Multiple sclerosis: Is there neurodegeneration independent from inflammation?

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Abstract

Clinical and magnetic resonance imaging studies in multiple sclerosis have recently suggested that neurodegenerative events may take place in multiple sclerosis brains, which occur independently from inflammation. Here we summarize the results from recent pathological studies, which show, that inflammation is invariably present at all stages and in all forms of the disease. However, the patterns of inflammation differ between different disease stages. This may in part explain, why anti-inflammatory or immunosuppressive treatments fail in progressive multiple sclerosis.
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1. Introduction

Multiple sclerosis is defined in pathology as a chronic inflammatory disease of the central nervous system, which leads to the formation of multiple focal demyelinated lesions in the white matter. Very similar lesions, as those seen in MS patients, can be induced in models of experimental autoimmune encephalomyelitis (EAE), an autoimmune disease, which is induced by active sensitisation of genetically susceptible animals with brain antigens [1]. In addition, autoreactive T-lymphocytes as well as autoantibodies directed against antigens of the central nervous system can be detected in the circulation of multiple sclerosis patients [2]. For this reason it is widely believed that multiple sclerosis is an inflammatory autoimmune disease, specifically directed against myelin antigens. In support of this concept, immunosuppressive or immunomodulatory treatments are effective at least in the early relapsing stage of the disease.

Recent data, however, suggest that the pathogenesis of multiple sclerosis is much more complex and that autoimmune mediated inflammation may only be responsible for a part of the disease spectrum. Several arguments have been put forward during the last years, supporting neurodegenerative mechanisms, which are independent from inflammation, being responsible for at least some aspects of the disease. Serial MRI studies show that subtle focal changes in the white matter can be seen weeks before a classical new lesion is formed [3,4]. Since these alterations precede gadolinium enhancement, they may indicate neurodegenerative events, which occur prior to inflammation. Brain tissue atrophy progresses in multiple sclerosis and these progressive changes are not associated with inflammation, visualized by contrast enhancement in MRI [5,6]. Furthermore, immunosuppressive and immunomodulatory therapies have little effect on atrophy development at least in the progressive stage of the disease [7]. As will, however, be discussed in this short review, neuropathology investigations suggest that these putative neurodegenerative lesions are too driven by inflammation, although the type of inflammation apparently differs from that in classical focal active plaques.

2. What are the initial events in the formation of focal white matter lesions in MS?

As mentioned above, recent MRI based studies suggest that subtle focal tissue alterations may precede the appearance of classical active MS plaques in the white matter. These changes consist of increased signal intensities in magnetisation transfer ratio (MTR) scans [3] and a mild reduction of *N*-acetyl aspartate in magnetic resonance spectroscopy [4]. These alterations may persist for several weeks until they develop into classical active plaques with contrast enhancement and the appearance of lipid degradation products.

To identify the neuropathological correlate of the initial tissue alterations is difficult to address in neuropathological studies, since it requires the availability of serial biopsies or biopsy autopsy combinations. For obvious reasons this is an exceptional situation. One example for this approach is given in a recent study, in which a biopsy was performed in a patient with fulminate inflammatory demyelinating disease, who died a few months later [8]. In this unique situation the biopsy revealed an inflammatory process in the absence of demyelination. The respective autopsy specimen showed a classical active inflammatory demyelinating lesion, consistent with the diagnosis of multiple sclerosis. This study shows in principle that MS plaques may start by inflammation. Since it is, however, a unique case it does not account possible heterogeneity in the mechanisms of plaque formation [9].

The other option to address this question is to study in detail the neuropathological alteration within and in the vicinity of actively demyelinating plaques in patients with acute and rapidly progressing disease, for whom detailed information on the clinical course is available. Gay et al. [10] have followed this strategy and stratified their patients according to time after disease onset. In their material they found mild perivascular infiltration in most recent lesions, but initial tissue damage and demyelination was associated with microglia activation and complement deposition. A massive secondary wave of inflammation with dispersion of T-lymphocytes within the tissue was seen, when full-blown demyelination was apparent. In a similar approach, Barnett and Prineas [11] described initial oligodendrocyte apoptosis and demyelination associated with microglia activation in the absence of infiltration of the CNS parenchyma by T-lymphocytes. Massive T-cell infiltration too was only encountered in lesions with advanced myelin destruction. However, even in this study mild perivenous lymphocytic inflammation was already present in initial lesions.

In a third study demyelinating lesions in MS brains were analysed in relation to pre-mortem MRI changes [12]. Using this approach it was found that a substantial number of focal white matter changes revealed by MRI, were not visible in the sectioned brain. These lesions, called (p)reactive, were characterized by mild perivascular inflammation, edema and microglia activation. It was suggested that these lesions may represent very early stages of focal demyelinated plaques, although it was left open, to what extent remyelination [13]

or secondary Wallerian degeneration can account for similar tissue changes.

Taken together, all these studies agree that the most initial tissue changes in focal white matter lesions occur on a background of mild perivenous inflammation. However, initial damage of myelin sheaths is associated with activated microglia in the absence of local tissue infiltration by T-cells. With progression of demyelination and tissue injury there is a massive augmentation of T-cell infiltration into the lesions. What drives microglia activation in the initial stages of lesion formation and why such lesions may persist for several weeks is currently unknown.

3. Inflammation and neurodegeneration in the progressive stage of multiple sclerosis

Actively demyelinating focal plaques in the white matter of the central nervous system, showing profound gadolinium enhancement [14], are the hallmark of pathology in acute and relapsing MS [15]. Such lesions, however, become increasingly rare in the progressive stage. In contrast, in primary and secondary progressive MS diffuse brain atrophy – affecting both the grey and the white matter – and diffuse axonal loss within the normal appearing white matter (NAWM) are prominent [5,16,17]. In pathology, massive primary demyelination is present in the cerebral cortex [18,19,15], and in addition profound diffuse injury of the NAWM is seen [15].

Cortical lesions are characterized by primary demyelination, associated with a mild but variable degree of axonal injury and neuronal loss [19]. Demyelination in active cortical lesions occurs at sites of microglia activation, but the tissue infiltration by T- and B-lymphocytes is sparse [20]. Is this an indication for neurodegeneration in the absence of inflammation? Pathology reveals a different interpretation. Cortical plaques, at least when they are active, are invariably associated with inflammatory infiltrates in the meninges, covering the lesions [15]. The inflammatory infiltrates are composed of T-lymphocytes, B-lymphocytes and plasma cells. These data in addition to the fine topographical orientation of cortical lesions suggest that demyelination is triggered by soluble factors produced by lymphocytes and plasma cells, which induce myelin damage either directly or indirectly through microglia activation. This interpretation is supported by recent studies, analysing the pathogenesis of cortical plaques in autoimmune encephalomyelitis. Cortical demyelination in similar extent and lesional distribution as in MS is found in marmoset EAE, induced by immunisation with myelin oligodendrocyte glycoprotein or myelin [21]. In this model too lymphocytes and plasma cells are present in the meninges, while demyelination is associated with activated microglia. In the phase of active demyelination cortical myelin sheaths are dressed by immunoglobulin and activated complement.

In addition to cortical demyelination, diffuse injury of the normal appearing white matter is prominent in patients with primary and secondary progressive MS [22,15]. Injury in the NAWM is mainly reflected by axonal degeneration with

secondary myelin destruction. This is a feature, which is distinctly different from that seen in focal white matter plaques. It has been suggested that axonal degeneration in the NAWM is due to Wallerian degeneration, resulting from axonal loss within plaques [23]. Although secondary Wallerian degeneration exists without doubt in chronic MS brains [24], alone it is not sufficient to explain the extent of axonal damage in the NAWM. Extensive injury in the NAWM is not only found in patients with large and destructive focal white matter lesions, but also in patients with very few and small focal plaques [25,6,26]. Furthermore, we found no significant correlation between diffuse axonal damage in the NAWM with the global load of focal white matter lesions [27,15]. Thus, diffuse WM injury in MS patients develops at least in part independently from focal demyelinated plaques. Diffuse white matter injury is also associated with perivascular and parenchymal infiltration of the CNS tissue by T-lymphocytes and with massive microglia activation [28,15].

Why is such a global and diffuse inflammatory reaction in progressive MS not associated with contrast enhancement in MRI and why does it not respond to immunosuppressive or immunomodulatory treatment? Serafini et al. [27] recently showed that in progressive MS lymph follicle like structures are formed in meninges and perivascular spaces. In addition, several different cytokines and chemokines, which are involved in leukocyte homing within lymph nodes are expressed in the chronic inflammatory environment in progressive MS [29]. These data suggest that inflammation in MS becomes in part compartmentalized within the central nervous system and is located behind a normal or repaired blood brain barrier. A paraclinical correlate of such a compartmentalized immune reaction appears to be the intrathecal immunoglobulin synthesis, which is a characteristic feature of chronic MS.

4. Conclusions

Neuropathology does not provide any support for the concept, that in MS brains there is a neurodegenerative component, which occurs in the absence of or independently from inflammation. On the contrary, inflammation is present at all stages of the disease. The type of inflammation is however different between different stages, providing a possible explanation for the absence of contrast enhancement and the failure of immunosuppressive therapies in primary and secondary progressive MS. Whether inflammation is always the cause of progressive tissue injury in this disease awaits further clarification.

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