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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 T_2 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

Banati RB, Newcombe J, Gunn RN, Cagnin A, Turkheimer F, Heppner F, et al. The peripheral benzodiazepine binding site in the brain in multiple sclerosis. Quantitative in vivo imaging of microglia as a measure of disease activity. Brain 2000; 123: 2321–37.

Coles AJ, Wing MG, Molyneux P, Paolillo A, Davie CM, Hale G, et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol 1999; 46: 296–304.

Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, et al. Tracking neuronal fiber pathways in the living human brain. Proc Natl Acad Sci USA 1999; 96: 10422–7.

Davie CA, Barker GJ, Webb S, Tofts PS, Thompson AJ, Harding AE, et al. Persistent functional deficit in multiple sclerosis and autosomal dominant cerebellar ataxia is associated with axon loss. Brain 1995; 118: 1583–92.

Ebers GC. MRI: measure of efficacy [editorial]. Brain 2000; 123: 2187–8.

European Study Group on interferon beta-1b in secondary progressive MS. Placebo- controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. Lancet 1998; 352: 1491–7.

Evangelou N, Esiri MM, Smith S, Palace J, Matthews PM. Quantitative pathological evidence for axonal loss in normal appearing white matter in multiple sclerosis. Ann Neurol 2000; 47: 391–5.

Miller DH, Grossman RI, Reingold SC, McFarland HF. The role of magnetic resonance techniques in understanding and managing multiple sclerosis. [Review]. Brain 1998; 121: 3–24.

Miller DH, Albert PS, Barkhof F, Francis G, Frank JA, Hodgkinson S, et al. Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. Ann Neurol 1996; 39: 6–16.

Miller DH, Thompson AJ. Nuclear magnetic resonance monitoring of treatment and prediction of outcome in multiple sclerosis. [Review]. Philos Trans R Soc Lond Biol Sci 1999; 354: 1687–95.

Molyneux PD, Kappos L, Polman C, Pozzilli C, Barkhof F, Filippi M, et al. The effect of interferon beta-1b treatment on MRI measures of cerebral atrophy in secondary progressive multiple sclerosis. Brain 2000; 123: 2256–63.

O'Riordan JI, Thompson AJ, Kingsley DP, MacManus DG, Kendall BE, Rudge P, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. Brain 1998; 121: 495–503.

Reddy H, Narayanan S, Arnoutelis R, Jenkinson M, Antel J, Matthews PM, et al. Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis. Brain 2000; 123: 2314–20.

Sailer M, O'Riordan JI, Thompson AJ, Kingsley DPE, MacManus DG, McDonald WI, et al. Quantitative MRI in patients with clinically isolated syndromes suggestive of demyelination. Neurology 1999; 52: 599–606.