LUPINE PUBLISHERS

Online Journal of Neurology and Brain Disorders

DOI: 10.32474/OJNBD.2021.05.000218

ISSN: 2637-6628

Mini Review

CSF-Mediated Damage in Multiple Sclerosis: More than a Hypothesis

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Received: April 28, 2021 **Published:** May 10, 2021

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), with a neurodegenerative component, representing a major cause of disability in young adults. Although etiopathogenetic mechanisms underlying MS are largely unknown, recent pathological and MRI studies raised the hypothesis of a cerebrospinal fluid (CSF)-mediated mechanism of CNS damage. Since the earliest neuropathological studies [1-3] a preferential location for brain MS lesions in the periventricular white matter (WM) has been observed, although no conclusive explanation for this distribution has been provided. In a single histopathological study [4] a focally abnormal ependymal tissue overlying periventricular WM lesions was found; and it was interpreted as evidence of "ependymitis", namely inflammation of the ependyma. A breakthrough came from the identification of meningeal inflammation with B lymphocytes topographically associated with cortical – especially subpial – demyelinating lesions in MS [5]. This finding was more prominent in progressive than in relapsing-remitting MS patients [5]. In addition to subpial lesions, also subependimal demyelination was associated with the presence of B lymphocyte follicles [6]. These meningeal or ependymal immune system structures may release soluble factors in the CSF [7]. which in turn diffuse into CNS parenchyma, acting as toxic factors damaging gray matter (GM) tissue directly, or indirectly by microglia activation [8]. This pathogenetic mechanism has been referred to as CSF-mediated or surface-in damage in MS.

A defining feature of the CSF-mediated pathogenetic mechanism is that the penetrating lymphocytes (T and B cells) do not directly invade target tissue, but rather they accumulate in the meninges, producing produce soluble factors, which in turn diffuse into brain tissue, where they promote neuronal death and/or activate microglia [5, 9,10]. Indeed, elevated proinflammatory cytokine levels were detected in the CSF of MS patients, which are able to cause neuronal dysfunction and death arise through cytokine-induced synaptic hyperexcitability, glutamate-dependent neurotoxicity or direct cytokine-induced death receptor signaling [11,12]. A recent study [13] demonstrated that CSF from MS patients contains increased levels of C16:0 and C24:0 ceramides, which induce mitochondrial dysfunction and increased glucose and lactate uptake. This condition was defined as "virtual hypoglicosis", because of impaired glucose utilization, despite normal levels in the CSF [14]. Severe or long lasting mitochondrial dysfunction leads to cell swelling and subsequent death, suggest a critical temporal window of intervention for the rescue of impaired neuronal bioenergetics underlying neurodegeneration in MS patients.

Confirmatory in-vivo evidence of the surface-in theory of CSF-mediated inflammatory damage in MS was provided by MRI studies. As first, Liu and colleagues [15] investigated the relationship between periventricular normal-appearing WM abnormalities and the distance from the ventricles by using quantitative MRI. A prominent reduction of magnetization transfer ratio (MTR) near the ventricles was observed in MS patients compared to healthy controls, indicating microstructural WM damage. This abnormality was more prominent in progressive compared to relapsing remitting MS patients, in accordance with the postulated more widespread distribution of the CSF-mediated pathogenetic mechanism in the former phenotype. A similar pattern was observed for WM lesions as well, with more prominent MTR reduction adjacent to the ventricles, decreasing with distance from the ventricles in relapse onset MS patients. A subsequent study [16] demonstrated that an abnormal periventricular MTR gradient can be detected within 5 months of a clinically isolated optic neuritis, independently from the presence of WM lesions. Further confirmation came from the observation of an association between the severity of normal-appearing WM damage assessed by using diffusion tensor imaging (DTI) and the presence of CSF oligoclonal bands [17].

A similar surface-in distribution of damage was also observed within the GM. A gradient of atrophy [18] and microstructural damage [19] of the thalamus, decreasing from the CSF boundary

moving inwards, was observed in pediatric MS patients, demonstrating an early appearance of this pathogenetic mechanism in MS natural history. Furthermore, a surface-in gradient of intracortical pathology was observed by using ultra-high field MRI across MS stages [20] supporting the hypothesis that cortical pathology in MS may be – at least in part – the consequence of a pathogenic process driven from the pial surface. This pattern of damage is likely to reflect meningeal inflammation, accompanied by a substantial gradient of microglial activation in the most external cortical layers [5]. Interestingly, leptomeningeal enhancement identified on post-contrast T2-Fluid attenuated inversion recovery (T2-FLAIR) sequences was proposed as an in vivo marker of meningeal inflammation [21]. Although it was later found not to be very specific for meningeal inflammation, this finding correlates well with cortical GM atrophy [22] suggesting an association with neurodegenerative processes.

Finally, the CSF-mediated pathogenetic mechanism is not limited to the brain compartment but also involves the spinal cord. A recent ultra-high field MRI study [23] showed a peculiar pattern of cervical spinal cord lesion distribution, with prominent involvement of subpial and subependymal surfaces in relapsing-remitting and progressive MS patients, respectively. These findings appear in line with the observation of prominent WM and GM damage in the cervical spinal cord of relapsing-remitting and progressive MS, respectively [24] suggesting different relevance and distribution of CSF-mediated damage between MS phenotypes. Considering the conspicuous evidence supporting the existence of a CSF-mediated damage in MS, this pathogenetic mechanism should be considered more than a hypothesis. Moreover, surface-in gradients of damage were associated with disability independently from WM and GM lesions [16,20,25] underscoring how the underlying mechanisms might represent potential targets for neuroprotective treatments.

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