Chapter 2
Demyelination and Remyelination in Multiple Sclerosis

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2.1 Introduction

The defining trait of multiple sclerosis (MS) histopathology is the presence of spatially separate focal areas of demyelination (called MS lesions, or plaques) of different age and inflammatory activity in the central nervous system (CNS). Although the nature and cause of the initial MS lesion change are not known, recent years have seen major advances in our understanding of MS pathology and pathogenesis. The aim of this review is to give a brief account of the histopathology of demyelination and remyelination in MS, with an emphasis on some issues of current interest in MS pathology research, including MS lesion staging, pathological heterogeneity, gray matter pathology, and axonal loss.

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2.2 Demyelination in MS

2.2.1 MS Lesion Classification

Lesion staging is important in order to distinguish the sequence of events in MS pathogenesis. Several staging systems have been proposed (van der Valk and De Groot 2000), partly reflecting an uncertainty about the nature of initial lesion changes. Despite the recent advances of imaging studies, MRI still lacks pathological specificity, and hence the evolution of MS lesions has to be deducted from pathological studies. Unfortunately, animal studies are also of limited value in lesion classification as MS is a disease specific to humans and the lesion evolution can only be indirectly extrapolated from experimental autoimmune encephalomyelitis (EAE) models. Any MS lesion staging system is thus a hypothesis that attempts to reconstruct a temporal sequence of lesion evolution from still images from different lesions. Complicating this issue is the MS pathological heterogeneity, clinical heterogeneity, and variability of MS lesion pathology dependent upon lesion location (Bo et al. 2003a; Confavreux and Vukusic 2006; Lucchinetti et al. 2000; Peterson et al. 2001; Revesz et al. 1994). The choice of MS classification system will to some extent reflect the research area of interest, for example, the role of chronic inflammation in MS pathogenesis or the mechanisms of early demyelination. MS lesions have therefore been classified according to multiple variables, including lesion location and distribution, pattern and extent of inflammation, presence of myelin/myelin degradation products in macrophages, extent of remyelination, pattern of oligodendrocyte loss, and presence of complement deposition (Bo et al. 1994, 2003b; Frohman et al. 2006; Gay et al. 1997; Lassmann et al. 1998; Lucchinetti et al. 2000; Sanders et al. 1993; Trapp et al. 1998; van der Valk and De Groot 2000).

2.2.2 MS Lesion Location

The location of MS lesions is critical in any therapy aiming to repair individual lesions, such as cell transplantation. Any treatment employed will likely to be met with partial response unless it can be used in gray and white matter, in the brain as well as the cord. Furthermore it is important to note that only a proportion of pathologically proven lesions are visualized with our current MR techniques and this is especially important for the gray matter (Seewann et al. 2011). MS lesions may occur anywhere in the CNS parenchyma, the predilection sites being the optic nerve and chiasm, periventricular white matter, subpial cerebral and cerebellar cortex, brain stem, and cervical spinal cord. Gray matter demyelination has been recognized to be widespread in MS, and especially in the spinal cord, it appears to be even more extensive than white matter demyelination (Fig. 2.1) (Bo et al. 2003b; Gilmore et al. 2009; Kutzelnigg et al. 2005; Sanders et al. 1993; Vercellino

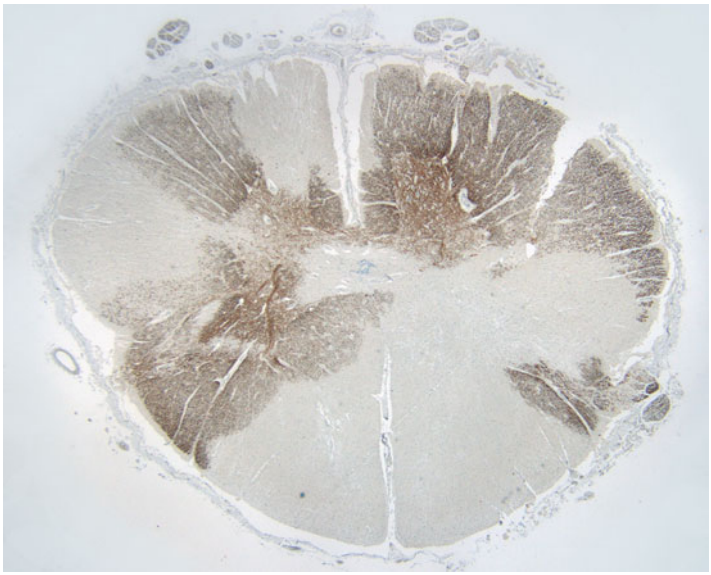

Fig. 2.1 Spinal cord demyelination. The spinal cord is a predilection site for MS lesions, and in many advanced cases, only islands of myelinated tissue remain in both the white and gray matter. Immunolabeled for MBP

et al. 2005). A proportion of chronic MS patients have a pattern of subpial cerebral demyelination in all cerebral regions; this has been termed general subpial demyelination (GSD (Bo et al. 2003b; Vercellino et al. 2005)). GSD probably represents the extreme end of a spectrum, rather than a distinct subgroup. In some GSD patients, the percentage of demyelinated area in cerebral cortex may approach 70 % (Bo et al. 2003b). The GSD patients do not have an increased percentage of demyelination in white matter, indicating that the pathogenesis in some MS cases may have a specificity for gray matter myelin (Bo et al. 2003b; Vercellino et al. 2005). Cortical GM lesions may be divided into three subtypes depending on lesion location: (1) combined WM/GM lesions, (2) lesions located entirely within GM, and (3) subpial lesions (Peterson et al. 2001).

2.2.3 Inflammation

White matter MS lesions are usually divided into active, chronic active, or chronic inactive, based upon pattern and extent of inflammation (Bo et al. 1994; Trapp et al. 1998; van der Valk and De Groot 2000). In active lesions, there is macrophage infiltration throughout the lesion; in chronic active lesions, there is macrophage infiltration at the lesion border but little infiltration at the lesion center; and in chronic inactive lesions, there is little infiltration throughout the lesion. In chronic

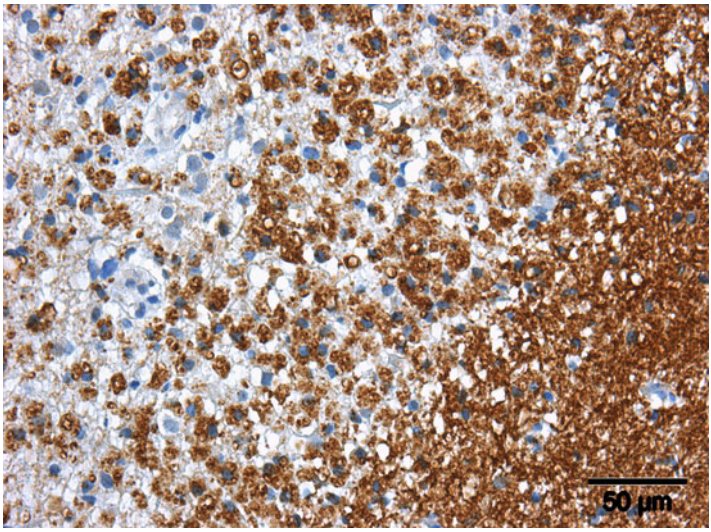

Fig. 2.2 Actively demyelinating MS lesion. Myelin basic protein (MBP) is a major constituent of the myelin sheath of oligodendrocytes in the central nervous system. Macrophages phagocytosing myelin debris can be easily detected in actively demyelinating lesions

MS, chronic active lesions are the most common lesion subtype in the brain (Bø, unpublished observation), whereas most of the lesions in the spinal cord are inactive (Tallantyre et al. 2009). The chronic persistence of inflammation in MS lesions may be clinically relevant as it may mediate lesion growth and chronic axonal loss.

2.2.4 Myelin/Myelin Degeneration Products in Macrophages

The degeneration of myelin and myelin degeneration products in macrophages after myelin phagocytosis follows a predictable time course, which may give information about the age and activity level of individual MS lesions/lesion areas. Major myelin proteins, such as PLP and MBP (Fig. 2.2), can be detected immunohistochemically in macrophages for 2–3 days, while the smaller in size myelin protein MOG, which accounts for only 0.05 % of the total myelin proteins, or CNP (Fig. 2.3a) is only detectable for approximately 1 day after phagocytosis (van der Goes et al. 2005). In one of the proposed clasification systems, immunopositivity for minor myelin proteins within macrophages is considered to signify early active lesions, minor myelin proteins late active lesions and all other lesins were considered inactive (Bruck et al. 1995 Davie et al. 1994). It is possible that the sensitivity of immunohistochemistry for minor myelin proteins in macrophages also may depend upon the rate of ongoing myelin degradation, however, so that minor myelin protein degradation in "slow burning" demyelination may go undetected. As for histochemical myelin lipid

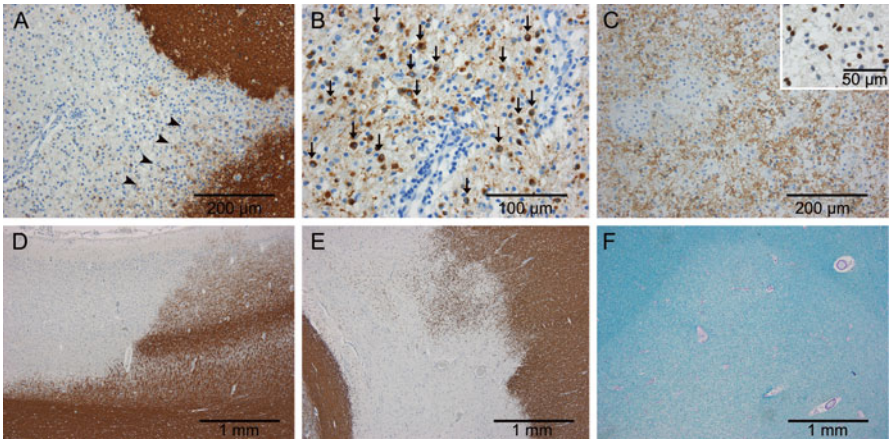

Fig. 2.3 Remyelination. In early MS lesion stages (**a**–**c**), remyelination is a common phenomenon, whereas remyelination is often limited or absent in chronic MS lesions (**d**, **e**). In early MS lesions with ongoing demyelination characterized by macrophages containing myelin degradation products (*arrow heads* in **a**), oligodendrocytes are frequently preserved even in completely demyelinated lesion areas (*arrows* in **b**). Remyelinating lesion areas are characterized by thin irregularly formed myelin sheaths (**c**); furthermore numerous olig2-expressing oligodendroglial lineage cells are present (*insert* in **c**). In chronic MS, demyelinated lesions are localized not only in the white matter but also in the cortex (**d**). Remyelination is frequently limited to the lesion border (**e**); however, approximately 20 % of the chronic MS lesions are completely remyelinated (so-called shadow plaques) (**f**). Immunohistochemistry for CNPase (**a** and **c**), immunohistochemistry for NogoA (**b**), immunohistochemistry for MBP (**d** and **e**), Luxol-Fast-Blue staining (**f**), immunohistochemistry for Olig2 (*insert* in **c**)

stains, Luxol Fast Blue is thought to persist for a few days within macrophages, while oil red O may persist a few months (Davie et al. 1994).

2.2.5 Pathological Heterogeneity

An interindividual heterogeneity in the pathology of white matter MS lesions has been described in a material of biopsies and autopsies from MS patients with acute MS or MS with a short disease duration (Lucchinetti et al. 2000). Four pathology subtypes were described (1) lesions with oligodendrocyte loss within the demyelinated area, no signs of complement activation; (2) lesions similar to (1), but with signs of complement activation; (3) lesions with a lesional and perilesional loss of oligodendrocytes by apoptosis, no sign of BBB loss, and no sign of complement activation; and (4) lesions characterized by lesional and perilesional extensive loss of oligodendrocytes, but no signs of oligodendrocyte apoptosis. Type 4 lesions are very rare. In individual patients, all active lesions had the same pattern; no intraindividual heterogeneity was observed. In a later report, early lesions with elements

in common both with the type 3 and type 2 lesion pattern were described in seven MS patients with a short disease duration (Barnett and Prineas 2004). These changes were detected in areas of only slight myelin pathology, which may have represented a very early lesion stage. In the great majority of chronic MS patients, complement and immunoglobulin deposits were found similar to pattern 2 lesions (Breij et al. 2008).

The examination of autopsy specimens cannot predict the clinical classification of MS. In all types of MS, the pathological hallmarks of inflammation, demyelination, and axonal loss are present. In PPMS, fewer demyelinating gray and white matter lesions are detected, but the degree of axonal loss seems to be similar to SPMS. This raises the possibility that axonal loss is, to a significant degree, independent of demyelinating lesions or that axons in PPMS are more vulnerable to damage even with a modest degree of inflammation (Tallantyre et al. 2009).

2.3 The Cellular Components of the MS Lesion

2.3.1 Oligodendrocytes and Myelin

Oligodendrocyte loss has been postulated by Barnett (Barnett and Prineas 2004) to be the initial event in lesion formation. Certainly in the center of chronic inactive lesions, oligodendrocytes are in general not detected, but in other lesion types, there is a large degree of variability of oligodendrocyte numbers, as high numbers of oligodendrocytes may be present both in active lesions and at the inflammatory edge of chronic active lesions. A recent study indicates that this variability may be mainly interindividual, as in a subgroup of MS patients a high number of oligodendrocytes were retained in lesion areas (Patrikios et al. 2006). The failure to detect oligodendrocytes in chronic lesions may be due to technical factors, as PLP-immunopositive oligodendrocytes were detected in chronic lesions using highly sensitive immunohistochemical methods (Chang et al. 2002). In the chronic MS lesions, oligodendrocyte processes were extended to axons but did not seem to be able to initiate the formation of myelin. This suggests that there are molecules expressed by demyelinating axons in MS lesions that inhibit the initiation of myelination. PSA-NCAM, an adhesion molecule expressed by axons in lesion areas, may have such a function. The extent of oligodendrocyte loss in gray matter lesions is similar to that in white matter lesions. The mechanisms of oligodendrocyte death in MS are not well characterized. In active lesions, cells with dense pyknotic nuclei are frequently observed, indicating an apoptotic process. Oligodendrocyte nuclear fragmentation is rare, however, and cells with dense “apoptotic” nuclei are not immunostained with anti-caspase 3 antibodies, suggesting an apoptosis through non-caspase-dependent mechanisms. In some MS patients, a pattern of “dying back oligodendrogliopathy” has been described, where the initial change observed is in the most distal part of the oligodendrocyte, the periaxonal process, suggesting a critical role of disturbed oligodendrocyte function in the initiation of demyelination

(Rodriguez and Scheithauer 1994). Oligodendrocytes in MS lesion areas express MHC class I which may make them susceptible to damage by CD8 positive T cells (Hoftberger et al. 2004) with vesicular dissolution of myelin, prior to phagocytosis by macrophages.

2.3.2 Astrocytes

In the majority of chronic inactive white matter MS lesions, there is prominent astrogliosis, with a dense meshwork of glial fibrillary acidic protein (GFAP)-positive processes. In active lesions, large hypertrophic astrocytes may be present, which may appear to be in close proximity or even contain the cell bodies of one or more oligodendrocytes. This process seems to be different from phagocytosis. The reactive astrocytes of MS lesions frequently contain myelin or myelin degradation products. Astrogliosis is also detected in diffusely abnormal white matter areas with concomitant microglial activation and BBB abnormality. The cause of the general astrocyte activation outside of lesions is unclear, possibly related to inflammatory mediators, diffusing from lesions, stimulating this proliferation. In contrast, in purely cortical lesions, astroglial changes are small or absent. Astroglial scar has been thought to impair the recruitment of OPC in MS lesions, although direct evidence is lacking.

2.3.3 Microglia/Macrophages

Demyelination in MS generally is thought to be mediated by resident microglial cells, or infiltrating monocytes/macrophages. The relative contribution of these two cell types is not known. In confocal microscopy studies, it has been demonstrated that macrophages that are close to myelin sheaths extend processes to the myelin sheaths. By electron microscopy, it has been observed that outer lamellae are separated from the myelin sheaths and attached to coated pits on the surface of macrophages. Myelin was observed to enter the cytoplasm of the macrophages through elongated pinocytic vesicles (Prineas and Connell 1978). Ultimately the myelin sheath may become loosened from the axon and macrophage processes may be interspersed between the axon and the myelin sheath. Myelin fragments have been observed in coated pits in macrophages, and macrophages display a “capping” of Fc receptors, indicating a receptor-mediated endocytic process. Complement activation products and IgG are polarized to the macrophage/myelin interface at areas of demyelination, suggesting an opsonization of myelin by complement and IgG (Breij et al. 2008; Prineas and Graham 1981). Other investigators have described a vesicular dissolution of myelin sheaths prior to the phagocytosis by macrophages (Guo and Gao 1983; Lassmann 1983). Lipid-laden macrophages accumulate in perivascular spaces in the lesions and also in the normal-appearing white matter (NAWM). The macrophages may be transported to regional lymph nodes in the neck, as lipid-laden macrophages have been observed in cervical lymph nodes.

The morphology of microglia changes toward the edge of active and chronic active lesions, from cells with small elongated cell bodies, rod-shaped nuclei, and thin, highly branched processes to larger rounded cells with thick and less branched processes, to that of large lipid-laden macrophages within the lesions (Revesz et al. 1994). Lipid macrophages in MS lesions may be recruited from microglia or from blood-borne monocytes; the relative contribution of these cell populations is not known. Although MHC class II expression has been detected on astrocytes, the majority of studies indicate that macrophages/monocytes, microglia, and perivascular macrophages are the main cell types expressing MHC class II in MS lesions and thus being able to present antigen to CD4 T cells. Activated microglia have been shown to express a variety of proinflammatory cytokines, noticeably IL-1, TNF-α, IL-6, IL-12, and IL-23. The cytokine profile of MS lesion macrophages indicates that they constitute a mixture between a proinflammatory and anti-inflammatory phenotype, with anti-inflammatory cells being the majority.

2.3.4 Blood Vessels

The BBB is damaged early in the pathogenesis of MS lesions, and there is leakage of plasma proteins throughout all MS lesion stages (Barnes et al. 1991; Kwon and Prineas 1994). Vascular inflammation does not seem to require myelin as periphlebitis has been elegantly demonstrated in the retina that lacks myelin (Green et al. 2010). The leakage of plasma proteins may be due to a combination of increased pinocytic transport and to the disruption of intercellular tight junctions (Brown 1978; Plumb et al. 2002). Similarly, there is increased transport of cells through the vessel wall, by migration of leukocytes through the endothelium and by migration between endothelial cells. The blood vessel wall is thickened in old MS lesions by the deposition of collagen, and the perivascular spaces (Virchow-Robin spaces) are widened. The expression of adhesion molecules on parenchymal blood vessels is increased, including the expression of ICAM-1. In the majority of WM MS lesions, there is a central small blood vessel, suggesting that the vascular compartment determines the direction of lesion spread (Dawson's finger). As antigen presentation by perivascular macrophages seems sufficient to initiate brain parenchymal inflammation, the mechanisms of lesion spread could be through perivascular traffic of perivascular macrophages that present myelin autoantigens.

2.3.5 Lymphocytes

In white matter MS lesions, the majority of infiltrating T cells are lymphocytes, distributed in perivascular infiltrates, but also scattered through the parenchyma. CD8-positive T cells are more prevalent at the lesion border than at the lesion center, while the opposite was true for CD4-positive cells; in all locations, CD8 T cells

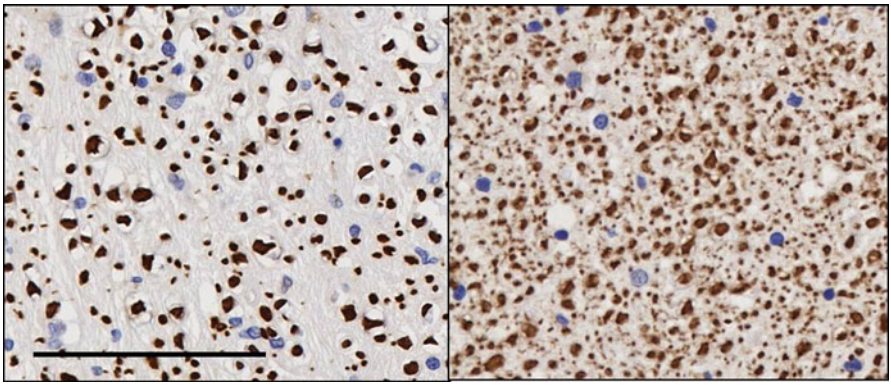

Fig. 2.4 Axonal loss. Neurofilament stain of the lateral corticospinal tract of a patient with MS (*left*) demonstrates extensive axonal loss compared to control tissue (*right*). *Scale bar* 100 μm

were predominant (Bo et al. 2003a). There is also a small minority of gamma delta T cells present in lesions; this may be pathogenetically important, as these may lyse cells expressing heat shock proteins, such as lesion oligodendrocytes. Distinct T cell clones, some of which were CD8 positive, were detected in lesion and NAWM areas in several anatomical regions in individual MS patients, indicating that T cells in different lesions in these patients responded to common antigens. T cells may be cleared from the lesions by transport along perivascular spaces or through apoptosis (Ozawa et al. 1994). B cells are present in lower numbers in the brain parenchyma, as are plasma cells. B cells are seen more commonly in chronic lesions particularly when active (Esiri 1977). Granulocytes are rare, except in very acute cases with destructive lesions (Marburg 1906).

2.3.6 Axons

Axonal loss occurs in all demyelinated MS lesions and is considered the main cause of irreversible chronic disease progression in MS (Fig. 2.4). The extent of ongoing axonal loss correlates with extent of macrophage infiltration. The rate of axonal loss is thus highest in early lesion stages, where there is intense inflammation, and is also high at the inflammatory edge of chronic active lesions (Bitsch et al. 2000; Ferguson et al. 1997; Trapp et al. 1998). In areas with few or no perivascular infiltrates or macrophages, in chronic/inactive MS lesions, there is a low-grade axonal loss, suggesting that persistent demyelination mediates axonal pathology and loss independent of inflammation (Bitsch et al. 2000; Ferguson et al. 1997; Trapp et al. 1998). Significant axonal loss has also been detected in NAWM (Evangelou et al. 2000a), and a recent study supports the assumption that significant degree of axonal loss is due to Wallerian degeneration even in early MS cases (Dziedzic et al. 2010).

A strong correlation of regional lesion load with axon numbers in the corresponding projection areas in the corpus callosum indicates a substantial role for lesional axonal transection to diffuse axonal loss in the NAWM (Evangelou et al. 2000b).

Axon pathology is observed in lesions both as axonal caliber changes and as transected axons form end-bulbs or ovoids (Trapp et al. 1998). In transected axons, there is an accumulation of amyloid precursor protein (APP) and non-phosphorylated neurofilament (Ferguson et al. 1997; Trapp et al. 1998). In acute MS, in response to demyelination, sodium channels are distributed along demyelinated axons, thereby providing an anatomical basis for continuous nerve impulse conduction in demyelinated areas. In chronic MS lesions, continuous sodium channel expression in axons is lost. The sodium channel Nav1.6, seen in healthy white matter at the nodes of Ranvier, was present in chronic lesions at approximately one-third of the axons, and then in a patchy manner (Black et al. 2007; Craner et al. 2003). The Na+/K+ ATPase is necessary for the ion balance of functional axons. It is retained in acutely demyelinated axons but frequently absent in chronic MS lesions, indicating that the majority of axons in chronic demyelinated lesions are not functionally active (Young et al. 2008). The epidemiological evidence for gender differences in disability accumulation is conflicting; hence a recent comparison of axonal loss in acute lesions that failed to show any gender differences in the APP-positive spheroids in either acute of chronic lesions is of interest.

2.4 Gray Matter Pathology

In chronic MS patients, extensive cortical subpial MS lesions are frequent, and the percentage demyelinated area is similar in gray matter and white matter. GM demyelination is extensive also in cerebellar cortex; this may be a cause of cerebellar dysfunction in MS (Kutzelnigg et al. 2007). Extent of gray matter and white matter demyelination is weakly correlated, if at all (Bo et al. 2003b, 2007; Kutzelnigg et al. 2007). Episodic and anterograde memory is frequently affected in MS. This could be due to hippocampal MS pathology (Figs. 2.3 and 2.5). Extensive demyelination has been detected in the hippocampus in MS patients with substantial alterations in the cholinergic neurotransmitter system in the MS hippocampus, which were different from those in AD hippocampus (Geurts et al. 2007; Papadopoulos et al. 2009). There is increased neuronal apoptosis in cortical MS lesions, and significant neuronal death has also been demonstrated in the thalamus in MS. Specific subpopulations of neurons are vulnerable in MS. In primary motor cortex, parvalbumin interneurons within layer 2 were significantly reduced, with no concurrent change in the number of calretinin-positive neurons. In the lateral geniculate nucleus, there was disproportionate pathology of small neurons, which correlated with axonal loss in the optic nerve in MS patients (Evangelou et al. 2001). Cortical demyelinated lesions are not specific for MS; intracortical

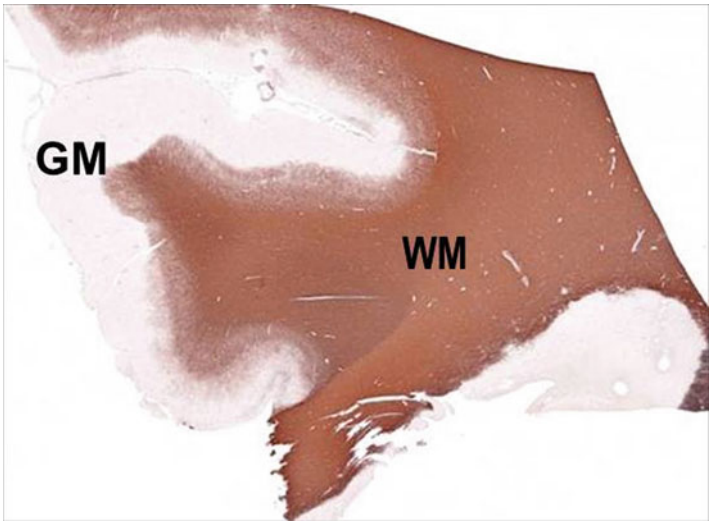

Fig. 2.5 Gray matter demyelination. Extensive demyelination of the hippocampus has been observed in a number of studies and has been implicated as a significant cause of the memory symptoms MS patients report frequently. In this tissue block, subpial demyelination is seen throughout the cortical ribbon

and leukocortical lesions were also detected in progressive multifocal leukoencephalopathy (PML). Subpial lesions were not observed in PML, however (Moll et al. 2008). Cortical lesions using conventional MR scanners are largely undetectable in vivo because of the low sensitivity of MRI (5 %) for purely gray matter plaques (Geurts et al. 2005). Extensive cortical pathology is not associated with increased focal or diffuse WM pathology, indicating that the extent or distribution of WM abnormalities cannot be used to identify patients with extensive GM demyelination (Bo et al. 2007). The presence and extent of remyelination in MS cortex are not easy to characterize. In a direct comparison of remyelination of WM and GM MS lesions of the same patients, GM remyelination was consistently more extensive (Albert et al. 2007). Until recently it was accepted that the pathology of gray matter demyelination differs from white matter lesions in that there is less inflammation in the GM. In fact, in purely cortical lesions, no significant increase in T lymphocyte infiltration, no BBB damage, and no complement activation were detected (Bo et al. 2003a; Brink et al. 2005; van Horssen et al. 2007). The GM part of combined lesions (type 1) has levels of inflammation intermediate between that of white matter and purely gray matter lesions. Recent evidence suggests that in some early MS patients, cortical demyelination was frequently inflammatory (Lucchinetti et al. 2011).

During inflammation, white matter neurons are destroyed, but there is evidence of neurogenesis in a subgroup of chronic subcortical white matter lesions (Chang et al. 2008). The subventricular zone is a possible source of those neurons as an increase of progenitor neurons was found in the SVZ when bordering demyelinating lesions.

2.4.1 Meningeal Inflammation

A low-grade meningeal inflammation is frequently detected in chronic MS (Black et al. 2007; Dawson 1916; Gay et al. 1997). Recently structures similar to B cell follicles containing germinal centers were detected in meningeal inflammatory infiltrates (Serafini et al. 2004). Meningeal B cell follicles were present in approximately 40 % of secondary progressive MS (SPMS) patients, but not in primary progressive MS (PPMS) cases. Follicle-positive SPMS cases have been reported to show a more rapid disease development, with a younger age at disease onset, irreversible disability and death, and more extensive cortical pathology, indicating a detrimental effect of meningeal B cell follicles in MS pathogenesis (Magliozzi et al. 2007; Serafini et al. 2004). On the contrary, the presence of meningeal inflammation (predominantly T cells) does not seem to be correlated with the occurrence of cortical lesions (Kooi et al. 2009). Recent publications offer conflicting evidence regarding the presence of Epstein–Barr virus in MS brains and specifically in meningeal B cells. Although clearly there is epidemiological evidence in support of EBV playing a pathogenetic role, the pathological evidence is still weak (Lassmann et al. 2011).

2.5 Normal-Appearing White Matter

The concept of NAWM was proposed in the years when conventional MR techniques failed to show abnormalities outside WM plaques. Now it accepted that at least in chronic MS there is probably a low-grade inflammation in MS brain white matter, outside of established lesions (Kutzelnigg et al. 2005). This inflammation is variable among individuals and consists of nodules of activated microglia and perivascular infiltrates of lymphocytes/monocytes. In LFB-stained sections, large WM areas of diffusely lighter staining are present outside of lesions, suggestive of edema, remyelination, gliosis, axonal degeneration, or combinations of these. Some authors refer to those abnormalities that are increasingly easier to detect with high-field MRI scanners and different sequences as diffusely abnormal white matter. In MS NAWM and normal-appearing gray matter (NAGM), there is a slow ongoing loss of axons, as evidenced with APP or nonphosphorylated neurofilament-positive axonal end-bulbs. White matter interneurons are lost in MS, but in a subpopulation of patients, there is an increase in white matter neuron number at the lesion edge. Vascular fibrinogen leakage in the NAWM has been demonstrated by immunohistochemistry, indicating that the BBB is damaged also outside of demyelinated lesions.

2.6 Remyelination in MS

The thickness of the myelin sheaths depends on the axon diameter and is tightly regulated under physiological conditions. Remyelinated axons are characterized by uniformly thin and shortened internodes. The gold standard to detect remyelination is electron microscopy, and in MS, remyelinated axons were first described in 1965 (Perier and Gregoire 1965; Prineas and Connell 1979). By light microscopy, remyelination can be detected using conventional lipophilic stains such as Luxol Fast Blue or by immunohistochemistry using antibodies directed against myelin proteins such as myelin basic protein (MBP), proteolipid protein (PLP), or CNPase (Fig. 2.3). Lesion areas with advanced remyelination display a paler staining intensity due to thinner myelin sheaths and reduced numbers of axons (Fig. 2.3d).

Remyelination is frequently found at the lesion border, starts early during the formation of lesions, and is also present in lesions with active demyelination (Fig. 2.3) (Goldschmidt et al. 2009; Lucchinetti et al. 1999; Prineas et al. 1993a, b; Raine and Wu 1993). The comparison of lesions derived from patients with either a short or a long disease duration suggests that remyelination is more frequent and more extensively observed in early MS lesions stages (Goldschmidt et al. 2009). In average, about 10–20 % of chronic lesions are completely remyelinated (so-called shadow plaques) (Barkhof et al. 2003; Patani et al. 2007). However, remyelinated lesion areas may be more vulnerable to repeated demyelinating activity compared to NAWM (Bramow et al. 2010; Prineas et al. 1993b). Histological analyses do not allow longitudinal studies, and the lack of imaging techniques specifically measuring remyelination makes it difficult to determine exactly when remyelination occurs in individual lesions and how long it continues. However, the identification of differentiating oligodendroglial lineage cells in early disease stages and the lack of myelinating oligodendrocytes in chronic MS support the hypothesis that remyelination mostly occurs relatively early during lesion formation (Chang et al. 2002; Kuhlmann et al. 2008; Wolswijk 1998a, b, 2000). The extent of remyelination varies between individual lesions of the same patient and might be influenced by lesion size and lesion location (Goldschmidt et al. 2009; Patani et al. 2007). Periventricular and cerebellar lesions, for example, display a lower extent of remyelination than subcortical lesions (Goldschmidt et al. 2009). Similarly, cortical lesions show more extensive remyelination in the majority of patients compared to white matter lesions from the same patient (Albert et al. 2007). How the anatomical localization may influence remyelination is unknown; potential explanation includes differences in the microenvironment or location-dependent differences in the oligodendroglial progenitor populations and their remyelination capabilities. Additional factors might influence remyelination, such as patient-dependent factors. Patrikios et al. (2006), for example, could show that a subset of patients was more prone to remyelination than others. In rodent animal models, reduced remyelination capacity is associated with increasing age and male sex (Gilson and Blakemore 1993; Li et al. 2006; Shields et al. 1999; Sim et al. 2002); however, such a correlation has not been detected yet in MS which might be explained by the heterogeneity of the analyzed

tissue samples. Since a higher proportion of remyelinated shadow plaques and increased remyelination capacity was observed in primary versus secondary progressive MS, the disease course might be an additional factor contributing to remyelination outcome (Bramow et al. 2010).

Oligodendroglial precursor cells (OPCs) are believed to be the cells responsible for remyelination. In contrast to OPCs, transplanted mature oligodendrocytes are not able to remyelinate a demyelinated lesion (Groves et al. 1993; Keirstead and Blakemore 1997; Targett et al. 1996; Zhang et al. 1999). In demyelinated lesions depleted of oligodendroglial lineage cells, OPCs occur with onset of remyelination suggesting that OPC and not mature oligodendrocytes are responsible for remyelination (Fancy et al. 2004; Levine and Reynolds 1999; Watanabe et al. 2002).

2.6.1 Proliferation, Migration, and Differentiation of OPCs in MS Lesions

Prerequisite for successful remyelination is the proliferation, migration, and differentiation of OPCs. Every of these steps might be disturbed in MS lesions. Whereas proliferation of oligodendroglial precursor cells is a frequent phenomenon in de- and remyelinating animal models, proliferating OPCs are a rare event in human MS studies (Kuhlmann et al. 2008; Schonrock et al. 1998). However, this does not exclude that earlier lineage cells, for example, subventricular neural stem cells may proliferate, migrate, differentiate, and promote remyelination (Nait-Oumesmar et al. 2007). At the lesion border, higher numbers of oligodendroglial progenitors and mature oligodendrocytes are observed (Kuhlmann et al. 2008; Prineas et al. 1993b), suggesting that migration of OPCs into the lesions might be impaired. Migration of oligodendroglial lineage cells is regulated by a complex network of short- and long-range migration cues which are either secreted such as growth factors (e.g., FGF, PDGF), guidance molecules (netrins, certain semaphorins), and chemokines (e.g., CXCL1) or contact-mediated, for example, extracellular matrix molecules (for review see Jarjour and Kennedy 2004). Semaphorins 3A and 3F, for example, are upregulated in close proximity to active but not inactive MS plaques (Williams et al. 2007). Furthermore, animal studies demonstrate that overexpression of Sema 3A impairs the migration of OPCs, whereas overexpression of Sema 3F accelerates OPC's recruitment and remyelination (Piaton et al. 2011; Syed et al. 2011). Not only is the expression of long-range guidance molecules changed in MS lesions, but also changes of the ECM have been reported; tenascin-C expression, for example, that impairs the migration of OPCs in vitro is reduced in acute lesions, whereas chronic MS lesions display tenascin-C levels comparable to the NAWM (Gutowski et al. 1999). Furthermore, in active demyelinating lesions, upregulation of the migration promoting factors fibronectin and vitronectin has been reported (Gutowski et al. 1999; Sobel et al. 1995). In summary, these data indicate that guidance molecules are dynamically regulated in MS lesions and shift from a migration promoting to less favorable environment with lesion chronicity. However, since

OPCs are present even in chronic MS lesions, impairment of migration might not be the major cause for remyelination failure in chronic MS lesions.

Several publications indicate that the differentiation of oligodendrocytes is disturbed in chronic MS lesions (Chang et al. 2002; Wolswijk 1998a; 2002). In the majority of early MS lesions, differentiating progenitor cells are found (Kuhlmann et al. 2008), whereas in chronic MS lesions, OPCs are present but do not remyelinate despite close contact to axons (Chang et al. 2002; Wolswijk 1998a). This suggests that inhibitory signals, lack of remyelination promoting factors, or a combination of both mechanisms prevent successful remyelination. A complex and timely interaction of extracellular signals and intracellular transcription factors is required to initiate and perform remyelination successfully. This process can be disturbed by activation of inhibitory signaling pathways on many different levels. In experimental animal studies, a number of inhibitory pathways have been identified in recent years; however, whether these signaling cascades and factors also contribute to remyelination failure in MS is mostly unknown. Here, we describe a selected number of factors, such as the Notch/Jagged, Wnt, hyaluronan, and PSA-NCAM, which have been shown to might be relevant for MS.

2.6.2 Inhibitory Pathways

PSA-NCAM is an adhesion molecule that belongs to the immunoglobulin superfamily and plays a role in a number of developmental processes such as axonal pathfinding, nerve branching, cell migration as well as synaptic plasticity. During development, downregulation of axonal PSA-NCAM precedes myelination, whereas in demyelinated but not remyelinated CNS lesion areas, PSA-NCAM is reexpressed, suggesting that loss of PSA-NCAM may be prerequisite for (re-)myelination (Charles et al. 2000, 2002).

In and around MS lesions, Jagged1 is upregulated on astrocytes whereas oligodendroglial lineage cells express its receptors Notch1 and the downstream transcription factor HES5 that inhibits the differentiation of oligodendrocytes (John et al. 2002). In contrast, no Jagged1 was detected in remyelinating lesions indicating that the activation of the canonical Notch–Jagged pathway may contribute to remyelination failure in chronic MS lesions. This hypothesis was questioned by the finding that ablation of Notch1 in PLP-expressing oligodendrocytes had no effect on remyelination in demyelinating animal models (Zhang et al. 2009). However, inactivation of Notch1 in olig1-expressing oligodendroglial lineage cells resulted in accelerated remyelination indicating that Notch1 is critical early during the differentiation process (Zhang et al. 2009). Interestingly, Notch1 has not only inhibitory effects on oligodendrocytes. Binding of axonal contactin to Notch1 leads to the activation of a noncanonical pathway resulting into differentiation of oligodendrocytes and myelination via the nuclear translocation of the NICD/Deltex complex (Hu et al. 2003). In chronic MS lesions, TIP30 has been detected, a known inhibitor of the translocation of NICD to the nucleus, suggesting that not only activation of

the canonical Notch signaling pathway but also inhibition of the noncanonical pathway might contribute to remyelination failure in chronic MS lesions (Nakahara et al. 2009).

The glycosaminoglycan hyaluronan is another factor secreted by astrocytes that may contribute to remyelination failure in MS (Marret et al. 1994). Hyaluronan accumulates in chronic demyelinated and remyelinated MS lesions, but expression is most intense in demyelinated lesion areas. Furthermore, degraded hyaluronan inhibits oligodendroglial differentiation and remyelination in vitro and in vivo (Back et al. 2005; Sloane et al. 2010), and this effect may be mediated via Toll-like receptor 2, a known binding partner of hyaluronan.

The Wnt pathway is another signaling cascade contributing to oligodendroglial differentiation (Shimizu et al. 2005). TCF7L2, a transcription factor activated by the Wnt/β-catenin pathway, as well as other members of the Wnt/β-catenin signaling cascade expressed in active MS lesions suggest that a dysregulation of this pathway may contribute to remyelination failure (Fancy et al. 2009). This was supported by experimental animal studies demonstrating that this pathway is activated during myelination and remyelination. Mice with only one copy of the Wnt pathway inhibitor APCs suffer from delayed remyelination (Pohl et al. 2011). Interestingly, mice lacking TCF7L2 show as well-impaired remyelination, similar to mice lacking histone deacetylases 1 and 2 (Ye et al. 2009). Lack of HDAC 1 and 2, enzymes that regulate histone acetylation and transcription by DNA packaging, is among others associated with stabilization and nuclear translocation of β-catenin. Therefore the hypothesis evolved that TCF7L2, depending on its binding partners, either promotes or inhibits oligodendroglial differentiation and remyelination (Aarli et al. 1975). Furthermore, in animal studies, histone acetylation increases with age and correlates with impaired remyelination; exposure of young animals to inhibitors of histone deacetylases is associated with delayed remyelination suggesting that changes in histone acetylation modulate remyelination capacities of OPCs (Marin-Husstege et al. 2002; Shen et al. 2005, 2008). In the aged human CNS as well as in the NAWM of patients with chronic MS, an increased histone acetylation has been observed, whereas in early MS lesions, a significantly reduced number of oligodendrocytes with acetylated histone 3 was found, indicating that in MS histone acetylation may as well influences remyelination capabilities (Pedre et al. 2011).

2.6.3 Remyelination and Inflammation

As described above, remyelination is a frequent phenomenon in early but not in chronic MS lesions. This change in remyelination capacity is associated with changes in the extent and composition of inflammation suggesting that certain factors present in the inflammatory "milieu" early during lesion formation may support remyelination. Inflammatory cells in MS patients, for example, express not only cytokines and chemokines but also neurotrophic factors such as BDNF and CNTF

(Kerschensteiner et al. 1999; Stadelmann et al. 2002). Increased density of macrophages and microglia at the lesion border correlated significantly with more extensive remyelination in tissue samples from patients with a long disease duration (Patani et al. 2007). However, this can indicate that either macrophages/microglia are prerequisite for remyelination or inflammatory cells prevent further formation of new myelin sheaths. In animal studies, dampening of the inflammatory response or lack of certain cytokines leads to impaired remyelination (Arnett et al. 2001; Chari et al. 2006; Kotter et al. 2005). In contrast, mice deficient for CXCR2, a chemokine receptor, display accelerated remyelination, and certain inflammatory factors are cytotoxic for oligodendroglial lineage cells at least in vitro (Liu et al. 2010). These combined data demonstrate that inflammation and remyelination are characterized by complex interactions and that most likely not a single but the spatiotemporal interplay of many factors determines the outcome.

2.6.4 Remyelination Promoting Therapies in MS

So far, no directly neuroprotective treatments exist. However, few compounds are under development aiming at promotion of remyelination. One such compound is an antibody directed against the leucine-rich repeat and Ig domain containing NOGO receptor interacting protein 1 (LINGO1). Lingo1 is a transmembrane receptor that is expressed on neurons and oligodendrocytes. Inhibition of Lingo1 promotes oligodendroglial differentiation and myelination in vitro and in vivo as well as remyelination in different animal models. In MS lesions, Lingo1 could be detected on neurons, astrocytes, and macrophages/microglial cells but not on oligodendrocytes, and levels of Lingo1 are decreased in brain samples from MS patients compared to controls. However, a phase 1 clinical trial evaluating the safety of anti-Lingo1 is currently under way.

2.7 Conclusion

We have advanced a lot in our knowledge of the pathology of MS, especially in relation to MS plaques. We are still far from understanding the mechanisms of ongoing deterioration observed in progressive MS. Not surprisingly, we lack medicines that can arrest the progressive phase of the disease, the cause of disability to the majority of MS patients. While our efforts continue to explore the initial events, and possibly the trigger for the formation of MS plaques, increasingly mechanisms of neurodegeneration and remyelination (failure) are becoming the focus of research in MS.

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