Letter to the Editor

MRI and assessment of treatment in multiple sclerosis

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In an editorial commenting on a recent article on MRI evaluation of the effect of interferon beta-1b on the course of cerebral atrophy in secondary progressive multiple sclerosis (Molyneux et al., 2000), Professor Ebers has made a number of observations (Ebers, 2000). These relate both to the particular study and more generally to the role of MRI in monitoring treatment effects.

He reiterates well-known limitations in the relationship between MRI measures and disability and suggests a cautious approach in the application of this tool to measure treatment effect. This is in accord with the majority of investigators with an interest in multiple sclerosis, clinical trials and MRI. Such an approach is emphasized in publications arising from international consensus meetings in recent years (Miller et al., 1996, 1998).

The editorial does, however, raise a number of points which merit further comment. First, the writer is puzzled that more long-term natural history studies have not been undertaken to correlate MRI with clinical findings. This is not, in fact, surprising when one considers that the technology has only been available for about 15 years, and during that time almost all imaging sites have experienced upgrades with acquisition of new scanners, changes in field strength, and modifications of standard imaging sequences. Added to this are problems with long-term storage and compatibility of electronic image data, difficulties in funding long-term imaging follow-up studies and the widespread use of drugs known to modify certain MR parameters. Notwithstanding, there has already been a 10-year follow-up of patients with clinically isolated syndromes suggestive of multiple sclerosis which exhibited robust correlations between clinical measures of disability and MRI lesion number and volume, especially in the first 5 years (O’Riordan et al., 1998; Sailer et al., 1998). This work supports a role for MRI as a tool to monitor treatment in early relapsing–remitting multiple sclerosis.

Secondly, the editorial emphasizes the apparent discordance between the lack of treatment effect on cerebral atrophy and the positive effect on disability in the European trial of interferon beta-1b in secondary progressive multiple sclerosis (European Study Group 1998). However, a more striking discordance was the limited effect on disability compared with the large effect on inflammation (using gadolinium-enhancing lesions and T2 load as a marker of the latter). A relatively straightforward hypothesis could be proposed to explain these results: (i) disability progression in secondary progressive multiple sclerosis is related more to a neurodegenerative mechanism and less to inflammation; (ii) treatment modifies inflammation but not neurodegeneration; (iii) the marked anti-inflammatory effect of treatment was enough to exert a small effect on disability progression; and (iv) a difference in the relative contribution of inflammation and neurodegeneration to progression between different clinical subgroups might account for the discordant results of the three recent trials of interferon beta in secondary progressive multiple sclerosis.

Thirdly, as Professor Ebers suggests, there are undoubtedly several mechanisms for atrophy, and some are discussed in the paper, in particular pseudoatrophy due to anti-inflammatory agents. Nevertheless, the findings of a steadily increasing loss of brain tissue over 3 years, together with evidence that atrophy co-exists with abnormalities in other putative MR axonal markers (Davie et al., 1995; Coles et al., 1999), and with pathological evidence of axonal loss (Evangelou et al., 2000), suggests that loss of the neuronal/axonal substrate is occurring.

Finally, the use of MRI in therapeutic trials need not be seen solely as a measure of efficacy. It also provides insights into therapeutic mechanisms. Several agents, including interferon, have a strong effect in suppressing inflammation in lesions. However, multiple sclerosis lesions also exhibit demyelination, axonal loss and gliosis; and, in the normal appearing tissues, more subtle but extensive pathological changes are seen. There are a number of MR techniques, including the measurement of atrophy, which now provide a window into these pathological processes (Miller and Thompson 1999). There is also an emerging potential of more sophisticated MR methods for imaging structure (Conturo et al., 1999) and function (Reddy et al., 2000). Tools for monitoring the cellular pathology in multiple sclerosis are needed; one promising approach using a PET ligand marker for activated microglial cells was reported in the same issue of the journal (Banati et al., 2000).

Much can be learnt with judicious serial application of existing MR methods in well-defined clinical cohorts, both
to illuminate pathogenic mechanisms of the disease and the mechanisms by which therapies may modify it. The perceived importance of collecting and analysing longitudinal imaging as well as clinical data is emphasized by the recent initiative of the International Federation of Multiple Sclerosis Societies to establish a clinical and MRI repository which will collate and analyse data provided by willing collaborators, from both academia and industry. The aim of the imaging arm of that venture is, by meta-analysis of uniquely large and longitudinal data sets, to identify variables which predict clinical outcome.

References


