

## EDITORIAL COMMENTARY

## Benign multiple sclerosis

The ability to predict the development of disability in a disease as variable as multiple sclerosis is one of the major challenges facing researchers and clinicians alike. It focuses researchers on the mechanisms underlying irreversible deficit, while challenging clinicians to define criteria for the use of partially effective treatments with a not inconsequential side effect profile and cost. The concept of benign multiple sclerosis is of particular relevance to both these issues. However, although, as has been pointed out by Hawkins and McDonnell (pp 148–52, this issue) it has been recognised for over 40 years, the precise definition is extremely vague and would probably best be met by an index of progression rather than an arbitrary disease duration/Kurtze expanded disability scale score (EDSS) cut off.<sup>2</sup>

One of the key points made in the paper is the fact that many patients initially labelled benign will eventually develop progressive disability. This finding, previously documented by Weinshenker, raises important questions regarding the mechanisms underlying disability and, in particular, the role of axonal loss which, although well established, has only recently returned to centre stage. Of particular importance is the finding that axonal loss may occur early in the onset of the disease process<sup>3</sup> and is seen not only in chronic lesions but also in acute lesions and in normal appearing white matter.<sup>4</sup>

It is this realisation (at least in part) that has led investigators in North America to encourage all patients to start disease modifying therapy immediately relapsing-remitting multiple sclerosis is diagnosed. Is this sensible advice if moderate disability is unlikely to occur for 15 to 20 years in a percentage of patients?

It is important to appreciate that we are only just beginning to understand the mechanisms underlying disability, which are clearly very complex. One factor which is in danger of being overlooked is the effect of acute inflammation, an important component of the great majority of relapses. Weinshenker *et al*<sup>5</sup> and more recently Ebers (personal communication) have shown that the frequency of relapses in the early years after diagnosis has a significant effect on long term disability—that is, patients who have few relapses in the first 3 years are unlikely to develop major disability over 10 to 15 years. Although this relation

was not found in the seminal study of Runmarker and Andersen, they did find a significant relation between incomplete recovery from relapse and subsequent disability.<sup>6</sup> These findings pose intriguing and as yet unresolved questions regarding the relation between inflammation and axonal loss. The serial application of magnetic resonance measures of brain and spinal cord suggest progressive tissue loss changes in some patients, which in a proportion seem to be independent of inflammation.<sup>7</sup> However, the underlying mechanisms in relation to myelin loss and axonal loss are still being investigated.

Even if axonal loss is seen in most patients early in the course of their disease both the site of the loss and its severity will have a major bearing on the development of irreversible deficit. Although it is attractive to think that axonal loss continues to occur once it has started incontrovertible evidence to support this contention is not yet available and is unlikely to be forthcoming from current pathological studies. However, the serial application of more pathologically specific MR techniques, which can identify inflammation, myelin degradation, and axonal loss in patients with early multiple sclerosis, promises to provide important insights into the mechanisms underlying irreversible disability. Until that time we would be well advised to be circumspect in recommending treatment early in the course of the disease, particularly to those with few relapses and no disability.

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