Editorial

The mechanisms of lesion genesis in multiple sclerosis?

Dr M. A. Lee and colleagues at the Centre for Functional Magnetic Resonance Imaging of the Brain and the Department of Clinical Neurology of the Radcliffe Hospital and Infirmary in Oxford, the Montreal Neurologic Institute, the Institute of Neurology in London, and the Neuroimaging Research Unit of the University of Milan have collaborated to provide us with interesting and provocative new data that challenges evolving dogma on the evolution if not the pathogenesis of individual plaques in multiple sclerosis. Their data are presented, in rather convincing fashion, in this issue in their paper ‘Spatial mapping of T2 and gadolinium-enhancing T1 lesion volumes in multiple sclerosis: evidence for distinct mechanisms of lesion genesis?’ (Lee et al., 1999). The introduction of MRI to the study of multiple sclerosis has substantially altered our understanding of the dynamics of MRI-defined lesion formation in this disease. Increasingly the natural history of lesion formation as monitored by MRI is reshaping our concepts of therapeutic management. Management is now focused especially on approaches to prevent future lesion development, with the, as yet, only partially supported hope of retarding the generally relentless progression of neurologic impairment and disability that clinically characterize multiple sclerosis (Ebers et al., 1998).

Since the introduction of the use of gadolinium to define regional alterations of the blood–brain barrier that reflect active inflammatory change, there has been the increased expectation that the vast majority of lesions which can be seen with advanced MRI techniques follow a relatively stereotyped course. It is now generally accepted, based on serial observations, that the pathogenesis of individual lesions begins with a regional breach in the blood–brain barrier that is rapidly followed by alterations on T2-weighted images (Miller et al., 1998). However, while more frequent imaging intervals generally reduce any discrepancy between the presence of a new gadolinium enhancement and the finding of a new lesion on T2-weighted sequences, some gap has always remained (Miller et al., 1993). In addition, several groups of investigators, using a variety of different techniques, have suggested that regional changes are evident in otherwise MRI-defined normal-appearing white matter that may anticipate the development of an enhancement associated with a new T2-defined lesion (Filippi et al., 1998), and that these regions may even be abnormal before lesions develop without recognized prior enhancement (Narayana et al., 1998; De Stephano et al., 1999). To what extent these changes, often seen in MRI-defined normal-appearing white matter, reflect altered myelin-axonal interactions in relatively remote but anatomically associated regions is uncertain. But

The current paper adds substantial fuel to this fire. The investigators used an analytic technique based upon lesion probability maps to test the hypothesis that the spatial distribution of lesions appearing on gadolinium-enhanced T1-weighted images is identical to that of maps that define new T2-weighted lesions. Such a relationship should exist if all T2-defined lesions arise from regions demarcated by prior gadolinium enhancement. Their findings from a data set developed on 19 patients with relapsing–remitting multiple sclerosis imaged at 3-month intervals over 1 year caused them to reject this hypothesis. They encountered a substantially higher probability for new T2-defined lesions to form in the central as opposed to the peripheral white matter (regional risk ratio 2.4, range 0.5–6.5), while there was little evidence of an asymmetric distribution of the new gadolinium enhancements observed in this cohort (regional risk ratio 0.6, range 0–2.2). Several alternative explanations for their findings were explored in an additional 36-patient cohort that received triple dose gadolinium, and a five-patient cohort followed with weekly scans over 3 months. However, these analyses provided similar results, making it unlikely that their observations were dependent upon substantial regional differences in either the duration of enhancement, or the extent of barrier disruption occurring in diminishing gradient fashion towards the periventricular white matter.

How could these lesions develop? The investigators suggest that periventricular T2-defined lesions can increase de novo without prior local blood–brain barrier breakdown, possibly through progressive gliosis with Wallerian degeneration of axons traversing more peripheral lesions. This, they argue, may account for the confluent growth of lesions in the central white matter. Several centres performing magnetic resonance spectroscopic imaging have concentrated their efforts within a central slab of tissue located within the corpus callosum that corresponds in part to the central regions of the lesion probability maps used in this study. An interesting feature of the spectroscopic data is the not infrequent occurrence of relatively symmetric, but smaller magnitude alterations, supporting the release of lipid and diminution of regional N-acetyl aspartate in the white matter contralateral to MRI and metabolically defined active regions (Narayana et al., 1998; De Stephano et al., 1999). To what extent these changes, often seen in MRI-defined normal-appearing white matter, reflect altered myelin-axonal interactions in relatively remote but anatomically associated regions is uncertain. But
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It does seem that these changes presage plaque formation with or without antecedent blood–brain barrier disruption. It is also possible that these regional myelin-axonal alterations within normal-appearing white matter could target tissue for future immune-mediated attack. Obviously, more work needs to be done.

Whatever the mechanisms that contribute to the development of some lesions within the central white matter, the observation that multiple sclerosis lesions may develop in these and possibly other myelinated regions in the absence of a gadolinium enhancement-defined inflammatory phase has several practical implications. First, an unbridled emphasis of the effects of a therapeutic agent on enhancement frequency alone could lead to an over enthusiastic interpretation of the drug’s potential, unless carefully balanced with the agent’s effect on T2-weighted measures of evolving disease burden and clinical outcome. The experience with cladribine may be representative of drugs that further disassociate the relationship of gadolinium enhancement and T2-weighted lesion formation (Beutler et al., 1996). Secondly, if more than one path can lead to lesion formation, it may be that drugs could have a differential effect on these processes. Such may underlie the different signatures of the effects of the interferons and glatiramer acetate on MRI measures of disease (Stone et al., 1995; Comi et al., 1999).

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References


