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Review

Inflammation, demyelination, and degeneration — Recent insights from MS pathology

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which responds to anti-inflammatory treatments in the early disease phase. However, the pathogenesis of the progressive disease phase is less well understood, and inflammatory as well as neurodegenerative mechanisms of tissue damage are currently being discussed. This review summarizes current knowledge on the interrelation between inflammation, demyelination, and neurodegeneration derived from the study of human autopsy and biopsy brain tissue and experimental models of MS.

1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating CNS disease frequently starting in young adulthood. Supported by experimental evidence mainly derived from its principal model, experimental allergic encephalomyelitis (EAE), MS is generally considered a predominantly T cell-mediated autoimmune disease [1]. In line with this notion, immunomodulatory and anti-inflammatory therapies prove to be effective, especially early in the disease phase. However, the disease often progresses relentlessly in later disease stages without much imaging evidence for acute inflammation and no obvious effect of anti-inflammatory therapies. In addition, substantial atrophy and loss of neuron-specific amino acids, such as N-acetyl-aspartate (NAA), are already detectable early in the disease [2]. As MS etiology still remains unknown, the above mentioned findings raise the question of the interrelation between acute inflammatory damage to CNS structures and early as well as late stage damage to CNS tissue, especially to neurons and axons, commonly termed "neurodegeneration". Furthermore, the type of inflammation that prevails in the chronic disease phase and its effect on the target tissue is not well understood [3]. In addition, the recent identification of an astrocytic target of the immune reaction in a disease closely resembling MS, namely neuromyelitis optica (NMO), raises the question of whether the target structure in MS is necessarily the myelin sheath or oligodendrocyte [4]. This review summarizes current knowledge and recent advances in MS immunopathology.

2. Inflammation and demyelination

MS lesions can arise anywhere in the CNS. However, they show a predilection for the optic nerve, spinal cord, brain stem, and periventricular areas. Furthermore, brain tissue immediately adjacent to the subarachnoid space, i.e. subpial gray matter, is especially vulnerable to demyelination [5], a fact that has only recently been appreciated. Mostly, within a patient, lesions of similar age resemble each other with respect to the extent and pattern of inflammation and remyelination [6–8]. Mild meningeal inflammation consisting of T and B lymphocytes, plasma cells and macrophages is common [9].

2.1. Chronic MS lesions

The most common lesion types found at brain autopsy in patients with long-standing MS are chronic hypocellular demyelinated lesions with or without a variable extent of newly formed, thin myelin fibers at the edge, representing remyelination. With smaller lesions, their perivascular, or Dawson finger location, is often apparent. Single perivascular T cells are the rule. Few if any mature oligodendrocytes are detected; oligodendrocyte precursor cells are present, however scarce [10,11]. Axonal loss is often substantial and may reach around 70% compared to the normal appearing white matter (NAWM) [12,13]. In contrast, little "acute" axonal damage is detected when

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visualizing axonal transport defects using e.g. antibodies against amyloid precursor protein (APP). Reactive astrocytes may still be present at the lesion border; more prominent, however, is a dense, fibrous gliosis. Vessels are often markedly hyalinised within chronic, hypocellular demyelinated lesions.

In contrast to these seemingly inert lesions, scattered macrophages digesting myelin products may be present at the lesion edge, mostly accompanied by scattered perivascular and parenchymal T cells, indicating ongoing myelin destruction. Accordingly, signs of axonal damage are routinely found at the edge of slowly expanding lesions. It has been proposed that they are a pathological correlate of disease progression [14,15]. It is unclear so far what underlies the ongoing disease process in these lesions. In general, T cell lymphocytic infiltration decreases over time and is markedly reduced in late stage MS [9]. Additionally, these slowly expanding lesions can still be found after autologous bone marrow transplantation, suggesting that they are mainly driven by a CNS-resident immune response [16].

2.2. Early MS lesions

Early MS lesions are more likely to be encountered in patients who have been biopsied for reasons of differential diagnosis, but may also be found at autopsy, especially in patients dying early in the disease course [6,17]. The most studied lesions are "early active demyelinating" MS lesions where macrophages filled with minor, i.e. low abundance myelin proteins, such as myelin oligodendrocyte glycoprotein (MOG), cyclic nucleotide phosphodiesterase (CNPase) and myelin-associated glycoprotein (MAG) cover most or part of the lesion area [6]. The search for the "pre-lesion" has yielded areas of extensive oligodendrocyte apoptosis with microglia activation, but no dominant T cell infiltration or phagocytic macrophages [17]. It is unclear so far what determines the site of lesion location, but vascular factors are thought to play a role [18]. In addition to the dense infiltration by foamy macrophages expressing markers of early activation, such as MRP14 [19], early MS lesions are characterized by a variable density of perivascular and parenchymal T lymphocyte infiltration, and usually few B and plasma cells. In routine LFB/PAS staining or immunohistochemistry for myelin proteins, early MS lesions mostly appear pale, but not (yet) completely devoid of myelin. Oligodendroglial cells are present in the lesions, often displaying an activated phenotype with signs of early remyelination [20–22]. Axonal transport deficits, as demonstrated e.g. by amyloid precursor protein (APP) immunohistochemistry, are abundant throughout the lesion [23–25].

2.3. Heterogeneity of early MS pathology

MS pathology in recent years has predominantly focussed on early, actively demyelinating lesions and possible heterogeneous mechanisms of demyelination [6]. Studies based on a large set of biopsied patients with inflammatory demyelinating lesions suggest that a subset of patients displays antibody- and complement-mediated mechanisms of demyelination, whereas lesions from a subset of other patients show oligodendrocyte apoptosis as the probable cause of myelin decay [6]. In around 50% of patients, immunoglobulin and complement deposits are found in the lesions (pattern II), whereas the rest are mainly distributed among patients with an "immune-type" pattern of MS without complement deposition (pattern I) and cases with oligodendrocyte apoptosis (pattern III). Few autopsy cases so far were identified with dying oligodendrocytes in the periplaque white matter (pattern IV). A recent case study provided evidence for intraindividual homogeneity by demonstrating an identical immune pattern in two different lesions of a single MS patient over time [26]. The concept of heterogeneity is supported by imaging data suggesting that, in line with pathological findings, pattern III patients show diffuse, not well-delineated lesions in contrast to pattern I and II patients, where lesions are clearly demarcated and often highlighted by ring-shaped contrast enhancement [27,28]. Furthermore, patients with pattern II pathology respond to plasmapheresis, whereas patients displaying the apoptosis-dominated pattern III or the T cell-mediated pattern I do not show any response [29]. More evidence for this concept comes from antigen microarray analysis of MS sera demonstrating unique antibody patterns to lipids and CNS-derived peptides that were mostly associated with MS pattern I or II [30]. The pathological subtypes of MS do not segregate with the clinical evolution of the disease, such as the primary progressive or secondary progressive vs. the relapsing–remitting variant [31]. Currently, an intense search for imaging, serum, and CSF surrogate markers for the pathological MS heterogeneity is under way.

An alternative hypothesis brought forward by Prineas and Barnett proposes the concept of a stage-dependent heterogeneity in MS whereby oligodendrocyte apoptosis is thought to precede the formation of all MS lesions and to be present before an opening of the blood-brain barrier [17]. It is currently a matter of debate whether T cell infiltration follows the demise of the myelin-forming cells in these cases [32].

A further hypothesis is the concept of homogeneity suggesting that only one general mechanism of demyelination, which involves antibody- and complement-mediated myelin phagocytosis, plays a role in patients with established MS [33]. However, it is important to note that the lesions studied by the different groups [17,33] differed histologically with regard to their demyelinating activity [6]. Therefore, it remains currently difficult to draw final conclusions on the heterogeneous and homogenous aspects of MS pathology.

2.4. Normal appearing white matter

Although demyelination as hallmark of MS is largely restricted to focal lesions, other aspects of pathology are less confined. Perivascular and also scattered parenchymal T cell infiltration and microglia activation are widespread in many MS patients, even in the chronic disease phase [34]. In addition, the effects of local demyelination and axonal damage extend into the normal appearing white matter, especially with anterograde (Wallerian) and retrograde degeneration resulting in reduced axonal density and neuronal atrophy or loss in areas far away from the original lesion site.

3. Structural damage to axons and neurons

3.1. Axonal damage and loss in white matter lesions

Histopathological evidence for acute axonal damage, as determined by visualization of disturbed axonal transport, occurs very early in MS lesions and is most pronounced in the stage of active demyelination [25]. The detection of diffuse axonal injury (DAI) after brain trauma relies on the use of markers such as APP and synaptophysin, which accumulate as a result of immediate axonal damage, and persist for about 20–30 days [35]. Although part of the accumulation of APP may be reversible, the abundant large axonal spheroids most likely reflect irreversible axonal transections [23]. The loss of myelin greatly enhances the propensity of axons for transport disturbance [36]. On the one hand, non-specific immune mediators, e.g. nitric oxide (NO), reactive oxygen species (ROS), and proteases lead to damage of naked and also myelinated axons as indicated by experimental studies [37,38]. On the other hand, neuronal antigens have recently been identified as targets of the immune reaction. Specific immune reactions against neurofilament, beta-synuclein, contactin-2/TAG-1, and neurofascin lead to CNS inflammation [39–43]. Importantly, anti-neurofascin antibodies have been identified in a proportion of MS patients and these antibodies have been shown to aggravate axonal damage and clinical disease in the EAE model [41].

However, no primary demyelination has been observed so far after experimental immunization with neuronal antigens.

In chronic MS lesions, axonal damage continues at a markedly slower pace. However, APP-positive axonal profiles may be relatively abundant at the edge of slowly expanding lesions [16]. Recent studies have highlighted the importance of energy supply for axonal maintenance, and mitochondrial abnormalities have been identified in MS lesions [44–46]. Importantly, axonal densities are markedly reduced in chronic MS lesions in the majority of patients and can attain average densities of 20–30% compared to control white matter [47]. A recent study correlating clinical and pathological findings clearly provides evidence that the loss of corticospinal axons is the pathological substrate of motor disability in MS [48]. How and when does this enormous axon destruction take place? The mechanisms of axonal loss are most likely multifaceted, ranging from the numerically important axonal loss in the acute inflammatory demyelinating stage of lesion formation to axonal damage accumulating by ongoing disease activity. Furthermore, anterograde and retrograde degeneration as a result of other, more distant lesions certainly impact on lesional axonal densities. The clinical importance of the "slow-burning", but long-lasting axonal demise caused by enhanced axonal vulnerability as a result of demyelination and/or continuous low grade inflammatory damage is hard to determine, but may well correlate with the insidious clinical worsening observed in the progressive disease phase [49].

3.2. MS lesions of the gray matter

Largely overlooked for the last decades, demyelinated lesions of the gray matter are now known to cover substantial areas of cortical, deep, and spinal gray matter, mostly in chronic MS patients [50]. Subpial cortical demyelination may extend over several gyri and sulci, whereas intracortical lesions are mostly small and inconspicuous [5,51]. Leukocortical lesions characterized by a substantial white matter lesion part, are mostly more inflammatory and show more microglial and astroglial activation than subpial or intracortical lesions [52]. Quantitatively, subpial lesions are the most extensive and cover up to 70% of the cortical area in some patients [53]. Gray matter and especially subpial and intracortical lesions are difficult to detect in vivo by MR imaging, which hampers the correlation with specific clinical symptoms. However, first imaging evidence suggests that cortical lesions may contribute to cognitive deficits [54,55] and epileptic seizures [56]. The impaired visibility in standard MR imaging can largely be explained by gray matter anatomy and the location of cortical lesions close to the cerebrospinal fluid (CSF) on the one hand and the specific aspects of gray matter lesion pathology on the other: Myelin density in gray matter areas is low compared to the white matter, and partial volume effects pose a challenge to cortical signal alterations. Cortical, and especially subpial and intracortical MS lesions, in addition, are characterized by little inflammatory infiltration, little evidence for plasma protein extravasation, little microglia activation and often only mild astrogliosis [57,58].

Apart from their so far-debated clinical significance, cortical lesions may give us hints towards the pathophysiology of MS, whereby they suggest – together with periventricular lesions – a role for factors diffusing from the CSF. Recent microarray studies revealed a massive upregulation of immunoglobulin-related genes in cortical MS sections harbouring meningeal plasma cells [59]. Furthermore, meningeal B cell aggregates have been associated with the extent of cortical lesions and dendritic damage [60]. Other groups, however, have not observed any association between meningeal inflammation and cortical demyelinated lesions, at least in the chronic disease phase [61]. The presence of a similar extent of cortical gray matter lesions in primary and secondary progressive MS suggests similar pathological mechanisms operating in both diseases [34]. Of note, in PML patients, where demyelination is induced by the gliotropic JC virus, no subpial but only leuko- and intracortical lesions are observed [62]. No correlation of the extent of cortical lesion load with white matter lesions has been observed [34], suggesting that cortical lesions are more than just a secondary, degenerative phenomenon induced by focal white matter lesions. Nevertheless, cortical transcripts are biased towards excitotoxicity also in normal appearing myelinated MS cortex [44]. Furthermore, a down-regulation of mitochondrial proteins and upregulation of the neuroprotective CNTF pathway was observed to be in line with the notion that cortical damage in MS is the result of both direct local and indirect, more distant effects [44].

In experimental models, spontaneous demyelinated cortical lesions have been reported after immunization with MOG protein, especially in the common marmoset and in congenic Lewis rats bearing certain MHC I and II alleles [63–65]. Standardized procedures to induce cortical lesions in rats have been developed, relying on the presence of demyelinating anti-MOG antibodies and local opening of the cortical blood-brain barrier. There, inflammation in the gray matter resolves quickly, and, with certain similarities to human cortical lesions, repair is rapid and highly successful [66,67].

3.3. Neuronal damage and loss

Neuronal damage occurs early in MS, as suggested by pathological and spectroscopic studies [2,68]. In addition to retrograde degeneration with ensuing neuronal atrophy and death, neurons may be directly damaged by inflammatory cells and mediators, when inflammatory demyelinated lesions are located in the gray matter [68].

In the spinal cord, the extent of motor neuronal loss observed on different levels has been reported to range between 15% and 48% of control cases [68–70]. However, the magnitude of neuronal changes observed at cervical, thoracic and lumbar levels differs between these post-mortem studies. To date, it still remains controversial whether neuronal loss in the spinal cord is partly dependent [70] or quite independent [68] of gray matter demyelination. However, neuronal apoptosis was only observed in the presence of infiltrating T cells [69] and signs of early neuronal injury also appeared more prevalent in early MS lesions involving the anterior horn [68]. The latter study suggests that neuronal loss occurs early but is not progressive during disease evolution. Interestingly, the overall reductions of motor neuronal densities [68,70] are of a magnitude similar to the mean axonal loss of 31% in the corticospinal tract in MS [71]. Taken together, these findings of the spinal motor system emphasize that direct-inflammatory effects within lesions – and indirect retrograde degeneration due to axonal loss – contribute to motor neuronal loss in MS.

Similar mean reductions of neuronal densities in MS have been observed in other gray matter areas such as the thalamus (−35%), non-lesional caudate nucleus (−33%) as well as the hippocampal regions CA1 and CA2-3 (−30%) [72–74]. Within the deep gray matter more pronounced neuronal loss was observed in lesional than non-lesional areas [73] indicating that both factors – direct inflammation-related and indirect retrograde degeneration of neurons – play a role in neuronal damage and demise in MS.

The neuronal changes in the MS neocortex are smaller than in the spinal and deep gray matter. Neuronal numbers in leukocortical MS lesions were only found to be reduced by approximately 10%, but synaptic loss was more pronounced and added up to 47% [75]. Synaptic densities in upper cortical layers of subpial cortical lesions seem to be less affected [76]. In addition, cortical lesions have been reported to display a reduced expression of excitatory amino acid transporters [77], indicating that excitotoxic mechanisms may play a role in the pathogenesis of cortical demyelination.

Reactive oxygen and nitrogen species, which induce axonal and neuronal injury by impairing mitochondrial function, thus leading to

subsequent energy failure, appear to contribute to axonal and neuronal damage in MS lesions [44,45,78].

More insight on direct and indirect mechanisms of neuronal damage during the acute disease phase comes from experimental acute encephalomyelitis (EAE), the animal model of MS [79,80]. Recent experimental data provide evidence for direct-inflammation-mediated — neuronal damage in the spinal cord of EAE rodents. Lower motor neuron loss ranging from 47% to 74% was observed in different EAE models [69], whereby these changes could already be detected early in the pre-relapse (pre-disease) phase and were found to be already completed in the relapse phase. This study suggests that T cells directly induce neuronal apoptosis by expressing the cell death mediator TRAIL. Recently, another study showed that CD8-positive T cells targeted against oligodendrocytes via transgenic expression of ovalbumin-induced significant simultaneous oligodendroglial and neuronal apoptosis in both hippocampal and neocortical gray matter, whereby the ratio of apoptotic oligodendrocytes to neurons was 3:1 [81].

More evidence for indirect mechanisms of neuronal damage comes from a recent study reporting hippocampal neuronal loss in EAE mice with mainly spinal pathology [82]. Decreased CA1 volumes and loss of GABAergic interneurons were observed in the presence of chronic microglial activation, accompanied by little inflammatory infiltrates. Another study in rats with EAE observed cholinergic neuronal degeneration in the hippocampus, which might be related to peroxidase-dependant generation of nitric oxide and oxidative stress [83].

In conclusion, direct and indirect mechanisms seem to play a role in neuronal damage in multiple sclerosis and EAE. This is also illustrated by a recent study in the EAE marmoset model that closely resembles the human disease. This study found evidence of diffuse axonal and synaptic damage within the myelinated cortex and additional axonal, oligodendroglial and neuronal loss in demyelinated cortical lesions [84]. Changes in the normal appearing cortex have been shown in MS, whereby a down-regulation of GABAergic transmission as well as mitochondrial proteins and an upregulation of the neuroprotective CNTF pathway was observed in microarray studies [44,85].

4. The progressive disease phase

After a mean disease duration of ten years of relapsing–remitting disease, most patients experience secondary progression — characterized by insidious, non-relapse-related progression, and poor response to immunomodulatory treatments. The seemingly non-inflammatory (by MRI) nature of this therapeutically frustrating disease phase has stimulated the concept that neurodegeneration, by definition a relentless process of death and decay of neural structures, may be the reason [86,87]. Pathologically however, inflammation and demyelination are still important features of this disease phase [9,14]. Accordingly, diffuse infiltration of the white matter with T cells, microglia activation and disturbance of axonal transport has been reported [34]. To explain the seeming non-responsiveness of this inflammation, the idea of an inflammation that is trapped behind a closed blood-brain barrier - and thus not easily accessible to drugs and not visualized by MRI - has been developed [49]. In addition, the presence of chronic active, slowly expanding lesions has been related to disease progression, also accompanied by T cell infiltration, demyelination, and ongoing axonal damage [14]. By using immunofluorescent and confocal microscopy, evidence of leakage at the endothelial tight junctions of brain microvessels has been reported not only in lesions, but also in the normal appearing white and gray matter in primary and secondary progressive MS which suggests widespread and persistent leakage of the blood-brain barrier in the progressive stage [88]. As cortical demyelination is often extensive in patients with long disease duration [34], it has also been suggested that this feature contributes to symptoms observed in late stage disease. As such, there is so far little evidence that axonal damage and loss occur independent of an adaptive immune response, also in late disease stages [9]. The ever burning question of why this inflammation seems so resistant to therapy – in addition to the above concept that assumes altered characteristics of the blood-brain barrier – might be answered by the fact that disease accumulation is very slow, preventing the effect of anti-inflammatory drugs being seen on a short time scale (G. Comi, personal communication). Axonal damage and loss clinically presenting as neurodegeneration might be more related to the effect of multiple lesions along the neuraxis with ensuing Wallerian and retrograde degeneration than an autonomous neurodegenerative process. Clinically, notwithstanding, a reduction by 60–80% of axons is highly relevant and may, in the progressive disease phase, limit the effectiveness of structural plasticity, e.g. detour circuits around lesions [89] The notion that repair capacities may be exhausted is well in line with large natural history studies indicating that clinical variables only influence the first early disease phase until moderate disability has accumulated, whereas the secondary progressive phase is characterized by subsequent accumulation of irreversible disability as an apparently self-perpetuating process [90]. Also, recent data from therapeutical trials in MS using intense immunosuppression early on suggest that the development of the secondary progressive phase may be prevented or at least markedly delayed, supporting the idea that CNS tissue destruction in early disease influences the long-term outcome [91,92]. With regard to myelin sheath repair, no difference in extent and quality has so far been observed between patients with relapsing–remitting and chronic (primary or secondary) progressive disease.

5. Tackling the interrelation between inflammation, demyelination, and neurodegeneration

5.1. Inflammation and demyelination

In principle, several possible interrelations between inflammation, demyelination and axonal damage can be envisaged. The most favoured theory assumes that inflammation and demyelination are closely related, and in fact that inflammatory mechanisms, such as antibodies, T cells and macrophages and their products lead to demyelination in the majority of patients. The commonly used EAE model typically reflects these aspects of pathophysiology [1]. However, as discussed above, other scenarios have been developed in which oligodendrocyte damage and myelin destruction are considered the primary events, then followed first by local microglia activation and proliferation and only later by invasion of inflammatory cells from the circulation [93,94]. In models of oligodendrocyte impairment due to lack of essential metabolic constituents such as the cytosolic peroxisome targeting signal type 1 receptor (PEX5), or due to overexpression or deletion of myelin proteins, substantial axon degeneration and also inflammation have been observed in addition to the expected oligodendroglia phenotype [87,95]. In PLP-transgenic mice, an oligoclonal CD8 T cell response has been reported with less pathology after crossing into RAG1−/− mice with no functional T and B lymphocytes [96,97]. Of note, however, immune reactions with similar intensity as in MS are not regularly observed after traumatic brain injury or stroke. Accordingly, with regard to MS pathogenesis, an additional, strong pro-inflammatory stimulus or a massive local immune-regulatory defect has to be postulated to allow for ample invasion of blood-borne inflammatory cells in an initially purely degenerative, toxic or traumatic setting.

5.2. Does early inflammatory-demyelination predispose to late stage neurodegeneration?

There is ample evidence that inflammation is closely associated with acute axonal injury and that demyelination further predisposes

the axon to demise. The density of acutely damaged axons was found to be higher in the early compared to the later phase of disease, most likely indicating a change in certain axon-damaging components of the inflammatory infiltrate [25]. Also, inflammatory mediators, in this case NO, are especially toxic to demyelinated and electrically active axons [98]. However, little is known about the effect of chronic demyelination and low grade inflammation on axon function in chronic MS. In addition, so far no experimental models are available to test the question of whether inflammation or inflammatory-demyelination leads to self-sustained, autonomous, non-inflammatory neuronal or axonal degeneration. Cytoskeletal abnormalities, e.g. tau hyperphosphorylation, have been reported in chronic EAE; however, no increase in Alzheimer pathology has been found in MS patients [99–101]. In the models of oligodendroglial dysfunction mentioned above, axonal damage is a frequent finding in animals at an advanced age. However, the detailed relationships between oligodendroglial demise or malfunction, inflammation and axon degeneration are still being worked out [87]. So far, in patients the clear pathological correlate for the clinically suggested progressive neurodegeneration is lacking. However, single APP-positive spheroids indicating transected axons are found in chronic lesions, and might – despite their low density – suffice to markedly reduce axonal densities given that this process evolves over years [9].

5.3. Axonal damage and loss in the white matter independent of focal lesions — insight from imaging studies

Early focal inflammatory demyelinating lesions clearly harbor a lot of transected axons that potentially lead to anterograde and retrograde degeneration and corresponding changes in the white matter. In addition, diffuse, non-focal inflammation in the white matter which is not associated with demyelination but with signs of axonal injury has been reported [34]. Is there evidence for non-lesional axonal demise in imaging studies, suggestive of self-autonomous, non-inflammatory neuronal and axonal degeneration? As expected, a clear relationship between axonal density in the normal appearing corpus callosum and the cerebral hemisphere white matter lesion load was found, highly suggestive of Wallerian degeneration [102]. Also the extent of focal inflammation, as reflected by gadolinium-enhancing lesions, has been shown to be related to subsequent brain atrophy, providing evidence for a cascade of potentially irreversible tissue damage that may follow inflammation and result in loss of brain parenchyma [103,104]. Axonal transections occur at their highest densities in these focal regions of inflammatory-demyelination. In contrast, a loss of NAA is observed by MR spectroscopy already very early in MS, also in patients with very few lesions [2]. This has been brought forward to support the concept of a primary role of neurodegeneration in MS, and points at least to very early changes in neuroaxonal structures in inflammatory demyelinating disease. Another spectroscopic study points to a relationship between NAA loss in cerebral normal appearing white matter and concurrent demyelination in lesions [105]. Recent morphometric studies also provide evidence that distant white matter lesions contribute to retrograde and anterograde axon degeneration in MS. Patients with spinal cord injury in MS displayed bilateral atrophy of the primary somatosensory cortex [106]. In addition, white matter lesions in the optic radiations have been associated with up-stream gray matter atrophy in the lateral geniculate nucleus [107] indicating retrograde damage of the perikarya from axonal injury in plaques. However, this study did not find any association between lesions in the optic pathway and occipital cortex atrophy. This finding, together with the radiological paradox of less evident white matter lesions combined with diffuse axonal loss in the NAWM in primary progressive MS, highlights the fact that it remains difficult to explain the full range of findings only by antero- and retrograde changes from focal white matter lesions. However, at least in relapsing–remitting MS, clinical studies using highly efficient immune suppression provide strong evidence for a key role of inflammation – be it focal or not – leading to subsequent inflammation-mediated neuroaxonal damage [91,92].

6. Autoimmune inflammatory demyelinating CNS diseases — the search for the antigen

Incited by the most prominent feature of MS pathology, namely primary demyelination of axons, the search for the target of the immune reaction in MS was very much focussed on oligodendrocytes and the myelin sheath, respectively. Several antigens have been examined in detail in experimental models and MS patients, especially myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG). Of these, MOG, given its localization on the surface of the myelin sheath and oligodendrocyte, and thus its accessiblity to humoral immune reactions, was the prime candidate. Furthermore, immunization with MOG is able to mimic MS pathology in various animal species [108]. However, an important anti-MOG antibody response was only observed in a small proportion of MS patients, but much more frequently in patients, especially children, with acute disseminated encephalomyelitis (ADEM), which is characterized by perivenous non-confluent demyelination and mostly no persistant intrathecal antibody production [109–111]. In recent years, neuromyelitis optica (NMO or Devic's disease), a demyelinating disease considered a spectrum variant of MS, has emerged as a separate disease entity [4]. NMO, which is pathologically characterized by demyelinating lesions that are in general more destructive than MS lesions and show clear site preferences, namely severe affection of the optic nerve and the spinal cord, has emerged as a disease characterized by antibodies against an antigen of astrocytic foot processes, aquaporin 4 (AQP4) [112,113]. Vascular abnormalities and evidence for antibody-mediated pathology, such as complement, IgG and IgM deposits as well as attraction of eosinophilic granulocytes had been recognized already for some time [114]. Recent data indicate that anti-AQP4 antibodies from NMO patients are able to induce selective astrocyte death in vivo and – at higher dosage – demyelination and axon damage [115,116]. To date, no anti-AQP4 antibodies or astrocyte depletion have been observed in MS; however, the search for the antigen is still ongoing [117].

7. Conclusions

Although therapies and quality of life have enormously improved over the last years, there is still a desperate need for a concept to prevent and treat secondary progression. Current highly efficient therapies aim at nearly complete reduction of inflammatory cells invading the CNS — a very efficient way to reduce relapses, albeit prone to severe side effects. With less potent immunomodulatory agents, inflammation is less markedly reduced and even a few lesions already lead to substantial axonal damage and loss. Thus, the search for neuroprotective agents must continue to improve and expand our arsenal against inflammatory CNS diseases.

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