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**The only certain measure of the effectiveness of multiple sclerosis therapy is cerebrospinal neurofilament level: Commentary**

Michael Hutchinson

There have been a number of attempts to use the presence or absence of evidence of new disease activity by magnetic resonance imaging (MRI) scanning as a prognostic tool in relation to future acquisition of disability. Several groups involved in such studies in Barcelona and in Cleveland have assessed evidence of new T2 lesions on annual MRI scanning as an indicator of adequate/inadequate disease control by a disease-modifying therapy. As pointed out in a previous “Commentary”, both the sensitivity and specificity of these indices are relatively poor; an attempt to refine them does not seem to be, to this observer, any significant advance. Of course it is natural to use evidence of accrual of new T2 lesions on an annual scan as being indicative that a particular therapy is not achieving adequate disease suppression. The problem is of course, as has been previously discussed, MRI scanning as used routinely on a 1.5 Tesla scanner is not a sufficiently sensitive tool to detect either grey matter disease or diffuse white matter disease. Basically MRI scanners and sequences that we use in daily life are blind to at least 50% of ongoing disease activity. In order to address this deficiency, quantitative measures of cerebral atrophy have been introduced in order to monitor the effects of the hidden grey matter disease. Whether these techniques can be applied in general neurological practice and provide a read-out which can be understood by neurologists is yet to be determined. It is also necessary to demonstrate whether reducing the rate of...
brain volume loss is predictive of better disability outcomes (although we of course intuitively believe that this would be the case). The problem with annual measures of brain volume (apart from the technical aspects) is that there is also the element of “closing the stable door after the horse has bolted”.

What is attractive about measuring cerebrospinal fluid (CSF) neurofilament levels is that one can actually measure tissue destruction in real time (not one year after it has happened, as with volumetric techniques). Clearly what is not attractive is the necessity to perform repeated lumbar punctures. The opponents in this debate argue that there is not, as yet, sufficient evidence to use CSF neurofilaments as a marker to base therapeutic decisions upon. They are probably right in this argument. We do need more studies of serial lumbar punctures measuring CSF neurofilaments on an annual basis in patients with relapsing multiple sclerosis (MS) with intermediate follow-up periods of four to five years and assessment of disability outcomes between baseline and five years later. Recruiting patients into such a study could be difficult. However, if the patient realised that the aim was to determine a sensitive measure of disease suppression and to understand how to prevent disability, then I feel it might be achievable. Of course in order to prevent or reduce the risk of post-lumbar puncture headache, non-traumatic Sprotte needles would be needed; not all neurologists are experienced in their use. Also it would be important to ensure that the laboratory measuring the CSF neurofilaments complies with best practice. There are variations in the technical aspects of measuring CSF neurofilaments and it is important that standardised processing of specimens, storage and reporting are applied as recommended by expert groups.7–9

There is a lot of debate about “No Evident Disease Activity” (NEDA) and which (and how many) measures should be included in the NEDA criteria.10 Although we are not there yet, I do believe that the normalisation of CSF neurofilament levels should be part of the criteria to determine NEDA (and indeed if one could demonstrate persistent normalisation of CSF neurofilament levels, I suspect that these levels on their own would be sufficient evidence of adequate disease suppression). Thus, although the works of the Barcelona and Cleveland clinic groups have been an important advance in our understanding of the relationship between annual MRI T2 lesion accrual and future disability, I am not convinced that MRI scanning, as routinely practiced, is either sufficiently sensitive or specific as a marker of adequate disease suppression or of NEDA.

Conflict of Interest
Michael Hutchinson served on a medical advisory board for the CONFIRM study (BG00012) for Biogen-Idec, serves on the editorial board of the Multiple Sclerosis Journal, has received speaker’s honoraria from Novartis, Biogen-Idec and Bayer-Schering, and receives research support from Dystonia Ireland, the Health Research Board of Ireland and the European Dystonia Foundation.

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