LETTERS TO THE EDITOR

Variation between observers in classifying multiple sclerosis

There has been no study of the reliability between observers of the widely used Poser criteria[1] for the diagnosis of multiple sclerosis. We aimed to determine if the Poser diagnostic criteria could be consistently applied in practice, and whether the course of multiple sclerosis could be defined reliably.

The case records of 85 consecutive outpatients with multiple sclerosis attending a general neurology outpatient clinic at St James's University Hospital were retrospectively analysed by two independent observers (HLF: observer 1; MHJ: observer 2). The patients had an average age of 46 (range 23–74) years; 62 (73%) of the patients were women. The patients were classified according to the Poser criteria[1] as clinically definite multiple sclerosis, laboratory supported definite multiple sclerosis, clinically probable multiple sclerosis, laboratory supported probable multiple sclerosis, suspected multiple sclerosis, and unable to classify. The course was defined as early relapsing-remitting, benign, secondary progressive, primary progressive, and unable to classify.[2]

Overall, there was substantial agreement between the two observers in classifying multiple sclerosis according to the Poser criteria ($\kappa = 0{\cdot}65$, 95% confidence interval (95% CI) = 0·52–0·78).[3] There was poor agreement in the historical information used to classify the cases ($\kappa = 0{\cdot}30$, 95% CI = 0·03–0·57). There was also disagreement as to whether a patient had had one or more "attacks" of multiple sclerosis. Agreement was substantial for clinical evidence of separate lesions and was almost perfect for both paraclinical evidence and laboratory support (all κ values above 0·90). There was only moderate agreement between the two observers in describing the clinical course of multiple sclerosis ($\kappa = 0{\cdot}57$, 95% CI = 0·43–0·71). In particular, the two observers differed in their opinion in nine cases of whether there was progressive deterioration from the outset without any relapses or remissions (primary progressive disease) or whether there was an initially relapsing-remitting course followed by progressive deterioration (secondary progressive disease).

The main variation between observers in classifying multiple sclerosis lay in defining "attacks" of multiple sclerosis. In practice clinical judgement is used to decide whether new symptoms are due to a relapse or are the result of other factors such as infection, psychological factors, temperature, or fatigue. This is much more difficult in retrospective analysis of case records. Retrospective analysis may also underestimate the extent of variation between observers.

Some of the variation may have been due to differences in abstracting information from the case notes. However, when a standardised proforma of clinical information about 30 cases was sent to neurologists worldwide to classify each case as either probable, possible, or unlikely multiple sclerosis, the diagnostic accuracy for a group of 108 neurologists was only two thirds overall.[4] There were wide discrepancies in the evaluation of individual patients.

Reliability between observers has been found to be poor for many neurological symptoms and signs.[5] Neurological examination is the basis for many of the currently used rating scales. Variation between observers is of considerable importance when these scales are used in multicentre trials as a means of assessing clinical change.

The main difficulty in defining the clinical course of multiple sclerosis was in distinguishing a secondary progressive course from a primary progressive course. This may have been due in part to poor documentation of relapses early in the course of the disease. Whereas the development of new symptoms was often reported, whether they resolved, persisted, or progressed was often not. Also, early symptoms may not be recognised as such or reported by the patient. On analysis of the cases in which we differed on defining the course, there were a significant number of patients who did not fit readily into any of the defined categories. These patients had relapsing disease but without full recovery and tended to have increasing disability with each relapse. Their course was thus progressive from the outset but with superimposed relapses.

Consensus is needed on a classification of the course of multiple sclerosis. We propose a division between those patients with relapsing-remitting disease with full recovery between relapses and those patients with relapsing disease who may have partial recovery but have increasing disability.

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1 Poser CM, Paty DW, Scheinberg L, *et al.* New diagnostic criteria for multiple sclerosis. Guidelines for research proposals. *Ann Neurol* 1983;**13**:227–31.
2 Miller DH, Barkhof F, Berry I, *et al.* Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: concerted action guidelines. *J Neurol Neurosurg Psychiatry* 1991;**54**:683–8.
3 Landis RJ, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.
4 Poser CM. Clinical diagnostic criteria in epidemiological studies of multiple sclerosis. *Ann NY Acad Sci* 1965;**122**:506–19.
5 Shinar D, Gross CR, Mohr JP, *et al.* Interobserver variability in the assessment of neurologic history and examination in the Stroke Data Bank. *Arch Neurol* 1985;**42**:557–65.

High dose intravenous immunoglobulin does not improve abnormalities in the blood-brain barrier during acute relapse of multiple sclerosis

High dose intravenous methylprednisolone (IVMP) has an established role in the treatment of acute relapse in multiple sclerosis. Treatment with IVMP increases the rate of recovery in relapses and therefore shortens hospital stay.[1] However, some patients do not improve after a single course of high dose IVMP. An alternative treatment would be useful for all these patients. The role of intravenous immunoglobulins (IVIgs) in treatment of relapses in multiple sclerosis was first investigated using 5 g at two to four week intervals; improvement was noted within 24 hours of infusion but lasted only for a mean of 14 days.[2] Interestingly, Yan and colleagues obtained spectacular results using IVIg in a patient with previous unresponsiveness to IVMP.[3] Nevertheless there is a lack of controlled trials and MRI monitoring of this treatment. We describe the results on the efficacy of high dose IVIg treatment in reducing blood-brain barrier impairment in exacerbation of multiple sclerosis by means of serial Gd-DTP MRI performed in a few patients.

We prospectively studied six patients with clinically definite multiple sclerosis in acute relapse of the disease. They were randomly assigned to either IVMP (1 g daily for five days), followed by oral prednisone tapered over 18 days, or IVIg (400 mg/kg, daily for five days). Duration of symptoms of the current attack was less than 10 days in all patients. All patients were assessed at entry using the Kurtzke expanded disability status scale (EDSS) which was repeated at the third and 10th days. Clinical assessment was carried out by a non-blinded examiner but MRI assessment was blinded. Informed consent was obtained for each patient before inclusion in the study. All MRI was performed on either a 1·5 T (Magnetom SP) or a 1·0 T (Magnetom Impact) superconducting imager (Siemens, Erlangen, Germany). Individual patients were always scanned on the same system.

T2 weighted double echo (2200/20–90) (repetition time/echo time) spin echo pulse sequences in the transverse plane were used in all patients through the whole brain using 5 mm slice thickness and 0·5 mm interslice gap, one excitation and 256×256 matrix. T1 weighted spin echo (600/20) transverse images were performed before and after Gd-DTP injection at a dose of 0·1 mmol/kg. (Magnevist, Schering, Germany), using 5 mm slice thickness and 0·5 mm interslice gap, two excitations and 256×256 matrix.

Brain MRI was carried out three times in each patient (except in patient No 6 who was treated after the third day with IVMP because of considerable clinical worsening, therefore his third MRI was not performed). The first scan was performed at time minus one and follow up scans three and 10 days after the beginning of treatment using the same scan parameters. The middle transverse slice was oriented parallel to a line joining the most inferoanterior and inferioposterior parts of the corpus callosum, to facilitate accurate repositioning.

Image evaluation was visually performed by a neuroradiologist experienced in grading white matter abnormalities and blinded to the clinical data. Measures of outcome on MRI evaluated were the number and size of enhancing lesions. In the first scan, contrast enhanced T1 weighted images were compared with non-enhanced T1 weighted images, to detect enhancing plaques that were easily recognised as increased signal intensity areas in the white matter. The second and third scans were compared simultaneously with the previous scan to establish enhancing lesions as new or persistent, and to assess the increase or decrease in the enhancement pattern of the multiple sclerosis plaques. On completion of the study, all scans were reread.