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New insights into the pathology of multiple sclerosis: towards a unified concept?

Abstract Understanding the disease processes underlying multiple sclerosis is crucial to optimise treatment and to develop new therapeutic entities. Our understanding has been dominated by the inflammatory model of multiple sclerosis. More recently, a neurodegenerative model of the disease process has been developed which complements the inflammatory hypothesis in understanding the disease process and suggests a way forward to develop more effective treatments. Histopathological studies have shown that the early disease stage is characterised by acute inflammatory attacks, with T-cell infiltration, gliosis and acute demyelination. Axonal damage is also generally visible at this stage. In late-stage disease, continuing slow axonal damage may remain in the absence of signs of inflammation. Inflammation may not always have a deleterious outcome in multiple sclerosis since the release of growth factors from immune cells may protect neurones against axonal damage or facilitate axonal repair. The processes underlying lesion development appear to be heterogeneous, in some cases being driven by immune-cell mediated gliotoxicity and in others by primary gliopathy. Remyelination occurs to differing degrees in different individuals, and the reasons for this heterogeneity are poorly understood. Finally, the antigens that trigger the autoimmune response have not been characterised and may differ between patients. Candidates include myelin proteins, oligodendrocyte precursor proteins and axonal constituents. These different aspects of pathophysiology need to be brought together in a unified hypothesis of disease, but current knowledge does not permit such a hypothesis to be proposed.

Key words Multiple sclerosis · information · neurodegeneration

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Introduction

Understanding the disease processes underlying multiple sclerosis is crucial to optimising treatment and to developing new therapeutic entities. Our understanding has been dominated for fifty years by the inflammatory model of multiple sclerosis. Although this has been very successful in providing improved diagnosis of multiple sclerosis and has led to the development of partially effective anti-inflammatory treatments for the disease, the inflammatory model has difficulty in explaining all the pathological and clinical features of the disease. More recently, a neurodegenerative model of the disease process has been developed which may help explain certain deficiencies of the inflammatory hypothesis and suggests a way forward to develop more effective treatments. However, the relationship between the inflammatory and neurodegenerative models remains a subject of much debate, particularly with respect to the causal and temporal association between the two postulated disease mechanisms. In particular, different contributions of inflammation and neurodegeneration may help explain differences in clinical presentation both across the course of disease, within individual patients and between different patients. This article reviews the contribution of histopathological studies to our understanding of the mechanisms of disease in multiple scle-

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rosis and addresses the question of whether these data support a unified concept, or a single disease mechanism, for the disease process.

This approach requires a detailed and accurate description of the neuropathology in a large number of patients at key stages in the disease process throughout the disease course, including at first clinical presentation (clinically isolated syndrome), during the early relapsing-remitting stage, before and after conversion to a secondary progressive course and at end stage disease. However, unlike what can be done with non-invasive diagnostic procedures such as magnetic resonance imaging, it is very difficult to obtain histopathological material across the disease process.

In general, autopsy material is gathered very late in the disease process, whereas biopsy material supplies information in the early stages of disease when this has been performed to aid differential diagnosis. More rarely, autopsy material is available from early stage disease in the case of accidental death or acute fulminant disease leading to the death of the patients (the so-called Marburg's variant of MS) (Fig. 1). On the other hand, material is usually unavailable for the very early stages of the disease and for the critical period when relapsing-remitting disease converts to a progressive course. Histological samples prepared from biopsies show clear differences between early and established disease, but finer characterisation of the disease process is proving more difficult to demonstrate due to the shortage of material across the course of the disease.

Identifying the CNS targets of the autoimmune response

The central epitopes that trigger the autoimmune response in multiple sclerosis are still unknown and their role in producing the characteristic pattern of tissue damage seen in the disease remains to be elucidated.

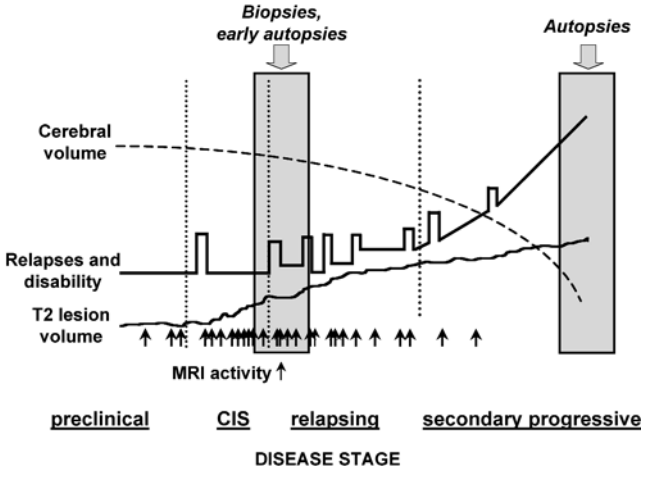

Fig. 1 Autopsy and biopsy sampling in relation to the disease stage

Antibodies against myelin components generated in the autoimmune response (Table 1) may interfere with remyelination. These include myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte protein (MOG). For example, anti-MOG antibodies have been identified in brain tissue removed from patients with multiple sclerosis at autopsy [21] and are indeed found in higher amounts within the brain than in serum or CSF. Local production or accumulation of anti-MOG antibodies within the lesions may drive the process of demyelination.

AN2 is a cell-surface glycoprotein expressed on oligodendrocyte progenitor cells in the developing and adult CNS [26]. Antibodies against AN2 have been reported in the cerebrospinal fluid from certain patients with multiple sclerosis with active relapses [20]. In in vitro systems, these antibodies block migration of oligodendrocyte precursor cells, synthesis of myelin and may lead to lysis of oligodendrocytes. The presence of such antibodies may play a pathological role in multiple sclerosis by preventing remyelination and explain why some patients are unable to remyelinate.

Axon-directed antibodies have also been detected in the cerebrospinal fluid of patients with multiple sclerosis [29]. Immunostaining for these antibodies can be detected in autopsy material and is associated with the characteristic axonal pathology of multiple sclerosis (axonal transection, swollen APP-staining ovoids and Wallerian degeneration). This staining was not restricted to the active lesion itself but also extended into white matter without apparent demyelination. Interestingly, axonal damage was dissociated from oligodendrocyte pathology.

Evidence for a specific CNS-directed antibody has been well characterised in Devic's disease (neuromyelitis optica). Seropositivity for a specific immunoglobulin (NMO-specific IgG) is present in around three-quarters of all cases of Devic's disease. Recently, the epitope recognised by NMO-specific IgG has been

Table 1 Proteins expressed in oligodendrocytes that may be targets for the autoimmune response

Myelin basic protein (MBP)
Proteolipid protein (PLP)
Myelin associated glycoprotein (MAG)
Myelin oligodendrocyte glycoprotein (MOG)
Transaldolase
Oligodendrocyte surface protein (OSP)
Oligodendrocyte myelin glycoprotein (omGP)
NOGO
NG2
Glycolipids

identified as aquaporin-4 [15]. This is a channel protein specifically expressed in astrocytes that allows the passage of water across the cell membrane. Although these antibodies have not been identified in classical multiple sclerosis, they may represent the first example of the characterisation of a specific antibody responsible for an autoimmune demyelinating disease.

Inflammation in early versus late disease

Although it is rare to see very early disease biopsies, there has been one report of two serial biopsies taken from a patient at initial presentation of multiple sclerosis [5]. The first sample was obtained 33 days after the first appearance of disseminated neurological symptoms. At this stage, the sample showed inflammation without demyelination. Macrophages and T lymphocytes could be observed infiltrating across the walls of small vessels and distributed diffusely throughout the white matter. In addition, biochemical markers of inflammation, such as mRNA for tumor necrosis factor alpha (TNFα) and for inducible nitric oxide synthase (iNOS) were expressed abundantly. On the other hand, there was no evidence for damage to myelin sheaths at this stage. In contrast, by the time the second biopsy was taken 76 days later, confluent demyelinating lesions had developed, and this was seen alongside a diffuse infiltration of macrophages with inclusions that stained for myelin markers. Expression of mRNA for TNFα and iNOS was observed in close proximity to damaged axonal sheaths [5].

Generally speaking, biopsy material from early-stage disease provides a picture of disease activity characterised by acute inflammatory attacks, with T-cell/macrophage infiltration, active ongoing demyelination and the presence of reactive astrocytes (Fig. 2). However, there is also evidence right from the beginning of acute axonal damage [9] which can be visualised as swollen axonal terminals and transected neurites staining for axonal precursor protein (APP).

By contrast, in samples taken from late-stage disease, chronic lesions are demyelinated, with few T-cells visible. Glial scarring represents the stigmata of reactive gliosis seen earlier in the disease. Activated microglia are however present in these 'burnt-out' lesions. Impor-

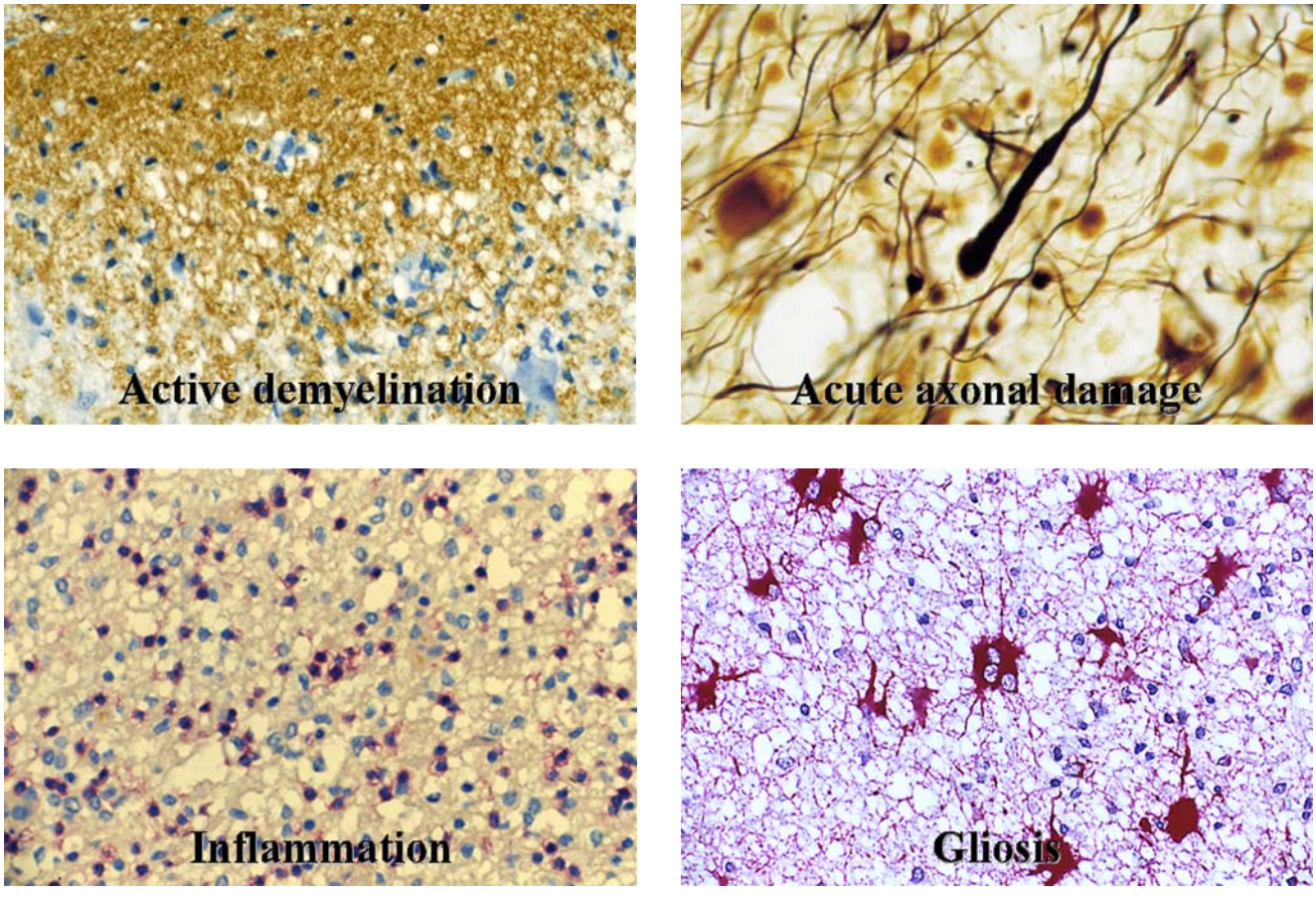

Fig. 2 Typical histological markers of disease observed in early-stage multiple sclerosis

tantly, demyelination can be observed not only in white matter but also in more remote cortical grey matter [12, 22]. Extensive axonal loss is observed systematically in juxtaposition with these lesions and can also be seen in tissue without visible demyelination [22, 27]. Even in late-stage disease, some continuing slow axonal damage may remain.

One study has quantified the extent of axonal damage as measured with APP staining and compared this to the presence of markers of inflammation at different stages of the disease process [14]. As expected, the presence of T-cells, CD3- or CD8-positive cytotoxic T-cells, macrophages and microglia is more pronounced in lesions during the early stages of disease. Moreover, the highest number of APP-staining axons, a marker of acute axonal damage, was also observed in these early lesions (Fig. 3) and their number correlated well with the extent of infiltration by immune cells [14]. Although the number of these APP-positive neurones was highest in these actively demyelinating lesions, significant numbers could also be observed in the inactive demyelinated lesions found in later disease stages (Fig. 3). This finding would be consistent with the idea that an active process of axonal damage can persist, albeit at a low level, in multiple sclerosis lesions for many years after inflammation has ceased.

The notion that axonal damage may persist independently of inflammation in multiple sclerosis is also supported by studies of autopsy samples from patients who had undergone autologous haematopoietic cell transplantation. This procedure aims to eliminate the 'immune memory' of whatever epitope triggers the autoimmune inflammatory attack on the nervous system and has been shown to suppress inflammatory activity in multiple sclerosis effectively. Although there were very few T-cell infiltrates detected in these autopsy samples, extensive staining for APP was visible as well as markers of acute demyelination (personal observation). Again, this study suggests that axonal damage and demyelination can continue in the brains of patients with multiple sclerosis despite effective suppression of inflammation.

Detrimental versus beneficial effects of inflammation in multiple sclerosis

Although immunosuppressive therapy may seem a rational approach to multiple sclerosis treatment, given the evidence for the underlying inflammatory processes, several studies suggest paradoxically that inflammation may not always have a deleterious outcome in multiple sclerosis. In particular, the release of growth factors from immune cells infiltrating the nervous system may protect neurones against axonal damage, or facilitate axonal repair, remyelination or both. For example, brain-derived neurotrophic factor (BDNF) is expressed and secreted by activated T-cells, B cells, and monocytes. This can be demonstrated for myelin-reactive T-cells in inflammatory infiltrates in the brain of patients with multiple sclerosis [11]. In addition, cytokines or growth factors released from activated macrophages may facilitate the promotion or differentiation of oligodendrocytes thus facilitating remyelination [8].

Evidence for this beneficial neuroprotective role of

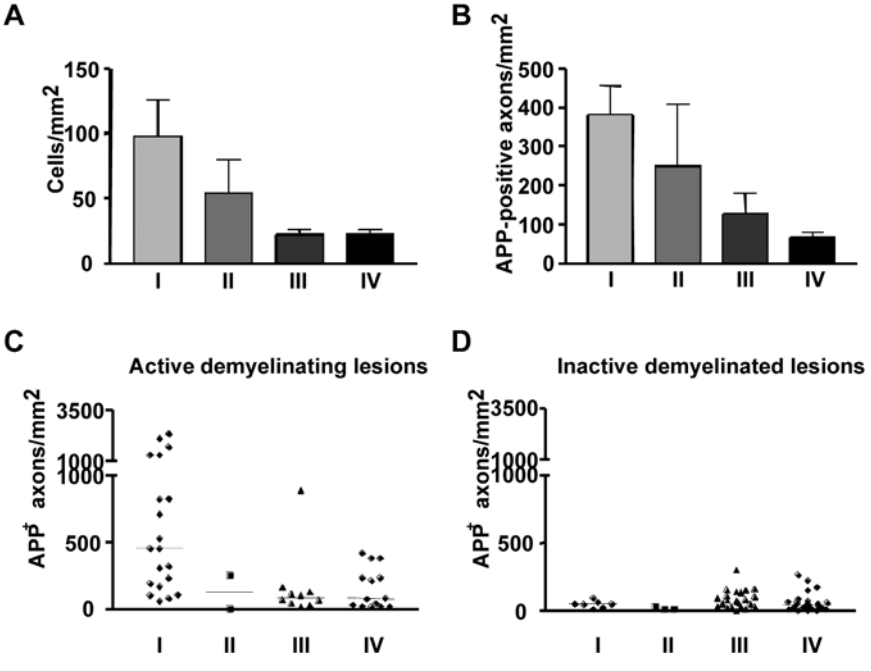

Fig. 3 **A** Number of CD3-positive T-cells in multiple sclerosis lesions as a function of disease duration. **B** Number of amyloid precursor protein (APP) staining axons in multiple sclerosis lesions as a function of disease duration. **C** Number of APP staining axons in active demyelinating lesions as a function of disease duration. **D** Number of APP staining axons in inactive demyelinated lesions as a function of disease duration. I: less than one year; II: one to five years; III: five to ten years; IV: over ten years. Data taken from [14] by permission of Oxford University Press

inflammation has accumulated recently, notably from studies in experimental animals and in vitro. For example, the inoculation of rats with autoimmune T-cells specific to myelin basic protein can protect retinal ganglion cells from degeneration following a partial crush injury to the optic nerve [19]. On the other hand, depletion of macrophages in rats has been shown to lead to a reduction in the rate of oligodendrocyte-mediated remyelination following lysolecithin-induced demyelination in the spinal cord [13]. In vitro, macrophage enrichment of brain cultures promotes myelination and enhances the capacity to remyelinate following a demyelinating episode [8].

BDNF appears to play a key role in promoting remyelination and axonal repair in multiple sclerosis [7, 25]. BDNF is expressed in active lesions, notably by immune cells (T-cells and macrophages or microglia) and reactive astrocytes, whereas the BDNF receptor trkB is present on neurones and glial cells around the lesion [25]. Furthermore, the extent of BDNF expression is related to the degree of anti-inflammatory activity within the lesion. The possibility that inflammatory infiltrates have a neuroprotective effect in the nervous system may account for the limited effectiveness of non-selective immunotherapies in preventing disability progression.

Heterogeneity of multiple sclerosis

A challenge to uncovering the fundamental disease mechanisms underlying multiple sclerosis is the high degree of pathophysiological heterogeneity of lesions. This heterogeneity may exist between patients (inter-individual heterogeneity), between lesions in the same patient (intra-individual heterogeneity) and over time or according to disease stage (temporal heterogeneity). It is not clear to what extent heterogeneity in lesion presentation relates to the variation in clinical phenotype and clinical course observed between different patients with multiple sclerosis, although it would be reasonable to expect that such associations exist.

The heterogeneity of disease seen in different lesions, at different stages or in different patients may be due to heterogeneity in the mechanisms of disease that lead to the formation of the lesions [17]. A classification of lesion types based on immunocytochemical characteristics has been proposed as a framework to distinguish between different mechanisms of lesion formation (Table 2) [6, 16]. This classification proposes four fundamental lesion types.

Type I and Type II lesions appear to arise from immune-mediated damage. In the Type I lesion, originally characterised by Traugott et al., immunostaining for CD4+ and CD8+ T-cell populations and macrophages predominate [28]. Demyelination is driven by T-cell-activated macrophages that damage and phagocytose the myelin. T-cell markers are also present in the Type II lesion, but B-cell activity, visualised by staining for immunoglobulin G, is also present [24]. In these lesions, antibody-complement-mediated damage may make an important contribution to demyelination. Type II lesions are the most frequently observed, making up approximately 50% of total lesion load. Type III and Type IV lesions are proposed to arise primarily from gliopathy rather than from immune-mediated attack. The pattern of gliopathy typical of Type III lesions was first described by Itoyama et al. [10], who demonstrated that expression of myelin-associated glycoprotein was altered in otherwise normally appearing oligodendrocytes and suggested that this may be the first immunocytochemical signal of lesion formation [10]. This type of gliopathy was subsequently replicated in an animal model and shown to lead to retrograde degeneration of the distal processes of affected oligodendrocytes [18]. It has been suggested that this pattern of gliopathy represents apoptotic cell death [16]. Type IV lesions, on the other hand, correspond to a currently unknown mechanism of oligodendrocyte degeneration [16]. Type IV lesions are encountered only rarely.

Intra-individual heterogeneity of lesion types appears to be limited, at least at a given stage of disease, with multiple active lesions from the same patient generally showing a similar immunocytochemical hallmark [16]. In particular, there is no evidence for different patterns of demyelination being specific for different parts of the nervous system.

On the other hand, it is possible that different lesion types may appear at different stages of the disease. This

Table 2 Patterns of disease in multiple sclerosis. MAG: myelin associated glycoprotein. Adapted from [16]

Pattern	Primary disease mechanism	Characteristic feature	Reference
Pattern I	T-cell-mediated or T-cell plus antibody-mediated autoimmune mechanisms	T-cell/macrophage mediated lesion	Traugott et al. 1983 [28]
Pattern II		Antibody/complement mediated lesion	Prineas and Graham 1981 [24]
Pattern III	primary oligodendrocyte dystrophy, reminiscent of virus- or toxin-induced demyelination rather than autoimmunity	Distal oligodendrogliopathy with MAG depletion. Oligodendrocyte death predominantly from apoptosis	Itoyama et al. 1980 [10], Ludwin and Johnson 1981 [18]
Pattern IV		Oligodendrocyte death in the periplaque white matter	Lucchinetti et al. 2000 [16]

is difficult to assess directly as it is extremely rare to have access to serial biopsy samples from the same individual. Barnett and Prineas assessed a series of twelve patients who died shortly after the occurrence of a relapse, and investigated the newly-forming lesions in autopsy material [2]. They found that, in several of these patients, the initial lesions corresponded more or less to the Type III lesions described above. They were characterised by extensive oligodendrocyte apoptosis and microglial activation in the absence of notable infiltration by T lymphocytes or phagocytic cells. In other patients, more mature lesions showed signs of complement-mediated damage to myelin. These authors postulated that the initial event in lesion formation was apoptotic oligodendrocyte death which triggered infiltration by phagocytic macrophages with subsequent amplification of the inflammatory response [3]. This notion led them to suggest that the pathological heterogeneity observed in multiple sclerosis was principally due to temporal changes in the pathological mechanisms, rather than heterogeneity in these mechanisms per se.

An alternative hypothesis would be that the different lesion patterns are specific for individual subgroups of patients, and remain stable over time (i. e. inter-individual heterogeneity). This hypothesis is supported by the lack of correlation between the lesion patterns observed and the time between disease onset and when the biopsy or autopsy sample was obtained, as well as by the failure to demonstrate 'mixed' patterns of intermediate lesion pathology where complement deposits (characteristic of Type II) could be observed superposed on dystrophic oligodendrocytes (i. e. Type III). In one patient who underwent a first biopsy in February 2002 followed by another in August 2004, no differences in the lesion pathology could be seen between the two biopsy samples, which in both cases corresponded to Type II pathology (personal observation).

Such studies are also leading to a fundamental change in the way we view the pathogenesis of multiple sclerosis. Thus, rather than starting with an initial immune attack on the nervous system, at least in some patients, neurodegenerative changes may occur before inflammation can be detected. Nonetheless, whatever the initial pattern of lesion pathology, all active lesions appear to converge to a unique form of 'burnt-out' chronic lesion and the same residual neuroaxonal loss. Clinically, this is reflected in the observation made in the Olmstead County cohort that clinical outcome is quite similar in all patients, regardless of the nature of the lesions observed in biopsy samples at earlier stages of the disease [23].

Remyelination in chronic multiple sclerosis lesions

Clinical outcome may depend to a significant degree on the extent of subsequent remyelination of chronic lesions. In autopsy material, some lesions seem to be successfully remyelinated, whereas no relevant remyelination occurs in others. Although not all patients have plaques capable of remyelination, an estimated 40% of all plaques may remyelinate to some extent [1]. Understanding the mechanisms of remyelination is limited by the fact that it is not possible to determine from autopsy samples when during the disease process the remyelination occurred, and by difficulty in distinguishing and tracking remyelinating plaques using magnetic resonance imaging [1]. However, the extent of remyelination does not appear to be related to the pathological characteristics of the early active lesions, at least in early stages of disease. Little clinical data are available on the consequences of remyelination, although patients with extensive remyelination tend to be older at the time of death, suggesting that remyelination may promote survival.

Further characterisation of the factors that determine the balance between demyelination and remyelination are required in order to help identify targets for therapy. Even in the chronic disease stage, treatment may still be an option, due to plasticity of the oligodendrocyte lineage, even in the adult, which provides the potential for myelin repair [4].

Conclusion

Although recent years have seen important advances in our understanding of the pathophysiology of multiple sclerosis, the complexities of the disease process have become evermore apparent and we are still far from being able to construct a unified concept for the disease. There appear to be several facets of the disease process whose relationship may vary between affected individuals and across the disease course. A unified concept of disease would need to take into account target antigens, which remain to be identified, lesion heterogeneity, and the relative importance of deleterious and beneficial inflammation and of inflammation and neurodegeneration at different stages of the disease process.

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