System Viral Disease; Seizures

1. Introduction

1.1. Homogeneity vs. heterogeneity in MS: clinical and neuroimaging studies

Multiple sclerosis (MS) is a chronic demyelinating disease of the human central nervous system (CNS), which mainly affects young adults. The proposed pathogenesis of MS has two main components: inflammatory demyelination and axonal degeneration (Table 1) [1,2]. The demyelination of nerve fibers causes significant neurological impairment including sensory and motor disturbances, vision loss and paralysis. Inflammation is often associated with demyelination. Axonal damage and neuronal loss (neurodegeneration) have also been reported in MS, which results in brain atrophy and permanent neurological damage, particularly cognitive decline [1,3,4] In general, it is hypothesized that inflammatory demyelination causes secondary axonal degeneration [5]. However, there is evidence of axonal degeneration in the absence of demyelination, suggesting that axonal degeneration can precede demyelination [6]. It is also possible that inflammatory demyelination and neurodegeneration run parallel and concurrently.

The clinical course of MS may present in one of four forms. In the relapsing-remitting (RR) form, relapses and remissions occur with either a full recovery or a partial recovery with residual deficits. In progressive-relapsing (PR) MS, the disease progressively worsens, with intermittent attacks and relapses which may lead to partial or full recovery from the attacks. Secondary progressive (SP) disease occurs when the initial RR course is followed by progressive disease, and the primary progressive (PP) course is

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doi:10.1016/j.pathophys.2012.03.003

Table 1
Two neuropathologies in MS.

Pathology	Cell component	Reference
Inflammatory demyelination	T cell infiltration	[15–19]
	Myelin loss, oligodendrocyte apoptosis	
Neurodegeneration	Axonal damage	[2,20,21]
	Loss of neurons	

MS: multiple sclerosis.

characterized by the steady and progressive worsening of neurological condition without any prominent relapses from the onset. [7]. Generally, MS begins as the RR disease which in ∼85% of patients eventually evolves into SP-MS within ∼10 years of the onset [8]. The onset and clinical course of MS are for the most part unpredictable, although there are some trends [7]. African-Americans represent a group who are less likely to develop MS, but are more likely to exhibit the progressive disease course of MS, and suffer from more rapid neurodegeneration [40]. Caucasian Americans and Europeans are more likely to develop the RR form of disease that will eventually turn progressive [9]. In both Caucasian Americans and Europeans, there is an increased MS incidence which is associated with decreased ultraviolet (UV) exposure [9,10]. Perhaps the most significant factor that contributes to MS incidence and severity is gender: women are 2–3 times more likely to develop MS than men [11,12]. Although it is unknown what triggers MS to transform into the progressive disease, neuroimaging studies suggest that MS could be a 2-stage disease, in which inflammatory demyelination is followed by neurodegeneration [13,14].

Inflammation has been linked with RR-MS since active lesions can be seen by gadolinium enhancement during RR-MS [8]. However, gadolinium-enhanced lesions are less prevalent during progressive disease than in RR-MS. Therefore, the progressive form of MS has been speculated to begin when the brain can no longer compensate for neurodegeneration (axonal loss) [3].

Neurodegeneration has been associated with the progressive forms of MS. In the progressive forms of MS, atrophy of gray matter accelerates compared with RR disease and cannot be blocked by the use of anti-inflammatory drugs [22,23]. Additionally, the regions of the brain where the atrophy occurs differ between RR and the progressive forms of the disease [24]. While ventricular enlargement is predominant in RR-MS, patients with SP-MS develop atrophy in the cortex and deep gray matter. These findings have lead to the hypothesis that inflammatory demyelination in the white matter is a major effector mechanism during the RR stage, while neurodegeneration develops during the progressive stage. Therefore, based on neuroimaging studies, MS could embody two heterogenous pathological events, inflammation and neurodegeneration. However there is currently no etiopathologic mechanism to explain how and whether MS shifts from inflammatory demyelination to neurodegeneration.

1.2. Homogeneity vs. heterogeneity in MS: pathology studies

Pathology studies on active demyelinating MS lesions suggest heterogeneity in several immunopathological parameters, including T cells, macrophages, immunoglobulin (Ig), and oligodendrocyte apoptosis, among patients (inter-individual heterogeneity) [25]. Lucchinetti et al. classified MS lesions into four patterns, all of which contained T cells and macrophages. Some differences were, however, recognized: pattern I was mediated by T cells and macrophages alone; pattern II was Ig and complement dependent, pattern III exhibited apoptosis of oligodendrocytes in the absence of Ig, complement, and remyelination, and pattern IV showed oligodendrocyte dystrophy with no evidence of remyelination. In these classifications, there appears to be neither an overlap in pattern, nor a change in pattern during the clinical course of individual patients (intra-individual homogeneity). Although the classification by Lucchinetti et al. has been widely used, Breij et al. reported that the pathology is homogenous among all MS patients from the various disease courses (inter-individual homogeneity) [26,27]. All active lesions had antibody, complement, and macrophages associated with them (similar to pattern II in the Lucchinetti scheme).

On the other hand, Barnett et al. observed two lesion types (patterns II and III) in a single patient, consistent with intra-individual heterogeneity, or stage-dependent pathology [26,28,29]. Here the finding may represent the transition from the first stage of disease (oligodendrocyte apoptosis) to the second stage (T cell-mediated inflammation). This conflicts with the reports by Breij and Lucchinetti who only reported single lesion types within individuals (intra-individual homogeneity). These seemingly conflicting reports can be resolved by considering these lesions to be on converging paths where most lesions would ultimately display homogenous characteristics if allowed to progress. Another explanation could be that the different lesion types reflect the heterogeneity of individual's immune responses and possibly stage-dependent alterations in MS. To this date there is still no general consensus explaining different MS lesion types.

In summary, it remains controversial whether the pathomechanism in MS is homogenous or heterogenous and what triggers the transition from RR to SP disease. Most neuroimaging studies do support a conversion from inflammation to neurodegeneration. In contrast, most neuropathology studies support no stage change in individual MS patients.

We will now consider what experimental models of MS have taught us about the underlying immune etiopathology of MS (Table 2). We will propose (1) that MS can be caused by single pathomechanism (1-stage disease theory) or (2)

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