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Changes observed in multiple sclerosis using magnetic resonance imaging reflect a focal pathology distributed along axonal pathways

Abstract Multiple sclerosis has long been recognized as a multifocal inflammatory demyelinating disease of the central nervous system. The fact that patients with multiple sclerosis can develop a secondary progressive phase of their disease which is resistant to anti-inflammatory therapies, together with the fact that brain atrophy can develop in patients with a relatively low volume of white matter lesions, has led to suggestions that multiple sclerosis may be a degenerative disease. However, primary degenerative disorders are not usually associated with recurrent episodes of inflammatory demyelination. Support for neurodegeneration in MS being associated with focal lesions comes from topographical mapping of the spatial relationship of axonal injury and tissue loss to lesions using advanced image analysis methods.

Key words multiple sclerosis · MRI · information · neurodegeneration

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Introduction

Axonal degeneration is now considered to be a central pathological feature of multiple sclerosis. The course of progressive forms of multiple sclerosis, which show a steady irreversible progression of disability in the absence of relapses, is suggestive of a degenerative disorder. Evidence for axonal loss has been obtained directly, by counting transected axons in lesions of autopsy specimens [7, 32] and also indirectly from imaging studies which have shown a decreased density of the neuronal marker compound, *N*-acetylaspartate (NAA) [1, 2], as well as the development of brain atrophy [13].

A degenerative pathology has sometimes been inferred from the fact that the low NAA observed by magnetic resonance spectroscopy (MRS) is found not only in lesions [15] but also in normal-appearing white matter [2, 8] and the fact that brain atrophy has been reported to occur early in the evolution of MS and in patients with low white matter lesion volumes [3]. These observations have led to speculation that diffuse axonal damage throughout the nervous system may result from a pathological process that is independent of the focal inflammatory lesions. However, it does not necessarily follow that the two processes are etiologically independent. Indeed, we argue here that MS lesions are a prerequisite for subsequent axonal loss, which may occur directly or indirectly as a consequence of inflammatory demyelination.

Inflammatory demyelination causes neuro-axonal injury

There are several mechanisms whereby neuro-axonal injury in multiple sclerosis may occur as a result of focal inflammatory demyelination. In the acute lesion, axons are transected during the inflammatory process by immune cells and the release of toxic substances such as perforin or nitric oxide [16]. Once an axon has been transected axonal transport to the distal portion of the axon is lost and the axon will undergo Wallerian degeneration. This provides a mechanism for axonal degeneration in areas remote in space and time from the initial lesion. Wallerian degeneration in human brain is much slower than in rodent models and can progress for years after lesion appearance [26]. Disruption of the axon can

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also cause retrograde degeneration of the proximal part of the axon and apoptosis of the cell body. This is a potential mechanism for neuronal pathology in grey matter. Furthermore, disruption of synapses also can lead to loss of mutual trophic support between neurons and result in secondary trans-synaptic degeneration within neuronal networks.

Even if axons running through lesions are initially spared, they may become vulnerable to premature degeneration as a delayed consequence of segmental demyelination. Oligodendrocytes provide trophic support for the axons that they surround as well as signals that are essential for the normal organization of nodal and paranodal structures. Insertion of new sodium channels in demyelinated axonal segments can result in cationic overload and increased susceptibility to degeneration [12, 31, 33]. This vulnerability continues long after the initial inflammatory event has finished and also can contribute to a temporal dissociation between lesion formation and axonal loss (Fig. 1)

Atrophy in white matter can be spatially related to white matter lesions

As discussed above, there is still controversy about whether axonal degeneration in MS is due to a diffuse primary axonopathy or a selective secondary degeneration of axons which pass through lesions.

The relation of axonal loss to white matter lesions can be tested in white matter tracts with a clear topographical organization such as the corpus callosum. De Stefano et al. [5] demonstrated that axonal injury in periventricular lesions is reflected across the corpus callosum. Evangelou et al. [6] examined the correlation between lesion load in the white matter within different areas of the cerebral hemispheres and axonal loss in the corresponding segment of the corpus callosum. Strong associations were identified between regional lesion load and both the axonal density ($r = -0.673$, $p = 0.001$) and the total estimated number of axons crossing the corresponding projection area in the corpus callosum ($r = -0.656$, $p = 0.001$) (Fig. 2). The authors proposed that Wallerian degeneration of axons transected in the demyelinating lesions contributed substantially to the extensive, diffuse loss of axons in the corpus callosum, thus illustrating the relevance for multiple sclerosis of remote consequences of lesions in functionally connected regions of the brain.

Another white matter tract where extensive atrophy remote from primary lesion sites has been observed is the corticospinal tract. In the cervical spinal cord, where essentially all the corticospinal axons pass, around 65 % of neurons in the lateral columns are lost [9, 14].

Magnetic resonance imaging can be used to visualize Wallerian degeneration directly in patients with multiple sclerosis. Transcallosal bands observable as diffuse

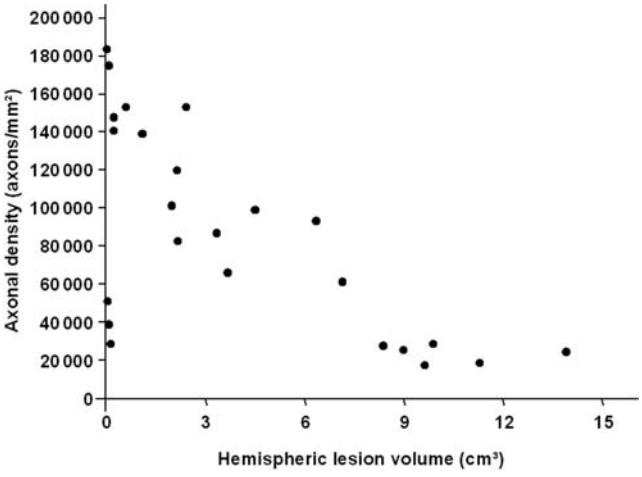

Fig. 2 Relationship between lesion volume in different volumes of the cerebral hemispheres and axonal density in the corresponding sections of the corpus callosum. Regression analysis yielded a correlation coefficient, r of –0.673 (p = 0.001) [6]

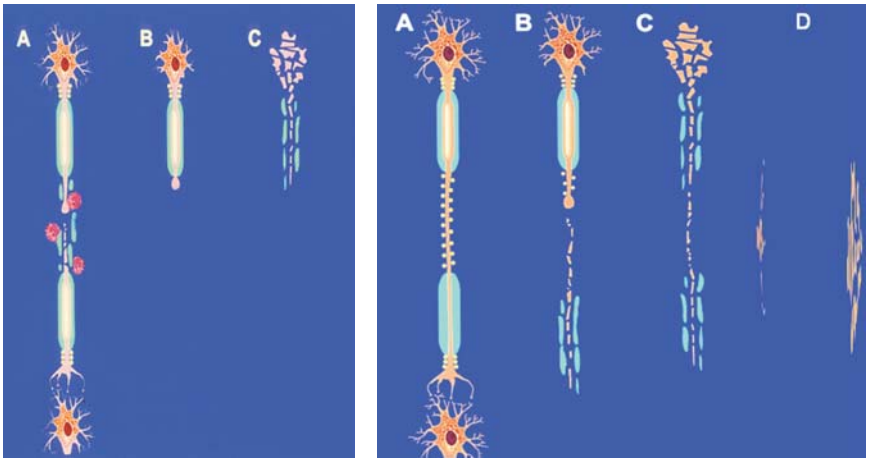

Fig. 1 Mechanisms of axonal damage in multiple sclerosis. *Left panel* Mechanisms of acute damage. **A** Axonal transection occurs within the inflammatory lesions due to the action of immune cells. **B** Anterograde Wallerian degeneration of the distal part of the axon follows. **C** Retrograde degeneration leads to loss of the neuronal cell body by apoptosis. *Right panel* Mechanisms of delayed degeneration. **A** Fragility of axons in regions where demyelination has occurred due to loss of trophic support. **B** Loss of axonal integrity. **C** Retrograde and anterograde degeneration of the neurone. **D** Neuron replaced by glial scar tissue. Reproduced by kind permission of Pr. B. Trapp, The Cleveland Clinic Foundation

hyperintense areas on T2-weighted images running across the entire structure are observed in patients with poor prognostic risk [25]. These bands appear early in the disease process and develop as the disease progresses over many years. Based on these principles, a technique has recently been developed to detect neuronal fiber tracts at risk for degeneration in the corpus callosum in patients with early disease. This involves using streamtube diffusion tractography to delineate axonal pathways that are interrupted by lesions [28]. Streamtube diffusion tractography illustrates well how lesions can affect volumes many times greater than their own.

Global brain atrophy can be temporally related to inflammatory lesions

If neurodegeneration results from focal inflammation, then one might expect a correlation between the two. This has not always been obvious, particularly in clinical trials of relatively short duration. This has led some authors to suggest that MRI-visible inflammation is not a factor in whole brain atrophy [24] and that a more global pathological process must be responsible. However, the relationship between the two can be obscured by the temporal dissociation between inflammatory lesions and atrophy.

Wallerian degeneration of axons starts soon after initial axonal transection and continues for much longer in the human central nervous system than in rodents. Serial MRI studies measuring the cross-sectional area of the optic nerve after a single episode of acute optic neuritis [10, 11] show that the optic nerve continues to atrophy for months and years after the acute inflammatory event, with a significant correlation between optic nerve area and time since the event ($r = -0.59$; $p = 0.012$). A similar observation was made in the corticospinal tract, where the axonal degeneration developed gradually over a period of one year following the initial inflammatory event located in the white matter of the superior aspect of the corona radiata [27].

Other studies have found a relation between contrast-enhanced lesion (CEL) frequency [20] and brain atrophy, particularly when a delay between the two was factored into the analysis [19] (Fig. 3). A relation between T2 lesions and brain atrophy has also been demonstrated over the long term [21].

Long-term clinical studies with immunomodulatory treatments provide an opportunity to evaluate the impact of changes in CEL activity on the rate of brain atrophy. This has been evaluated in a long-term study of interferon β–1b in 25 patients with relapsing-remitting multiple sclerosis [18]. The mean duration of treatment was four years (range 2.5–9.9). The rate of accumulation of CEL was compared with the rate of cerebral atrophy

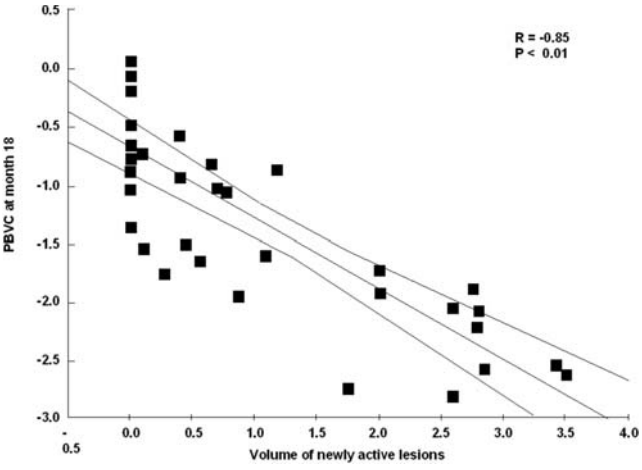

Fig. 3 Correlation between percentage brain volume change (PBVC over a period of 18 months and volume of newly active lesions during the first six months in 62 CIS patients with an abnormal baseline MRI scan [19]

on monthly MRI scans. Certain patients treated with interferon β–1b responded with a pronounced if not total suppression of CEL activity whereas others did not. Brain volume changes were higher in the non-responders than in the responders. For example, in a patient who continued to accumulate CEL (200 cm^3 over 39 months) the decrease in brain volume was 6 % over this period. In contrast, in a patient in whom CEL activity was extinguished following interferon β–1b treatment, the brain fraction volume decreased by only 1 %. There was a clear association between the extent of lesion accumulation and subsequent brain atrophy.

The importance of the temporal dissociation between lesion activity and cerebral atrophy may explain why certain clinical trials of immunomodulatory treatments show effects on the rate of brain atrophy (when this is the case) only in the latter part of the treatment period. For example, in a trial of interferon β–1a, a reduction in brain atrophy was only seen in the second year of treatment, in spite of a significant immediate reduction in CEL activity on starting treatment [22]. Similarly, in the European/Canadian MRI study of glatiramer acetate, brain atrophy was only slowed during the second half of the study [30].

Central white matter atrophy involving long tracts is proportionally greater as MS progresses

Advances in MRI technology [17] allow the question of where in the brain atrophy is occurring to be addressed. For example, atrophy can either arise from loss of periventricular tissue and subsequent ventricular enlargement or by thinning of the cortical grey matter leading to peripheral atrophy.

The SIENA technique (Structural Image Evaluation

Using Normalization of Atrophy) [29] is an automated method to determine longitudinal edges in MRI images and thus detect changes in boundaries in serial scans. Chen et al. [4] modified this technique to compare the relative importance of periventricular and peripheral atrophy in patients with relapsing-remitting and secondary-progressive multiple sclerosis. In the relapsing-remitting form, the rate of atrophy was similar in the periventricular and peripheral regions (Fig. 4). In contrast, in the secondary progressive form, the rate of periventricular atrophy was significantly higher than the rate of peripheral atrophy (9.17 % compared to 1.3 %; $p = 0.0001$). These findings suggest a progressively greater importance of atrophy of long tracts as MS progresses.

Lesional and peri-lesional tissue are focally atrophic

It is evident from neuropathological studies [7, 32] that axons are transected within the plaques, and in the peri-lesional tissue surrounding lesions. With appropriate image processing techniques, these regions also can be shown to undergo substantial local atrophy. We have calculated the local deformations over approximately one year in a pair of images from a patient with secondary progressive MS (unpublished observations). It is noteworthy that some voxels within lesions have lost more than 20 % of their volume (average 6 %) and voxels in perilesional tissue have lost proportionally more of their volume than voxels in more remote NAWM. This focal volume loss in lesions and surrounding normal-appearing brain tissue cannot be appreciated by simple visual inspection of the images without calculating the local deformations and is easily under-appreciated.

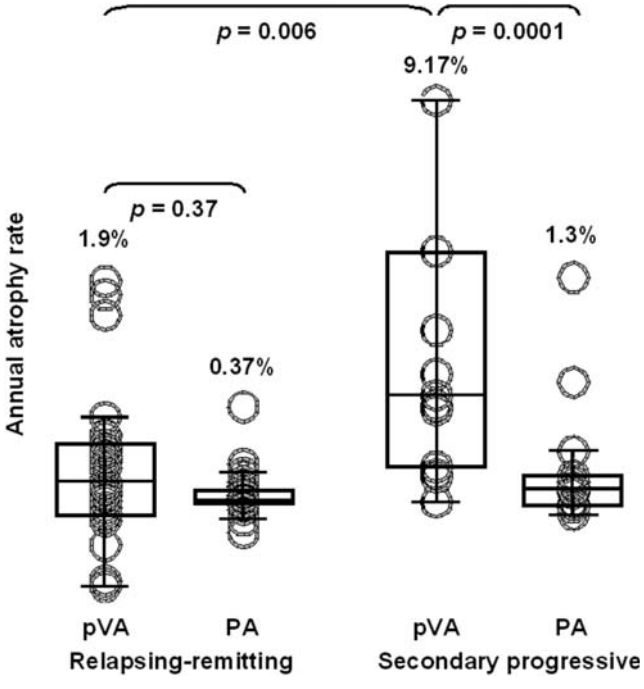

Fig. 4 Periventricular (pVA) and peripheral (PA) atrophy rates in patients with relapsing-remitting or secondary progressive multiple sclerosis

Cortical atrophy remains an enigma

The presence of cortical grey matter atrophy in MS also has been used to suggest that there must be a primary degenerative process producing atrophy in MS, regardless of what might be happening in the white matter lesions. Sailer et al. [23] have reported a general decrease in the thickness of the cortex which was to some extent related to T1- and T2-lesion white matter load. They also found cortical atrophy to be heterogeneous, with the presence of foci of tissue loss in different areas of the cortex, suggesting that there may be important intracortical differences in pathology. These studies point to the importance of cortical pathology, but do not necessarily support a primary neurodegenerative process as it has become clear [5] that substantial focal cortical lesional pathology may exist and be invisible on conventional MRI.

Conclusions

The primary pathology in multiple sclerosis is associated with focal white matter lesions due to an inflammatory attack on myelin/oligodendrocytes. This also can cause local injury to axons and pathology in other parts of the nervous system remote from the lesions in space and dissociated from them in time. This secondary pathology may best be explained by anterograde, retrograde or trans-synaptic degeneration of axons and neuronal cell bodies lying along projection pathways from foci of initial injury within the lesions. Together, axonal transection within lesions and associated Wallerian and transynaptic degeneration may be able to explain much, if not all, of the atrophy that occurs in MS.

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