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Relapsing and progressive forms of multiple sclerosis – insights from pathology

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Abstract

PURPOSE OF THIS REVIEW—The predominant clinical disease course of multiple sclerosis (MS) starts with reversible episodes of neurological disability, which transforms into progressive neurological decline. This review provides insight into the pathological differences during relapsing and progressive phases of MS.

RECENT FINDINGS—The clinical course of MS is variable and the disease can be classified into relapsing and progressive phases. Pathological studies have been successful in distinguishing between these two forms of the disease and correlate with the clinical findings in terms of cellular responses, the inflammatory environment, and the location of lesions.

SUMMARY—Available therapies for MS patients, while effective during the relapsing phase, have little benefit for progressive MS patients. Development of therapies to benefit progressive MS patients will require a better understanding of the pathogenesis of progressive MS. This review discusses and compares the pathological findings in relapsing and progressive MS patients.

Keywords

Multiple sclerosis; neurons; axons; myelin

1. Introduction

Multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system (CNS), affects more than two million people worldwide [1–4] and it is the leading cause of non-traumatic neurological disability in young adults in North America and Europe. Although descriptions of putative MS date back as early as the Middle Ages, the first pathological report was published by Jean-Martin Charcot, in the *Leçons du mardi* [5] where he documented characteristic ‘plaques’ and established the definition ‘*la sclerose en plaques*’. His diagnostic criteria based on nystagmus, intention tremor and scanning speech are still helpful in recognizing the disease. Identification of multiple foci of demyelination in the CNS of patients clinically diagnosed with MS is one of the cardinal pathological

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Conflict of Interest

None

findings for confirming the MS diagnosis. Although MS lesions can be found anywhere in the CNS, optic nerve, periventricular areas, spinal cord, and subpial gray matter are especially prone to demyelination.

Approximately 85% of MS patients have a biphasic disease course marked by alternating episodes of neurological disability and recovery, which is designated as relapsing remitting MS (RRMS) [1–4]. Following this course, within 20–25 years, ~60–70% of RRMS patients transform into a secondary-progressive disease course (SPMS) which is characterized by progressive neurological decline [1–4]. In addition, some MS patients (approximately 10%) also exhibit a disease course with steady decline in neurological function without recovery and are classified as primary progressive MS (PPMS). While, progressive MS often refers to the combined population of SPMS and PPMS patients, there are several important differences between PPMS and SPMS cases. For the purpose of the review we will focus on the pathological differences between progressive MS and relapsing MS. Histopathological comparisons of relapsing and progressive MS have been based on analysis of either biopsies or autopsy material derived from MS patients. While biopsy specimens represent more acute MS cases, a majority of autopsy specimens belongs to progressive MS patients. Apart from the few studies using biopsy material, autopsy tissues have been and continue to provide valuable insight into disease pathogenesis.

2. Pathological findings from acute MS lesions

Typically, MS lesions include breakdown of the blood-brain barrier, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axonal degeneration [3;6;7]. In line with imaging observations, actively demyelinating WM lesions (with abundant macrophages containing myelin degradation products) are more frequently observed in patients with RRMS than in patients with either type of progressive MS [8]; Inactive or chronic active MS lesions, characterized by a rim of microglia and/or macrophages (without cytoplasmic myelin protein degradation products) are usually observed in progressive MS brains [9;10]. In an attempt to study the heterogeneity of MS pathology related to early, actively demyelinating lesions, four neuropathological patterns were determined based on the presence or absence of complement and immunoglobulins, apoptotic nuclei, and/or preferential loss of myelin proteins [11]. Heterogeneity of lesion patterns was observed between patients but not within patients. A separate study challenged the concept of this heterogeneity in autopsy material from 39 confirmed MS patients using magnetic resonance imaging (MRI)-guided sampling and immunohistochemistry [12]. The study also determined complement activation products, immunoglobulins, oligodendrocyte apoptosis, and myelin loss in active MS lesions. A common mechanism of ongoing demyelination was suggested based on the homogeneous appearance of MS lesions in patients with established disease criteria [12]. Although most MS patients who had biopsies taken subsequently experience development of clinically definite MS, an open question is to what extent the biopsied patients are representative of the large majority of MS patients with a chronic disease course. These classically active lesions are common in relapsing MS patients but become rare during progressive MS cases [3;13]. Apart from the demyelination, axonal loss is frequent in acute lesions.

Axonal loss in relapsing MS

Axonal loss is common during relapsing MS and has been confirmed through magnetic resonance imaging (MRI) [1–4], magnetic resonance spectroscopy (MRS) [14–18], functional magnetic resonance imaging (fMRI) [18–20], and morphological analysis of MS tissue [3;6;9;13;21–23]. A variety of axonal changes, including accumulation of pore-forming subunits of N-type calcium channels [24;25] and metabotropic glutamate receptors [26] in acutely demyelinated axons [27], have been reported.

Using antibodies to non-phosphorylated neurofilaments, a dramatic increase in non-phosphorylated neurofilament epitopes [23] was detected in acute MS lesions. Disruption of axonal transport with subsequent formation of axonal ovoids is a hallmark feature of transected axons. Using confocal microscopy and three-dimensional reconstructions, many of the non-phosphorylated neurofilament-positive ovoids were detected at the transected ends of axons [23]. Transected axons in acute MS lesions were abundant and about 12 times greater compared to chronic lesions [23]. The identification of significant axonal transection even in patients with a short disease (2 weeks) duration when inflammatory demyelination is predominant established the concept that axonal loss occurs at disease onset and is a continuous process.

How are axons lost in acute lesions? Positive correlations between the inflammatory activity of MS lesions and axonal damage suggest several possibilities. The inflammatory environment of acute lesions can promote axonal damage in MS patients [3;7;10;23;24;28–30]. Demyelinated axons become vulnerable and are damaged due to proteolytic enzymes, matrix metalloproteases, cytokines, oxidative products, and free radicals that are released by activated immune and glial cells, a common feature of MS lesions [7;22;31;32]. Additionally, these cells are also potential sources for excessive levels of glutamate in acute MS lesions [22;33]. When released in excess, glutamate activates ionotropic and metabotropic receptors, resulting in toxic cytoplasmic Ca^{++} accumulation and cell death. Studies have demonstrated NMDA receptor-dependent signaling in oligodendrocytes [34], their processes [35], and the mature myelin sheath [36]. Excess glutamate may therefore play a major role in damaging oligodendrocytes, myelin and axons [36–38]. As activation of AMPA and/or kainate (but not NMDA) receptors can damage axons, antagonists to these receptors can be axon-protective under certain conditions [39;40].

Axonal loss in acute MS lesions could also occur through a specific immunologic attack on the axon [3;7;41]. This is supported by findings where terminal axonal ovoids in acute MS lesions are surrounded by macrophages and activated microglia [23]. The exact role of these cells in either attacking or protecting axons or removing debris remains to be determined. From an immunological standpoint, both CD4^{+} and CD8^{+} T-cells have been identified as possible mediators of axonal transection in MS lesions [42;43], in EAE mice [44], and *in vitro* [29;45]. Between acute and chronic MS, the T-cell repertoire changes [46] where CD4^{+} T cells are the most prominent cells in active lesions, but are absent in chronic MS lesions [47]. In some cases CD8^{+} cells outnumber the CD4^{+} T cells, thereby suggesting the former driving cytotoxicity [48]. Despite the lack of a distinct TH1-TH2 dichotomy in the human immune system, there is focus on the role of CD4^{+} subsets and their respective

cytokines in the pathogenesis of MS [49]. Despite the current paucity of direct evidence supporting a specific immunological attack on axons in MS, the possibility of cell-mediated mechanisms of axon loss is still necessary to investigate.

The majority of RRMS patients have alternating episodes of neurological disability where the edema associated with new “MS lesions” are a major contributor to neurological relapses through blockade of conduction potentials. Despite extensive axonal loss occurring in acute MS lesions, relapses are reversible, as the human brain has a remarkable ability to compensate for neuronal loss. For example, it has been estimated that Parkinson’s patients lose over 70% of dopaminergic neurons before they show clinical signs [50]. An acute demyelinated lesion it is unlikely to have 60–70% loss of neurons or axons. Initial axonal loss therefore does not have an immediate substantial clinical impact during early stages of RRMS. With time and additional lesions, however, axonal loss can drive the clinical aspects of MS. The conversion of RRMS to SPMS is therefore thought to occur when the brain exhausts its capacity to compensate for further axonal loss [3;7;31].

3. Pathology of chronic progressive lesions

Following the RRMS phase, most patients progress to a non-relapse-related course marked by continuous neurological decline. This course of SPMS is characterized by poor response to immunomodulatory treatments and an absence of new inflammatory demyelinating lesions as measured by MRI and histopathology. A majority of lesions contain a hypocellular, gliotic core and do not show active inflammation. Another feature of chronic MS lesions is axonal swelling. Histological comparison of axons in normal appearing white matter, acute MS lesions and chronic MS lesions detected a statistically significant increase in axonal diameter in chronic MS lesions [51] and axonal swelling correlating only with T1 and MTR (but not T2 only) MRI changes [51].

Axonal loss in progressive MS

Chronic demyelination during progressive MS may lead to loss of axons. Almost half of the demyelinated axons in spinal cords of severely disabled (EDSS > 7.0) MS patients have abnormal axoplasm with reduced organelle content and varying degrees of neurofilament fragmentation, with a dramatic reduction in the numbers of mitochondria and microtubules [52]. Support for the degeneration of chronic demyelinated axons is also provided by data derived from mice that lack individual myelin proteins [31;53]. Myelin-associated glycoprotein (MAG), 2',3' cyclic nucleotide 3'-phosphodiesterase (CNP), and proteolipid protein (PLP) can be removed from oligodendrocytes individually without major effects on the process of myelination [54–56]. All three lines of mice, however, developed a late onset, slowly progressing axonopathy and axonal degeneration [31;53].

How do chronically demyelinated axons degenerate? The central hypotheses of degeneration of chronically demyelinated axons involve an imbalance between energy demand and energy supply [3;7;31;32;57–59]. In normal myelinated fibers, Na⁺ channels are concentrated at nodes of Ranvier, allowing saltatory conduction of action potentials. Na/K ATPases, which maintain the ionic gradients necessary for neurotransmission, are the largest consumers of ATP in the CNS [60]. Continuous energy-dependent ion exchange is required

for maintenance of axonal polarization to support the repetitive axonal firing essential for many neuronal functions. Following demyelination, Na^+ channels are diffusely redistributed along the denuded axolemma. If axonal Na^+ rises above its nominal concentration [32;58], the $\text{Na}^+/\text{Ca}^{++}$ exchanger, which exchanges axoplasmic Na^+ for extracellular Ca^{++} , operates in the reverse Ca^{++} -import mode. With increasing electrical activity, axoplasmic Ca^{++} will rise and eventually a Ca^{++} -mediated degenerative response will be initiated [7;31;59]. Excessive axoplasmic Ca^{++} accumulation leads to a vicious cycle of impaired mitochondrial operation, reduced energy production and compromised axonal transport [7;32;61].

Due to the redistribution of Na^+ channels and the resulting increased influx of sodium, ATP consumption is greatly increased in demyelinated axons [7;58;59;61]. The mitochondria that reach chronically demyelinated axoplasm are likely to be compromised and have a reduced capacity for ATP production caused by decreased neuronal transcription of nuclear encoded mitochondrial genes [52]. Mitochondrial respiratory chain complex I activity was also found to be reduced in chronic active MS lesions [62;63].

Studies also support the notion that chronically demyelinated axolemma eventually lose critical molecules that are essential for propagation of action potentials. Many chronically demyelinated axons may be dysfunctional prior to degeneration because they lack voltage-gated Na^+ channels [64] and/or Na^+/K^+ ATPase [65]. In acutely demyelinated lesions, Na^+/K^+ ATPase was detectable on demyelinated axolemma while 58% of chronic lesions contained less than 50% Na^+/K^+ ATPase-positive demyelinated axons [65]. Chronically demyelinated axons that lack Na^+/K^+ ATPase cannot exchange axoplasmic Na^+ for K^+ and are incapable of repolarizing the axolemma. These data support the concept that many chronically demyelinated axons are non-functional before degeneration. Loss of axonal Na^+ channels and/or Na^+/K^+ ATPase therefore is likely to be a contributor to continuous neurological decline in chronic stages of MS.

4. Cortical demyelination in MS

Historically, MS was considered an inflammatory-mediated demyelinating disease of CNS white matter. In recent years, however, the possibility has been raised that cortical and deep grey matter demyelination may exceed white matter demyelination [66;67]. Little is known about the dynamics of cortical demyelination because there is no reliable way to detect or measure cortical lesion load in living MS patients. Cortical lesions are not visible macroscopically in slices of postmortem brains. Immunocytochemical detection of myelin proteins in histological sections is the only reliable way to detect cortical demyelination. While we cannot detect cortical lesions in living patients, increased cortical atrophy has been shown to be associated with increased disability progression [68;69] and gray matter atrophy is among the best predictors of neurological disability in MS patients [68;70].

Cortical Lesions

There are two major types of cortical lesions detected in MS brains: leukocortical and subpial. Leukocortical lesions are present in both subcortical white matter and lower layers of the cerebral cortex [8;66;67;71]. It is likely that leukocortical lesions begin in subcortical white matter and extend into cortex. The cortical portion of these lesions contained

increased numbers of lymphocytes and microglia/monocytes compared to normal appearing cortex from the same brain or to aged-matched control brains [71]. Infiltrating immune cells, however, are much more abundant in the white matter portions of leukocortical lesions than in the cortical portions and the distribution and density of MHC Class II-positive cells in the white matter lesion can be used to stage leukocortical lesions as active, chronic active and chronic inactive [71]. Using this staging criteria, axonal and dendritic transection was prominent in the cortical portion of active leukocortical lesions [71].

Unfortunately, there is no way to stage subpial cortical lesions which are by far the biggest contributor to total cortical lesion load [66]. These lesions often show myelin loss in cortical layers 1 through 4 and span several gyri [66;71]. On occasion, they can involve all 6 cortical layers, but they rarely, if ever, invade subcortical white matter [66;71]. Not all cortical areas contain subpial lesions. There is a predilection for subpial lesions in frontal and temporal cortices especially, in areas with deep sulci. B cell follicles identified in deep sulci may have a pathogenic role in inducing subpial demyelination [8;72]. With the exception of loss of myelin, subpial lesions lack many of the pathological signatures of white matter lesions which display breakdown of the blood-brain-barrier, infiltration of immune cells, perivascular cuffs, astrogliosis, loss of oligodendrocyte progenitor cells, or complement activation [3;8;71;73;74]. Subpial lesions can contain activated microglia and on occasion activated microglia can form a distinct “line” at the border of the cortical lesion [75]. In our experience, these microglial lines are patient related rather the lesion age related.

Mechanisms of subpial demyelination

While subpial lesions are one of the most intriguing features of MS pathology, little is known about how subpial demyelination occurs. Subpial lesions do not follow rules established for white matter or leukocortical lesions. There is no correlation between subpial and white matter lesion loads [73;74] suggesting that subpial demyelination occurs independently of white matter demyelination. There is a general consensus from autopsy studies that subpial lesions are abundant in progressive stages of MS (both PP and SPMS) and rare in MS patients with acute disease or in early stages of RRMS [3;8;68;76;77]. Subpial lesions from patients with progressive disease do not contain significant numbers of immune cell infiltrates [3;8;73]. At present there is conflicting data regarding the presence of subpial lesions and role of inflammatory infiltrates in early stages of MS. An autopsy study of 11 acute MS cases (death within 2 months of disease onset), 6 early RRMS cases, 15 PPMS cases and 20 SPMS cases detected little to no subpial demyelination in acute or early RRMS brains [67]. This study which included multiple hemispheric sections from each brain, concluded that subpial demyelination was primarily a feature of PPMS and SPMS and rare or absent in acute and RRMS. Meningeal infiltrates were present at all stages of the disease, but were not very abundant (< 1 immune cell/100mm length of meninges). In contrast, studies of biopsy tissue that included cortex superficial to tumefactive white matter lesions detected cortical demyelination in a significant portion (38%) of biopsies ($n=138$) [78]. Immune cell infiltrates were prominent in a subset of these biopsies with four of the 26 subpial lesions containing myelin laden macrophages. This study concluded that cortical lesions were frequent in early stages of MS and associated with cortical and meningeal inflammation [78]. There are two likely explanations of the conflicting

conclusions of the autopsy and biopsy studies. First, cortical inflammation occurs only at presentation of the disease and then rapidly resolves as proposed by Lucchinetti et al. [78]. Second, the cortical lesions and associated inflammation detected in the biopsy paper are a secondary effect of the tumefractive white matter lesions. The answer may relate to the type of cortical lesion. We described active leukocortical lesions in RRMS patients and their cortical portion contained increased T cells and microglia/monocytes and myelin laden macrophages [71]. Detection of inflamed leukocortical lesions in patients with tumefractive white matter lesions should be expected and because of the extensive white matter lesions may even be greater than that found in more classical MS patients. To date, subpial lesions have not been described as inflammatory except those derived from patients with tumefractive lesions. Therefore, it is possible that the inflammation detected in subpial lesions associated with tumefractive white matter lesions is related to the massive inflammation associated with the tumefractive lesions that can occupy a significant proportion of cerebral white matter.

B cell follicles and meningeal infiltration

Subpial lesions are abundant in progressive stages of MS and rarely contain T cells, B cells or amoeboid shaped macrophages [66;71;73]. The most consistent immune cell observation in subpial lesions is the activation of microglia [10;22;66;79]. While it remains to be determined if microglia activation is a cause or consequence of subpial demyelination, TNF and inducible NOS has been detected in subpial microglia in SPMS brains [80]. The additional possibility has been raised that meningeal infiltrates activate microglia and that brains with increased meningeal infiltration have increased B cell-like follicles [80]. There is no consensus on the presence of either meningeal infiltration or B cell follicles in postmortem brains. In a cohort of 29 SPMS and 7 PPMS autopsies from the UK Multiple Sclerosis Tissue Bank, B cell follicles were identified in a cohort of 12 SPMS brains from patients who had an early age of disease onset (average = 23.5 yrs), an aggressive disease course (death by 50) and extensive subpial demyelination [81]. In a follow up paper by the same group, that included 123 autopsies, 40 % of SPMS brains contained B cell follicles with variable frequency [82]. These brains also contained a quantitative increase in diffuse meningeal infiltration, subpial demyelination and cortical microglial activation. Based upon these correlations, the possibility was raised that B cell follicles lead to an increase in meningeal infiltrates which activate microglia which cause subpial pathology and accelerated disease progression [72;83]. In contrast, a study of 28 progressive MS autopsy cases from the Amsterdam Brain Bank failed to identify B cell follicles containing 4 MS cases that met the criteria of early disease onset and death by 50 identified by the previous study [84]. Meningeal infiltration was detected in these brains, but there was no correlation between the extent of meningeal infiltration and subpial demyelination [84]. As in other studies, meningeal infiltration was similar over myelinated cortex and subpial lesions [84]. Thus, there is no consensus on the role of B cell follicles and meningeal infiltration in the pathogenesis of subpial lesions. While it is likely that B cell follicles and meningeal inflammation can influence subpial demyelination, they do not appear essential for subpial demyelination. The possibility has also been raised that B cell follicles may be related to the inflammatory activity of white matter demyelination [10;72;83;85]. White matter

demyelination and white matter atrophy were also high in the subset of B cell follicle-positive progressive patients with early onset and early death.

5. CONCLUSION

Inflammatory-mediated white matter demyelination is an underlying cause of axonal loss during early stages of MS. The transition from RRMS to SPMS is thought to occur when axonal loss exceeds the compensatory capacity of the CNS. Additional axonal loss results in steady progression of permanent neurological disability. Cortical demyelination also plays an important role during the progressive stages of MS. This is particularly true for the subpial lesions that are rare in early and RRMS [3;8;67]. One of the biggest challenges facing the MS community is the development of therapies to treat progressive MS. The list of therapeutic targets for progressive MS is growing. Increased neuroprotection and reduced activation of the innate immune system are popular targets, but the lack of animal models for progressive stages of MS has hampered preclinical studies. Remyelination, the best documented neuroprotective strategy, is suited for all stages of MS [86;87]. Since subpial demyelination is a prominent feature of progressive MS, it should be added to the list of potential targets. The first goal would be to determine how subpial demyelination occurs and whether anti-inflammatory therapies would stop or delay subpial lesions. Development of brain imaging studies that detect subpial demyelination in patients receiving anti-inflammatory therapies would appear essential to attaining this goal. Recently, it has been proposed that progressive MS is inflammatory-mediated, but occurs behind an intact blood-brain-barrier [22;88]. If this hypothesis is correct, anti-inflammatory therapies that cross the BBB may delay progressive stages of MS. Low level leakage of the BBB is more common in progressive stages of MS [89;90], but most progressive patients do not have large GAD enhancing lesions indicative of significant focal BBB disruption. The possibility that the BBB becomes more intact in non-lesion white matter and cerebral cortex during progressive stages of MS is unlikely as BBB function decreases with age. Interest in developing therapeutics for progressive stages of MS is increasing. The list of potential therapeutic targets is extensive. Further knowledge of how subpial demyelination occurs and the development of preclinical animal models that mimic progressive stages of MS should accelerate the development of therapeutics that delay the continuous disability associated with progressive MS.

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Key Points

Autopsy tissue continues to provide important insight into the pathogenesis of both acute and progressive MS.

While inflammatory-mediated white matter demyelination is an underlying cause of axonal loss during early stages of MS, the transition from acute to progressive MS is thought to occur when axonal loss exceeds the compensatory capacity of the CNS.

Subpial demyelination is a prominent feature of progressive MS and it is important to determine mechanisms that lead to subpial demyelination.

One of the biggest challenges facing the MS community is the development of therapies to treat progressive MS and an important goal of MS research would be to determine if anti-inflammatory therapies stop or delay the progression of subpial demyelination.