Current Concepts in the Neuropathology and Pathogenesis of Multiple Sclerosis

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ABSTRACT: Multiple sclerosis (MS) has been classically regarded as an inflammatory demyelinating disease of the central nervous system. In recent years, the classification and pathogenesis of the disease have become controversial, particularly with respect to whether an individual patient demonstrates a single or multiple pathogenetic mechanisms in the establishment of the focal plaque of MS. It is also becoming increasingly apparent that there is a significant neurodegenerative component in the disease, involving not only plaques but the non-plaque parenchyma as well. Magnetic resonance imaging, together with histopathologic studies, will continue to shed light on the pathogenesis of these focal and diffuse abnormalities in MS.

RÉSUMÉ: Connaissances actuelles sur la neuropathologie et la pathogenèse de la sclérose en plaques. La sclérose en plaques (SP) est considérée comme une maladie démyélinisante inflammatoire du système nerveux central. Au cours des dernières années, la classification et la pathogenèse de la maladie ont fait l’objet de controverses, particulièrement en ce qui concerne la présence d’un ou de plusieurs mécanismes pathogènes dans la formation de la plaque focale de la SP. Il est de plus en plus évident qu’il existe une composante neurodégénérative significative dans cette maladie, impliquant non seulement les plaques mais aussi le parenchyme exempt de plaques. L’IRM a contribué et, conjointement avec les études anatomopathologiques, continuera à éclaircir la pathogenèse de ces anomalies focales et diffuses dans la SP.


1. THE CLASSIC NEUROPATHOLOGY OF MS
A. Histopathology of MS

The study of the pathology of MS dates back to the early 1800’s in the works of Carswell and Cruveilhier and was the subject of a beautifully illustrated monograph by Dawson in 1916. Details of the history of MS pathology may be found in a recent review. The primary pathologic features of MS are chronic inflammation and demyelination accompanied by gliosis (Figure 1). The reader is referred to extensive reviews of the subject for more detailed information. Briefly, the plaques of multiple sclerosis are macroscopically visible as focal lesions throughout...
the central nervous system (CNS) white matter. The white matter most obviously involved is periventricular where the lesions, or plaques, are characterized by large areas of gray discolouration. However, anywhere in the CNS may be attacked.

Microscopically, plaques show axons that have undergone or are undergoing demyelination. The active demyelination is carried out by macrophages (Figure 1), which degrade the phagocytosed myelin to neutral lipid within their lysosomes. It has been assumed that the macrophage is the effector cell of an autoimmune attack on the myelin-oligodendrocyte unit orchestrated by lymphocytes in the chronic inflammatory infiltrates in the perivascular spaces and parenchyma of the lesion (Figure 1F). Studies have shown that lymphocytic population of the MS lesion bear an array of markers corresponding to a variety of functional subtypes, including helper/inducer T-cells, with either α-β or γ-δ T-cell receptor types, cytotoxic T-cells, natural-killer cells, B-cells and plasma cells, all of which either singly or in concert have been implicated in the immunopathogenesis of the lesion. Accompanying all these changes is gliosis, initially in the form of large reactive astrocytes (Figure 1E) and eventually as fibrillary gliosis.

It is now widely recognized that remyelination occurs in the MS lesion and paradoxically this appears to be maximum during active ongoing demyelination and inflammation. Remyelination is characterized by thin myelin sheaths and short internodes, which may also undergo subsequent demyelination.

Still more recently has been the recognition that while the most obvious change in the MS lesion is demyelination, significant axonal loss also occurs (Figure 2), and this is, at least in part, due to the transection of axons from damage inflicted by the products of the inflammatory infiltrate. This is, in turn, reflected in the finding of Wallerian degeneration in long tracts in the MS spinal cord.

**B. The Classification of MS Plaques**

The classification of MS white matter plaques has been largely based on the degree and location of the inflammatory and demyelinative activity, which are taken to reflect the age of the lesion. Thus, it has been customary to classify plaques as acute, chronic active and chronic silent (or “chronic inactive”). The term acute plaque has been reserved for the lesion of acute MS (sometimes referred to as “Marburg type” of MS), which presents clinically as a single monophasic event with widespread lesions of more or less the same age. However, it may also refer to histopathologically similar lesions in the setting of chronic MS, these lesions presumably being the early stages of what will later be chronic MS plaques. Acute MS lesions are relatively uniform in their histopathology throughout their extent, being regions of ongoing demyelination with intense hypercellularity attributable to prominent perivascular chronic inflammatory infiltrates, numerous macrophages with myelin debris and/or neutral lipid, monocytes, lymphocytes, reactive astrocytes, and increased numbers of oligodendroglia involved in remyelination (Figure 1A-F). Remyelination may be extensive and is responsible for “shadow plaques”, which show relative reduction of stain intensity on myelin stains due to the presence of thin short internodes.

Correlating with the monophasic nature of acute MS, the lesions show a relative uniformity in histologic appearance in a given patient (Figure 1A-C). However, even in acute MS variability in lesion age, based on histologic features, may be evident, and in some cases these features may be consistent with a lesion developing before the time of emergence of clinical symptoms and signs.

In contrast, the chronic active plaque shows a distinct topography reflecting the fact that it is seen in the chronic form of MS, where the lesion has time to mature. Thus, older histopathologic features are seen in the centre of the lesion, which shows varying number of lipid-laden macrophages and fibrillary gliosis. The border of the lesion shows ongoing demyelinative activity in the form of inflammation, with macrophages engaged in active myelin removal and degradation, reactive astrocytes, oligodendrocyte hyperplasia and remyelination - in many ways resembling the features seen throughout the acute lesion. This border of demyelinative activity extends centrifugally into the adjacent “normal-appearing” white matter.

**Figure 1:** (opposite page) Illustrative classic neuropathology of MS. Acute MS: A-F: An acute MS plaque is characterized by a focal area of demyelination, demonstrated as loss of Luxol Fast Blue (LFB) staining (A), and perivascular cuffs of chronic inflammation (black arrows). The lesion has a uniform appearance throughout, containing numerous macrophages with LFB-positive myelin debris (red arrows), both in its centre (B) and at its edge (C). At the lesion edge (C), the macrophages (red arrows) are seen close to myelin sheaths in the adjacent white matter (yellow arrow). D, E, and F show immunofluorescence in an acute plaque, with myelin basic protein (MBP in myelin) in green, heavy neurofilament (NF-H in axons) in red, combined with lavender for HAM 56 (macrophages) in D, or glial fibrillary acidic protein (astrocytes) in E, or CD45 (a pan-lymphocyte marker) in F. Note the macrophages containing MBP-positive debris amidst axons that have been demyelinated (D), the prominent reactive astrocytes (E), and the large number of perivascular lymphocytes (F). Active MS lesion: G. Immunohistochemistry for Class II MHC shows an active lesion with positivity throughout (G). Chronic active MS lesions: H, I, and J: Class II MHC immunoreactivity is prominent at the border of several chronic active lesions (H). At the lesion edge there are Class II-positive activated microglia, which possess ramified processes, and macrophages which have a round appearance (I), whereas in the adjacent “normal-appearing white matter” only ramified microglia are positive for Class II MHC (J). Chronic silent MS plaque: K. The edge of a chronic silent lesion shows no evidence of inflammation, as evidenced by absence of hypercellularity (K). In the lesion there is virtual absence of myelin in the lesion (upper half of K), the edge of which has a relatively abrupt border abutting the adjacent white matter (lower half of K) that shows axons (black) with myelin sheaths (blue). A, B, C: LFB-PAS; D, E, F: Triple immunofluorescence for MBP and NF-H, combined with HAM 56 (D), GFAP (E), or CD45 (F); G, H, I, J: Immunohistochemistry for Class II MHC; K: LFB-Bielschowsky. Scale bars for high magnifications: Black = 400μm, White = 25μm.
For reasons that are unclear, the immune-mediated demyelination at the lesion edge in chronic MS may evolve into a quiescent phase, at which point the term chronic silent plaque applies. Such lesions have very little inflammation, sometimes in the form of a few perivascular lymphocytes and lipid-laden macrophages, in an oligodendroglial-depleted expanse of demyelinated axons with fibrillary gliosis (Figure 1K). However, plasma cells, responsible for the continuous production of oligoclonal IgG, may be abundant in the chronic inactive lesion. The border of the lesion may show a variable degree of remyelination that had survived the demyelinating onslaught during the active phase. If this is prominent, the plaque will have the appearance of a shadow plaque. It is important to note that the chronic inactive lesion may reactivate at any time with resumption of inflammatory demyelination, either focally or throughout its edge.

A classification system based on the degree of expression of Class II histocompatibility complex (MHC) by microglia/macrophages and the degree of myelin breakdown to neutral lipid as shown by Oil red O-positivity was proposed in 199323. More recently, many MS researchers have employed a classification system that determines the age and activity of an MS plaque based on the reactivity of microglia and their maturation to macrophages as assessed by immunohistochemistry for the Class II MHC24. Here an active lesion is defined as a lesion with a uniform distribution of Class II MHC-positive microglia (Figure 1G) indicating an early stage in the lesion evolution and corresponds to the acute plaque described above. A chronic active lesion has a border of intense Class II MHC positivity in macrophages and microglia (Figure H-J) and is the equivalent of the chronic active lesion with its edge of ongoing demyelination described above. A chronic inactive lesion is one in which Class II MHC expression is down-regulated indicative of the dampening of the immune response in the lesion and corresponds to the chronic silent lesion.

### 2. Neuropathology and Pathogenesis of MS: Current Concepts and Controversy

In the last decade a classification system has been developed by researchers at the Mayo Clinic and University of Vienna25,26. This system, based on the examination of lesions undergoing active demyelination, defines four patterns of MS lesions. Patterns I and II have an immunopathogenetic basis, whereas Patterns III and IV have changes more indicative of a toxic of dystrophic effect on the oligodendroglial-myelin unit. Pattern I shows macrophage-mediated demyelination in the absence of antibody and complement deposition, whereas Pattern II is characterized by immunoglobulin and complement deposition, implicating a role for antibodies in its pathogenesis25. Both show an equivalent loss of the various myelin proteins26. The Pattern III lesion differs from the others in that it is not perivenous in location, has an ill-defined outline and shows a selective loss of myelin-associated glycoprotein (MAG)26. There is extensive apoptosis of oligodendrocytes and oligodendrocyte loss in Pattern III26. This, together with the loss of MAG, which is located at the distal end of the oligodendrocyte process where it contacts the axon, suggests that this lesion results from a dying-back oligodendrogliopathy due to a perturbed oligodendroglial cell body. The Pattern IV lesion, which is a very rare lesion, is characterized by non-apoptotic oligodendroglial cell death in the periplaque white matter and was only found in chronic progressive MS.

However, a point of considerable controversy arises from the concept that was also put forth by the Mayo-Vienna group when this system was formulated, which stated that MS was a heterogeneous disease among MS patients but was homogeneous within an individual MS patient25. In other words, the mechanism of myelin and oligodendrocyte destruction, as indicated by one of the four lesion types, was the same within all lesions of an individual MS patient.

A number of publications have supported this view. One was the finding that patients with Pattern II, who have deposits of immunoglobulins and complement in their lesions, improved clinically after therapeutic plasma exchange, a predictable result if these lesions had a humorally immune-mediated pathogenesis27. Patients with the other lesion patterns did not respond to this treatment27. There has also been a suggestion that MR imaging may be able to predict the pattern type28. Further, Pattern III lesions, but not Pattern II lesions, have been found to have mitochondrial defects, as evidenced by absent immunohistochemical staining for the catalytic subunit of the fourth complex of the mitochondrial respiratory chain29. This finding correlates with the notion that Pattern III lesions, which are also prominent in Balo’s concentric sclerosis, may have a hypoxia-based pathogenesis30.

The concept of pathogenetic homogeneity within a given MS patient was challenged by an article by Barnett and Prineas in 2004, wherein they reported on the pathology of early lesions in relapsing-remitting MS. They observed oligodendrocyte apoptosis (Pattern III feature) and complement deposition (a Pattern II feature) in the same patients31, a combination that was not evident in the Mayo-Vienna material32. The controversy of lesion heterogeneity aside, this article also raised the possibility that MS, in the first instance, may not be immunologically mediated, since they observed very few lymphocytes in the early lesions. However, they could not exclude a role for antibodies in the early pathogenetic events33,34. Exploring these possibilities further, this group very recently has shown that antibody and complement deposition are not specific for the MS lesion and is evident in disorders that are not thought to have an immune-mediated pathogenesis, such as cerebral infarcts35, again questioning the validity of the Pattern II MS lesion and the role of antibodies in the pathogenesis of MS. Another group, based in Amsterdam, has studied a large group of lesions in established MS and has found that all chronic lesions show complement and antibodies in association with macrophages36. Therefore, they have concluded that in chronic MS all lesions are homogeneous in their pathogenesis36, essentially showing Pattern II histopathology. As noted in an accompanying editorial by Raine37, this report represents a significant negative in the tally of pros and cons in the re-examination of the four-pattern patient-specific classification of MS lesions based on pathogenesis.

Thus, it is clear there is considerable disagreement at the moment about the heterogeneity/homogeneity of MS and even the importance of the immune system in the early pathogenesis of MS has come into question. There are a variety of reasons why...
this is so, and it may not necessarily be that one approach is absolutely “correct” and the other absolutely “wrong”. Some of these disparities may find their explanation in the rarity of acute MS tissue (which is very often biopsy material), different immunohistochemical staining techniques, different antibodies and different antigens being examined, the vagaries of working with formalin-fixed tissue, the point in the evolution of the lesion in which it was sampled (early in studies with a predominance of biopsy material, or late in those with predominantly post-mortem material), and the variable factor of tissue autolysis in biopsy versus autopsy material\(^{38}\). However, it is probable that all these factors, either singly or in combination, do not account for all the discrepancies\(^{38}\).

Can these seemingly disparate findings and opinions be resolved? Is it possible that different research groups are seeing the same pathogenetic process at different time points is its maturation? Is it possible that during the immunopathogenesis of the disease or a single lesion different components of the immune system are operative in the progression from acute to chronic, and the different findings of various studies are simply a reflection of the sampling time\(^{39,40}\)? Is it possible that MS in its early stages is not a disorder of the immune system but rather a neurodegenerative/toxic condition which then triggers the immune system into action? Clearly, much more work needs to be done to resolve the issues in this controversial, but fascinating, study of the early and subsequent phases in the pathogenesis of the MS plaque. As suggested by Esiri in a recent editorial, one approach to these controversies would be the formation of a panel, which could assess material from a variety of workers and institutions and produce a consensus, much as has been done in Alzheimer’s Disease and other neurodegenerative disorders\(^{38}\).

### 3. Neuropathology of MS: Correlation with MRI

#### A. The MS Plaque

With the advent of MRI and its application to MS, it became clear that this technique was very sensitive in the detection of MS plaques (Figure 2). It was initially thought that specific abnormalities detected by MRI would have specific histologic correlates and that MRI would be a direct window on the pathology of MS. Early on post-mortem studies showed that MRI indeed detected MS plaques and the area and shape of these lesions on the MRI corresponded to that noted in the tissue\(^{39,40}\). Correlative studies showed that abnormalities seen on T2-weighted images could be attributed variously to demyelination, macrophages, vascular permeability, edema, expansion of the extracellular space secondary to tissue loss or gliosis, and that there was no histologic feature which could produce a specific T2-weighted abnormality\(^{41}\). The same proved to be true for T1-weighted imaging\(^{41}\), except for two notable exceptions. Firstly, permanent black holes on T1-weighted MRI corresponded to areas of severe parenchymal destruction with axonal loss\(^{42}\). Black holes which were transient were felt to have remyelination or edema resolution to account for their evanescence\(^{43}\). Secondly, contrast enhancement in T1-weighted MRI has been correlated with breakdown of blood-brain barrier secondary to inflammatory infiltrates\(^{44}\). Vascular neogenesis in the lesion also may contribute to contrast enhancement\(^{45}\).

However, specialized MRI techniques have been shown to have histological specificity or have the potential to do so. Intuitively, a technique which could detect a biochemical marker specific for a cell type should provide a high degree of specificity. One such technique is proton magnetic resonance spectroscopy (MRS)\(^{46}\). A marker widely used to assess axonal loss by MRS is N-acetyl aspartate (NAA)\(^{47}\) and indeed this has been shown to be reduced in MS plaques by MRS\(^{48}\). Increased choline in MS plaques has been attributed to cell membranes in inflammatory infiltrates\(^{49}\) and elevated lactate to macrophages\(^{50}\). Choline has also been thought to be due to gliosis\(^{50}\), as has elevated myoinositol\(^{51}\) and creatine\(^{52}\). The abnormal lipid peaks on MRS are felt to reflect myelin breakdown\(^{49}\), and the reduced phospholipids in the plaques are evident on MRS for phosphorous\(^{53}\).

Magnetization transfer imaging (MTI) detects the water associated with macromolecular structures. It has been correlated with the integrity of myelin in some studies\(^{54,55}\) and with axons in others\(^{56,57}\).

Diffusion-weighted imaging (DWI) measures the random motion of protons and abnormalities of its parameters, including apparent diffusion coefficient (ADC), mean diffusivity and fractional anisotropy (FA)\(^{58}\), have been associated with myelin and to a lesser degree axonal pathology\(^{59}\).

A relaxation MRI technique has been developed that appears to be associated with the lamellar structure of myelin and seems to be specific for myelin\(^{60}\). Mathematically, it is possible to separate the T2 decay curve of the central nervous system into three components: a long (greater than 1 ms) component from cerebrospinal fluid, and intermediate component (approximately 80-100 ms) thought to originate in extracellular and intracellular fluid, and the myelin-specific short-T2 component (less than 50ms)\(^{60}\). The short T2 component has been shown qualitatively (Figure 2)\(^{61}\) and quantitatively\(^{62}\) to correlate with the presence of myelin in MRI-pathologic correlative studies and is absent\(^{63}\) in MS plaques with complete loss of myelin but surviving axons. Thus, the fraction of the T2 signal attributable to the short T2 component has also been referred to as the “myelin water fraction” (MWF). There is also evidence to indicate that the short T2 component recognizes remyelinated myelin, in as much as a serial study has shown its return in lesions which previously were devoid of this signal\(^{63}\).

Aside from histologic specificity, the MRI scan can detect patterns within MS lesions, which may correlate with the pathogenesis of a specific lesion. For example, a change in the MRI signal at the periphery of the lesion may indicate on-going demyelination\(^{64,65}\). The characteristic ring pattern of Balo’s concentric sclerosis has also been confirmed by histopathologic-MRI correlation\(^{66}\).

It has become increasingly apparent that in addition to classic white matter plaques of MS, demyelinating lesions are also present in the gray matter. These cortical plaques can be quite extensive and usually abut the pia, but occasionally may be evident deep to the superficial cortical layers\(^{67,68}\) (Figure 2). Plaques within subcortical U-fibres may also extend into the deeper cortical layers forming leucocortical plaques\(^{49}\). Cortical plaques are thought to be responsible for much of the cognitive dysfunction of MS as well as MS-associated epilepsy and thus contribute to a significant burden of the disease\(^{69,71}\). This is not
particularly surprising given the extensive neuronal and synaptic loss in these lesions72. They have also been particularly associated with the progressive forms of MS71. Histopathologically these are quite distinct from white matter plaques in that there is generally very little, if any, inflammation73 and are much more readily detected by immunohistochemical stains for myelin proteins than by the routine stain used for myelin, luxol fast blue (LFB)74. The reason for the paucity of inflammation is unclear, but it has been proposed that early in their course that these are inflammatory but become inactive in the later stages of the disease when most cases are examined pathologically75.

Until recently, cortical plaques were largely invisible on MRI69. However, with high-field strength MRI, which is available at only a few centres at present, these can now be demonstrated with amazing clarity and this has been confirmed by histopathologic correlation76.

Studies of MS plaques in the deep gray matter (Figure 2) have been few. To date the findings include microglial activation and macrophage-mediated demyelination77 and a degree of inflammation intermediate between the paucity of inflammatory infiltrates in cortical plaques and the extensive inflammation seen in white matter lesions78.

B. The Non-plaque Parenchyma

Of considerable interest over recent years are the abnormalities in non-lesional parenchyma in MS. Thus, the so-called “normal-appearing white matter” (NAWM) (Figure 2) shows abnormalities detected both on the MRI scan as well as histopathologically. While the recent interest in this area has been largely driven by MRI, histopathologic abnormalities in MS NAWM have been known for quite sometime, but have not been emphasized until recently. These abnormalities include gliosis, perivascular inflammation, perivascular lipofuscin deposition, some demyelination79,80 widespread mild inflammation81, and microglial activation82,83. Lysosomes and lysosomal enzymes80,84-86, metalloproteinases87, breakdown of extracellular matrix proteins88 and blood-brain barrier breakdown89,90 have also been reported in NAWM. Of particular relevance is the finding of axonal loss in MS NAWM91, which is attributable to Wallerian degeneration in axons subsequent to their transection in plaques92. Consistent with this finding is the demonstration of reduced NAA in NAWM93 by MRS, a abnormality which is often present very early in the disease course94. These histopathologic and MRI findings in NAWM have highlighted the presence of a widespread neurodegenerative process that contributes significantly to the clinicopathologic spectrum of MS9. It is unclear at the present time whether this is secondary to or independent of the inflammatory demyelinating component that has been emphasized in the past. It is also possible both scenarios may be operative. Other abnormalities evident in NAWM by non-conventional MRI include abnormalities in lipids53,95, increased choline96, creatine96 and myoinositol97 on MR, a reduction in MTR on MTI, increased ADC99 and reduced FA100 on diffusion weighted imaging. Relaxation studies have shown prolongation of T1101, reduction in the short T2 component102 and an increase in the total water content103. At this point it is not known which histopathologic features are responsible for which MRI abnormalities. It would seem that axonal loss would be the basis for the NAA reduction. In any event, the abnormalities in NAWM are clinically relevant in MS, being correlated with disability102 and cognitive dysfunction94.

There are also diffuse abnormalities in the “normal-appearing gray matter” (NAGM) evident on non-conventional MRI of the cortex in MS. These consist of reduction in NAA and DWI and MTR abnormalities94. It is unclear whether this a diffuse abnormality independent of numerous cortical plaques or whether there is an independent neurodegenerative process in the cortex. Moreover, it is unclear as to what histopathologic features are responsible for these diffuse cortical abnormalities.

Diffuse MRI abnormalities are also seen in the deep gray matter. In the thalamus there is thought to be an increase in iron content evident on routine clinical MRI, evident as T2-hypointensity103. However, this has not been correlated with histopathology to date. Diffuse neuronal loss with atrophy and MRS abnormalities have also been documented in the thalamus in MS, indicative again of a neurodegenerative process104.

Whereas abnormalities in NAWM are detected only by non-conventional imaging, there are subtle abnormalities in the non-lesional white matter that are evident on routine proton density and T2-weighted imaging. This was termed “dirty-appearing white matter” when originally described by Zhao, Li and...

Figure 2: (opposite page) Illustration of MRI-pathology correlation in MS in a formalin-fixed cerebral hemisphere. Note the periventricular plaque in the frontal white matter (yellow arrows) and the much larger periventricular plaque in the occipito-parietal white matter (green arrows), which are evident as increased signal intensity on the proton density scan and as absence of signal on the short T2 component distribution (myelin water fraction). Note the short T2 component distribution corresponds to the distribution of myelin. The white matter plaques show loss of myelin as evidenced by absence of staining on the luxol fast blue (LFB), myelin basic protein (MBP) and 2', 3'-cyclic nucleotide 3'phosphohydrolase (CNP) stains. They also show severe axonal loss as shown by the absence of Bielschowsky staining. A plaque in the thalamus (blue arrow) shows similar imaging and staining characteristics. A cortical plaque (red arrow) best seen on the MBF and CNP stains is not detected by MR imaging. A leucocortical plaque (purple arrow) is more evident on the LFB stain than the cortical plaque, probably due to the demyelination of the myelin-rich subcortical U-fibres, but is also not evident on the MR scans. Diffuse-appearing white matter (DAWM; gold arrow), located peripheral to the periventricular plaques and deep to the normal-appearing white matter (NAWM; orange asterisk), is characterized by a signal intensity intermediate in strength between that of plaque and NAWM. DAWM is seen as pallor on the LFB and the Bielschowsky stains. It is not well discriminated by the MBP and CNP stains, which show somewhat more intense staining in the subcortical U-fibres in regions where the DAWM approaches them. MR images courtesy of Dr. A. MacKay. Histological sections courtesy of Ms. E. Leang. Modified after Sobel RA, Moore GRW. Demyelinating Diseases. In: Love S, Louis DN, Ellison DW, editors. Greenfield’s Neuropathology. 8th Edition. London: Hodder Arnold; 2008. p. 1513-1608 (6). Reproduced by permission of Edward Arnold (Publishers) Ltd.
colleagues\textsuperscript{105}, but more recently has been referred to as “diffusely-abnormal white matter” (DAWM). The abnormality is manifest as an increased signal intermediate between that of plaque and that of NAWM – essentially a signal intensity similar to gray matter, except located in white matter (Figure 2). DAWM is usually located around periventricular plaques, particularly posteriorly. Since DAWM is a relatively new concept, it is possible some prior MRI and histopathology studies may have included DAWM in NAWM in the assessment of non-plaque parenchyma. The pathology of DAWM shows myelin and axonal involvement\textsuperscript{106} with BBB breakdown\textsuperscript{107}. When various stains for myelin are employed, DAWM shows a reduction in staining with LFB, which stains phospholipids\textsuperscript{108}, but relative preservation of staining for MBP\textsuperscript{109}, suggesting there is a selective lipid abnormality in DAWM myelin (Figure 2). Axonal staining may also be reduced in DAWM, but not as severe or widespread as the reduction of LFB staining (Figure 2), suggesting that axonal pathology follows or is secondary to the myelin lipid abnormality\textsuperscript{109}. Further, the DAWM abnormality is well demonstrated on the MWF map, particularly at high field strength\textsuperscript{110}, suggesting that the short T2 component may be recognizing a myelin lipid perturbation, which may be responsible for a disruption of the lamellar structure of myelin thought to be the origin of the short T2 component. Further work is ongoing in the characterization of DAWM and its relationship to the histopathology and the pathogenesis of MS.

C. The Initial MS Lesion

The initial lesion in MS is unknown. It is presumed this is the first event in the genesis of the plaque. The histopathology of such a lesion has yet to be revealed. It is probable that the early MRI changes in a focal MS plaque are represented by very early changes seen at the locale of what will later be an established MS plaque. One of the earliest such changes is a reduction in the MTR, which can occur months prior to enhancement on routine imaging\textsuperscript{111,112}. Other very early findings include an increase in cerebral blood flow and volume\textsuperscript{113}, DWI changes\textsuperscript{114} and an increase in choline on MRS\textsuperscript{115}.

D. A ProposedSchema for Disease Manifestation based MRI-Pathology Correlation

Our current understanding of the evolution of disease in a given MS patient may be summarized as follows. Evidence would suggest that the very earliest focal changes of reduced MTR, DWI abnormalities and findings by MRS occur in a small region of what will later be evident as an area of focal enhancement. By the time enhancement has begun the lesion is probably what would be defined as an acute or active MS plaque, with uniform breakdown of the BBB associated with inflammation throughout the lesion. When the enhancement becomes localized to the lesion periphery the plaque has now entered the chronic active stage with ongoing inflammatory demyelination, BBB breakdown and neovascularization confined to the plaque edge. Myelin loss would be evident as reduction of the MWF and remyelination as regions with a return of the MWF. Reduction of MTR would be related to demyelination or axonal loss in the lesion. Demyelination would also manifest as lipid peaks, whereas axonal loss as a reduction in NAA on MRS. Gliosis would cause increase in creatine, inositol and choline. Choline increase could also be due to inflammatory infiltrates. Expansion of the plaque into the adjacent parenchyma would be manifest as progressive increase in the diameter of the ring of enhancement. Lesion expansion may be also be evident as just increasing size on the T2-weighed image, as it is probable the low-grade ongoing BBB breakdown at the lesion edge may not be of a sufficient degree to be detected as enhancement in some lesions. Those lesions where there had been such extensive inflammation that there was parenchymal destruction would appear as permanent black holes on T1-weighted images. The disappearance of a blank hole may indicate remyelination or the resolution of edema. Some lesions are associated with DAWM, evident as intermediate intensity in the periplaque white matter on routine T2-weighed or proton density imaging, such areas showing a perturbation in myelin lipids with a lesser degree and extent of axonal loss. While all these changes are occurring in white matter lesions there are lesions forming in gray matter that are largely undetected by routine MRI but well visualized by high field strength magnets. Widespread changes in NAWM and NAGM are also relatively undetected by MRI currently employed in routine clinical settings.

4. Summary

In summary, MS is a disorder characterized by plaques of inflammatory demyelination with significant axonal degeneration that is present early in the disease. These plaques show features that indicate both the innate and adaptive immune responses are involved in its pathogenesis. It has been proposed that, while these mechanisms are heterogeneous in MS, the immunopathogenesis of plaques in a given patient is uniform. This concept has generated controversy and evidence for and against it has been discussed above. Recent histopathologic studies have provided data to indicate that MS plaques may not necessarily have an immunopathogenesis in the first instance and that the immune response in the disease may be a secondary phenomenon. Abnormalities in the non-plaque white matter are evident in DAWM and NAWM. In DAWM there appears to be lipid loss with a lesser degree of axonal loss. In NAWM there is significant axonal loss, which appears to be associated with clinical progression and is present early in the course of the disease. In addition to white matter abnormalities there is a significant burden of disease in the gray matter, both in the form of focal plaques and diffuse abnormalities.

In the future, histopathologic and MRI studies will further probe the pathogenesis of the focal and diffuse abnormalities in MS, as to whether they are initially immunopathogenetic or neurodegenerative in nature and whether MS is a single disease or a final common pathway for a variety of etiologies and pathogenetic mechanisms.

Acknowledgements

The author thanks his colleagues in the the MRI Reseach Centre, the Department of Physics and Astronomy, and Medicine (Neurology) at the University of British Columbia, and the Multiple Sclerosis Clinic at UBC Hospital for fruitful collaborations, Esther Leung and Vlady Pavlova for technical
assistance, the patients and their families who donated tissue for research, and the Multiple Sclerosis Society of Canada for research funding.

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