The Pathologic Foundations of Multiple Sclerosis: Current Considerations

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system (CNS).[1,2] MS appears to involve a complex combination of genetic susceptibility and nongenetic triggers, such as environmental factors, that result in a steady or rapid progression of neurological symptoms.[1] The main characteristics of MS pathology include inflammatory demyelination, axonal injury, and development of CNS lesions.[1] The interaction of these pathologic events produces diffuse, irreversible neurodegeneration.[3,4] There are 4 clinical phenotypes of MS: clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis, and secondary progressive multiple sclerosis (**Table 1**).[1,5,6] The clinical course of the disease is highly variable; most patients experience chronic neurological deterioration over time.[4]

Understanding the neurodegenerative processes involved in MS, particularly the role of white matter (WM) and grey matter (GM), may help clinicians to diagnose the disease earlier and maximize opportunities to preserve neurological reserve. This article reviews MS pathogenesis and rationale for maintaining neurological reserve.

Mechanisms of Multiple Sclerosis

The pathogenesis of MS involves the initiation and perpetuation of inflammatory mediators, which leads to apoptosis of oligodendrocytes and damage to the myelin sheath of the axon.[2] Myelin is essential for impulse conduction from one nerve cell body to another.[7] Reduced conduction ability causes deficiencies in sensation, movement, cognition, or other functions depending on which nerves are damaged.[8] Remyelination occurs; however, repeated attacks on the myelin lead to successively less effective remyelination until a scar-like lesion, a plaque, forms around the damaged axon.[2,8]

An active lesion is a focal area of myelin loss that has been infiltrated with variable inflammatory components, myelin degradation products, scarring (gliosis), and relative axonal preservation.[9] The inflammation that is seen in acute lesions changes over time and decreases with the age of the patient and the duration of the disease.[9] Early in the disease course, these focal lesions are primarily located in the WM,[2] and as the disease progresses, widespread demyelination with axonal loss results in profound tissue atrophy in the brain and spinal cord.[2]

The exact mechanism of direct injury to oligodendrocytes and axons is not completely understood, but it likely includes cluster of differentiation (CD) 4+ and CD8+ T-cell activity, B-cell activity, antibody production, activated microglia and macrophages, and indirect effects of proinflammatory cytokines, such as interleukin-17, tumor necrosis factor alpha, and nitric oxide.[1] Results from recent studies have substantially broadened the view on the pathogenesis of MS. Although early concepts focused predominantly on T-cell interactions as key mediators in inflammatory damage within the CNS, emerging evidence suggests that B cells and other immune cells play a comparably important role.[10,11] The role of B cells in MS is corroborated by the success of clinical trials involving monoclonal antibodies that target the B-cell CD20 surface marker to reduce the formation of new

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TABLE 1. Clinical Phenotypes of Multiple Sclerosis[1,5,6]

CIS	• Presents characteristics of inflammatory demyelination that could be MS but has yet to satisfy the criteria of dissemination
RRMS	• Most common form; affects about 85% of patients • Characterized by relapses lasting from days to weeks, followed by complete or partial remission over months or years
PPMS	• Characterized by progressive accumulation of disability after initial relapsing course of the disease • Steady, functional worsening from the onset of the disease with no relapses or remissions • Affects approximately 10% of patients with MS. • More resistant to drug therapy
SPMS	• Approximately 75% of RRMS cases will transition to SPMS within 15 years of the initial diagnosis • Symptoms often worsen gradually following initial relapse or have no acute exacerbations. • No clear ability to know the transition point from RRMS to SPMS.

CIS indicates clinically isolated syndrome; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

inflammatory lesions in relapsing disease.[1,10] The benefits seen from anti-CD20 therapy do not appear to be related to a reduction of antibodies, and abnormal levels of antibodies remain in the cerebral spinal fluid, indicating an antibody-independent role of B cells.[11]

The immunopathogenesis of MS is thought to involve multiple complex events, including the activation of myelin-reactive T cells. The adaptive immune system requires lymphocytes, such as CD4+ and CD8+ T cells and B cells, to detect and respond to foreign antigens.[8,10] In MS, B cells may be capable of presenting myelin peptide antigens to autoreactive T cells, which results in their activation and proliferation.[10] More recently, there appears to be potential for more dynamic, bidirectional exchanges of B cells between the CNS and periphery-like clonal expansion, which occurs in both.[11] Lymphocytes gain access to the CNS through a disruption in the brain-blood barrier (BBB), presumably by an inciting factor, such as a virus.[1,8] Historically, the initiation of the inflammatory cascade has been attributed to CD4+ major histocompatibility complex (MHC) class II restricted T cells[2,8]; however, the CD8+ MHC class I restricted T-cell populations actually show dominant clonal expansion in MS lesions.[2]

Lymphocytes enter the CNS and trigger an inflammatory cascade, leading to the release of cytokines and chemokines. Some exert proinflammatory effects that cause direct injury to neurons and oligodendrocytes and some apply antiinflammatory effects that limit injury.[1] Additionally, B cells may contribute to CNS damage through the secretion of myelin-reactive antibodies, which, after binding to tissue surfaces, promote injury to neuronal structures.[10] Initial tissue injury in the CNS is also associated with the recruitment of other immune mediators, including microglia, macrophages, and astrocytes, and may exert deleterious effects and protective effects on myelin and axons.[1,12] Macrophages, when activated, secrete proinflammatory mediators such as nitric oxide, cytokines, glutamate, and reactive oxygen species.[12] Conversely, for axonal growth and remyelination to take place, macrophages/microglia phagocytosis of myelin debris is required.[11] Astrocytes release proinflammatory mediators[1,9] while also contributing to cell homeostatic functions, such as maintaining the BBB.[1] The dual mechanisms and the role of many of these inflammatory components in MS have not been fully elucidated.[1]

MS lesions evolve differently during early disease phases compared with chronic disease phases.[9] Acute active lesions that are characteristic of early or relapsing disease are infiltrated by macrophages that contain myelin debris.[9] In progressive disease, chronic lesions develop and consist of completely demyelinated axons and a substantial loss of oligodendrocytes, rendering them vulnerable to inflammatory mediators.[9] Microphages and microglia diminish over time while astrocytes produce glial fibers to fill the demyelinated lesion, which leaves a glial scar (plaque).[9] This astrocytic scar prompted Charcot, the first person to identify the MS lesion, to name the disease *sclerose en plaque*.[9] Inflammation, the hallmark of MS pathology, is present, but its severity decreases with advanced age and disease duration.[9] Furthermore, dense aggregates of inflammatory cells, which may be facilitated by B cells, organize within the CNS in structures and resemble features of lymph follicles. These compartmentalized structures, called tertiary lymphoid organs, continue to contribute to the inflammatory neuronal axonal and synaptic destruction in the cerebral cortex of patients with MS even after T-cell and B-cell inflammation has diminished.[2,9-11] Inflammation may be trapped in part behind a closed or repaired BBB as perivascular inflammatory infiltrates are sometimes identified in chronic lesions.[9] Continued axonal damage and neurodegeneration that occurs after the decrease in the inflammatory response implies that other mechanisms, such as mitochondrial failure, play an important role in perpetuating neuronal damage in advanced disease.[9]

Gray Matter and White Matter Pathology

MS has classically been thought of as a white matter disease.[13] Although it is now known that GM plays an important role in the disease course, understanding WM lesion progression provides valuable insight into the pathologic variability of the lesions.

Currently, active WM lesions are classified into 4 immunopatterns, each representing a different target of injury (**Table 2**).[9] Every pattern represents a distinct pathophysiological mechanism that involves macrophage activation and concomitant myelin degradation.[9] In lesional patterns I and II, demyelination is triggered primarily by direct damage on myelin components while lesional patterns III and IV are marked by the loss of periaxonal myelin components and death of the oligodendrocytes.[9] All 4 lesional patterns eventually become completely demyelinated and convert to a common inactive state.[7]

TABLE 2. Active Lesion Immunopatterns in Multiple Sclerosis[9]

Pattern I	• Present in approximately 15% of patients with MS • Characterized by sharp demarcated perivascular lesions, active demyelination, lack of immunoglobulin deposition, and lack of complement activation on a T lymphocyte • Damage to myelin may be caused by toxic factors produced by macrophages.
Pattern II	• Present in approximately 58% of patients with MS • Characterized by sharp demarcated edges, active demyelination with equal loss of myelin components, loss of oligodendrocytes at the active border • Demyelination triggered via direct damage on the myelin sheaths/antibody and other mediated mechanisms
Pattern III	• Present in approximately 26% of patients with MS • Characterized by poorly defined lesions, demyelination with oligodendrocyte apoptosis • Oligodendrocyte apoptosis may be driven by other metabolic process (ie, mitochondrial dysfunction)
Pattern IV	• Present in just 1% of patients • Characterized by significant nonapoptotic death of oligodendrocytes in periplaque WM, infiltrating T cells, activated microglia/macrophages

MS indicates multiple sclerosis; WM, white matter.

Since the introduction of myelin immunohistochemistry, the knowledge of GM pathology that is associated with MS has greatly expanded.[13,14] Additionally, new magnetic resonance imaging (MRI) methods have improved in vivo detection, although the majority of cortical lesions are still not seen by any MRI technique.[9] The appearance of cortical GM and deep grey matter (DGM) neurodegeneration is an important early event in the pathogenesis of MS.[9,15,16] Not only is GM pathology highly heterogeneous across patients,[15] but cortical demyelination and neurodegeneration is extensive and manifests throughout all phases of relapsing-remitting disease.[9,17-19] In studies of patients with CIS and RRMS, only GM atrophy was detected early in the disease course.[16,20] Additionally, postmortem and clinical MRI studies found no correlation between cortical lesion volume and WM lesion volume.[21,22] GM lesions were found to differ significantly from WM lesions and had less or absent immunoactivation.[14] Thus, the GM demyelination and axonal degeneration may be caused by an independent, primary disease process that arises in the GM or a secondary disease process caused by damage to WM.[9,13]

In recent years GM has emerged as a focal point of MS research. GM neurodegeneration may be more relevant to understand MS disability than WM neurodegeneration. An early study of the relationship between whole brain volume and disability found that patients with MS had low total brain volume ($P = .003$) and GM volume ($P = .003$). There was a nonsignificant trend for low WM volume ($P = .052$) relative to the control group.[23] GM volume was associated with progressive clinical MS involvement and high expanded disability status scale (EDSS) score ($P < .01$), which indicates that GM atrophy may be more relevant to clinical progression than WM atrophy.[23] Studies evaluating WM lesion load have resulted in similar outcomes.

Findings from a systematic review and meta-analysis of primary research that relates cognitive function to WM lesion burden identified a modest correlation of patients with MS ($r = –0.30$; 95% CI, –0.34 to –0.26) from MRI measures of the total WM lesions and cognitive function. There has been no study of more than 100 patients with results demonstrating a strong correlation between WM lesions and cognitive function.[24] In a longitudinal MRI study of patients with MS, there was no considerable difference in WM lesion volume at 3 years follow-up in patients who were clinically worsening than in those who were clinically stable.[25] Cortical lesion volume at baseline and follow-up correlated with EDSS score at baseline ($r = .36$; $P \leq .001$) and over time ($r = .51$; $P \leq .001$).[25] WM injury may be independent of the GM pathologic events, and WM changes cannot currently be used to discern those patients with extensive GM disease in clinical practice or to predict long-term clinical outcomes.[22]

The results of multiple cross-sectional and longitudinal studies that have evaluated the relationship of GM lesions with disability demonstrate that cortical lesions are related to physical and cognitive impairment.[25-28] Demyelination, neuron atrophy, neuronal loss, and axonal loss in DGM may contribute to clinical disability and long-term impairment in patients with MS.[29] Nelson et al attempted to classify cortical lesions into subtypes in order to gain a better understanding of their impact on cognitive outcomes.[28] They discovered that the size of the lesion, not its tissue, may better explain the correlation with cognitive impairment.[28]

Due to poor visualization, MRI brain volume, or brain atrophy, is often used as an alternative to cortical lesion

assessment in clinical trials. The results of several cross-sectional studies show a relationship between widespread GM atrophy and cognitive and physical disability.[23-33] Additionally, a robust association between GM atrophy and DGM atrophy on several measures of disease progression has been demonstrated across all phenotypes.[34,35] Moreover, GM atrophy has been shown to be a significant MRI variable when it comes to EDSS measurement.[31]

Of particular interest is the relationship between cognitive functioning and GM neurodengeration. DGM (eg, basal ganglia, caudate, thalamus, putamen, claustrum, hypothalamus, and amygdala) plays a role in cognitive function. The atrophy of specific regions correlates to cognitive impairment. Volume loss of the thalamus and putamen are significant contributors to information processing speed,[36] and hippocampal lesions show a strong association with impaired visuospatial memory and processing speed.[26] New data suggest that DGM volume loss may drive MS progression, particularly in advanced disease. The results of a large multicenter study demonstrate that volume loss in DGM was faster than what has been observed in other brain regions across all clinical phenotypes, and the DGM volume loss was the only region associated with disability accumulation.[35] Interestingly, atrophy rates of cortical regions in specific areas and clinical phenotypes were not associated with one another.[35] WM did not show a significant rate of volume loss in healthy controls or any clinical phenotypes.[35]

Azevedo et al reported results that indicated that thalamic atrophy may be utilized as a potential biomarker to assess neurodegeneration in patients with MS.[37] Thalamic atrophy presents early in the disease course and correlates well with physical and cognitive impairment; this makes it an attractive, potential biomarker.[37] Neurodegenerative DGM atrophy continues to progress throughout the disease and may have strong predictive potential for disability and cognitive impairment. Knowledge of mechanisms underlying GM and the identification of disease progression could help identify prognostic biomarkers and allow for individualized therapy in those who develop cortical pathology.

GM degeneration occurs not only in the brain but also throughout the CNS, including the spinal cord. The correlation of GM and WM atrophy in the spinal cord in patients with MS disability along with the disease type was evaluated.[38] Independent from GM atrophy, spinal cord GM areas correlate with disability and contribute to it more than WM volume or GM volume.[38] Spinal cord injury is more pronounced in progressive MS rather than relapsing MS, and it contributes to patient disability more frequently than spinal cord WM or brain GM atrophy.[38]

Imaging

MRI has played an important role in contributing to the understanding of the natural history of MS in the brain and spinal cord. Although MRI evaluation is the standard tool for the diagnosis of MS, conventional MRI methods (T1, T2, fluid attenuated inversion recovery) have limitations when examining the visualization of GM pathology with poor sensitivity and low signal to noise ratios; therefore, brain atrophy is typically measured.[39,40] Pathologic GM lesions are present in the brain early on and have a clear relationship to cognitive impairment. Although GM pathology has become more evident, mainly through novel imaging techniques, these new methods currently have not been incorporated into the clinical setting of patient care.[40]

GM lesion visualization has always been considered challenging to attain. GM lesions are usually small and have poor contrast resolution.[25] Overall, MRI sensitivity is much lower than histopathological assessment for GM lesions.[41] During the past few years, the introduction of 2 MRI pulse sequences, double inversion recovery (DIR) and phase sensitive inversion recovery (PSIR), have improved the detection of cortical lesions in patients with MS.[28,39] With DIR, 5 times the cortical GM lesions can be detected, and with the combination of DIR and PSIR, more reliable detections of these lesions can be found than with DIR alone.[28,39] The detection of cortical lesions has improved and now uses ultra–high-field MRI; however, it is not widely available.[39] Despite these improvements, cortical lesion assessments have not been incorporated into diagnostic criteria[40] and are not used as endpoints for treatment trials.[41] Additionally, there is an absence of standardized imaging acquisitions and analysis for cortical lesions.

Disability Progression

Although abundant information has been published about the role of GM atrophy in disease progression, WM atrophy may still prove to be a valuable sign in patient assessment and disability progression. Using a combination of WM and GM parameters may provide a more comprehensive view of MS pathology than individual assessments. To demonstrate this, Moccia et al conducted a 10-year retrospective cohort study of 149 patients with newly diagnosed RRMS[42] and evaluated the ratio in volume of GM to normal-appearing WM, the occurrence of clinical relapse, disability progression, and conversion to SPMS.[42] The results of the study showed that a low GM to normal WM ratio is a predictor of 10-year risk of disability progression and secondary progression conversion in early stages of RRMS. This suggests that the extent to which GM and normal WM are affected varies and may be determined by disease evolution from the early phases of MS.[42]

Rudick et al evaluated 70 patients with MS and 17 healthy controls to determine the connections between whole brain, GM, and WM atrophy with MS disability progression.[43] The results showed that whole brain, GM, and WM atrophy predicted disability progression over the following

6.6 years, although GM atrophy rates during 4 years of the study were associated with multiple sclerosis functional composite (MSFC), not EDSS score. Although EDSS is known to be more sensitive to ambulation, the 4-year data show that GM atrophy correlated with MSFC but not EDSS.[43] These results suggest that GM atrophy correlates with disability progression and that MSFC should be used to define disability progression.

Maintaining Neurological Reserve

Neurological reserve is the capacity of the brain to retain function and provide functional compensation following atrophy caused by MS disease activity[44] and comprises brain reserve and cognitive reserve. As new data continue to articulate the extent of the damage to GM and WM that occurs early in the disease course of MS,[15,20,34] preserving brain volume and function has become increasingly important. Before the progressive stage of the disease, the brain exhausts neurological reserve. Therefore, early diagnosis is essential.[44,45]

Brain reserve, or brain volume, refers to the size of the brain and the number of neurons that are available to process information.[44] This declines as the brain ages, but this process is accelerated in patients with MS.[44] Changes in brain volume have been assessed in the earliest and latter stages of the disease. A loss in brain volume has been associated with disability progression and cognitive impairment.[45]

Although the concept of brain reserve suggests that the brain can handle pathology prior to reaching a critical threshold for clinical symptoms to be apparent, cognitive reserve proposes that through brain damage, the brain actively attempts to cope by using cognitive processing, which allows patients with high cognitive reserve to respond to brain damage better than those with lower cognitive reserve.[46] Understanding cognitive reserve has opened up analysis opportunities through functional imaging studies and further investigations into the changes in brain behavior with age.[46]

In a longitudinal study that monitored cognitive reserve in patients with MS, investigators measured how brain reserve and cognitive reserve influence subcortical gray matter (SCGM) atrophy and cognitive decline in patients.[47] The study population consisted of 71 patients with MS and 23 controls, all of whom underwent an MRI and cognitive assessment at baseline and at a follow-up period of 3 years. Although no effects were observed in memory, SCGM volume and cognitive scores were lower in patients with MS compared with the control group ($P \leq .001$). Moreover, low cognitive reserve ($P = .002$) was associated with a decline in cognitive processing speed in patients with MS.[47]

With the heightening importance of neurological reserve in the broader scope of MS management, an increased emphasis on brain health and cognitive function may lead to greater efforts to diagnose the disease earlier.

Conclusions

Significant advances have been made in understanding the MS pathological processes and the treatment of disease. Although MRI has emerged as a useful diagnostic and monitoring tool, there is still a good deal to learn regarding MRI correlations and clinical disability. Current clinically useful MRIs have low sensitivity for the detection of cortical lesions and limited sensitivity, even in WM disease. Additionally, improved imaging techniques would allow for the visualization of early inflammatory cortical demyelination and provide a better understanding of the whole brain lesion load. The identification of a disease biomarker would allow for individualization of treatment and ultimately improve functional outcomes.

An improved understanding of pathology coupled with refined imaging technologies could yield more effective interventions from targeted disease-modifying therapies, with the goal of providing neuroprotection and delaying disease and disability progression. Maintaining neurological reserve and a regular monitoring strategy can help promote brain preservation in MS. Because a larger brain volume has been associated with positive cognitive function, healthy lifestyle and recreational activities have the potential to protect against any dismal loss in brain volume to influence cognition.

New research regarding comorbid conditions and lifestyle interventions offer additional perspective and could contribute to a more comprehensive approach to managing MS and achieving success with brain preservation. The next article in this publication explores the role of comorbidities in MS disease course and disability and the potential benefits of lifestyle wellness strategies in management.

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