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 criteria¹ 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 criteria¹ 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 ($\kappa = 0.65$, 95% confidence interval (95% CI) = 0.52-0.78).³ There was poor agreement in the historical information used to classify the cases ($\kappa = 0.30$, 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 ($\kappa = 0.57$, 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.

H L FORD
M H JOHNSON
Department of Neurology,
St James's University Hospital, Leeds
A S RIGBY
Nuffield Institute for Health and
Department of Clinical Medicine,
University of Leeds, Leeds, UK

Correspondence to: Dr H L Ford, Department of Neurology, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK.

- Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis. Guidelines for research proposals. *Ann Neurol* 1983;13:227-31.
- 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.
- Landis RJ, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-74.
- Poser CM. Clinical diagnostic criteria in epidemiological studies of multiple sclerosis. *Ann NY Acad Sci* 1965;122:506-19.
- Shinar D, Gross CR, Mohr JP, et al. Inter-observer 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 (IVIg) 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 inferoposterior 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.

There were non-significant differences at entry between both groups for sex (two men; four women, mean age 24, range 21–27 years), duration of disease (13, range 2–24 months), EDSS (3.25, range 2.0–5.0), and number of Gd enhancing lesions per patient (total 58).

Side effects were not seen in any patient. Two patients in the IVMP group had improved by at least one point in the EDSS at the 10th day and one did not show any changes; in the IVIg group two patients remained stable and one deteriorated 3.0 points after the third day, then IVMP was initiated.

By the third day, nine lesions no longer enhanced in the IVMP group, whereas four new Gd enhancing lesions were noted in the IVIg treated patients (mean change from basal values: 32% decrease in the number of enhancing lesions in the IVMP group *v* 10% increase in the IVIg group; $P = 0.009$, Welch's *t* test). These differences were also obvious at the 10th day (80 *v* 30% decrease respectively) although they did not reach significance because only two patients were studied at this time in the IVIg group.

Damage to the blood-brain barrier seems to be an important early event in the development of focal demyelination in multiple sclerosis; therefore, rapid normalisation of the blood-brain barrier could be of critical importance in inhibiting early demyelination. Impairment of the blood-brain barrier in multiple sclerosis lesions can now be readily detected and safely monitored by Gd-DTP enhanced-MRI.⁴ High dose IVMP rapidly suppresses Gd-DTP enhancement in acute demyelinating lesions and this correlates well with clinical improvement.⁵

The results of the present study suggest that IVIg does not rectify impairment of the blood-brain barrier during an exacerbation of multiple sclerosis and therefore it should not be considered as an alternative to standard steroid treatment for relapses in multiple sclerosis. However, the number of patients is too small and larger studies would be necessary to reach definite conclusions; furthermore, due to the short period of study, some beneficial effects of IVIg on other steps of myelin damage cannot be excluded. The clinical worsening in one patient could merely represent the natural history of exacerbation of multiple sclerosis, and may not necessarily be related to IVIg infusion.

C NOS
M COMABELLA
M TINTORÉ

J RIO
A CODINA
X MONTALBAN
Department of Neurology
A ROVIRA

Centre de Resonància Magnètica, Hospital General
Universitari Vall d'Hebron, Barcelona, Spain

Correspondence to: Dr C Nos, Unitat de Neuroinvestigació-Esclerosi Múltiple, Escola d'Infermeria 5^a P, Hospital General Universitari Vall d'Hebron, Psg Vall d'Hebron 119–129, 08035, Barcelona, Spain.

1 Milligan NM, Newcombe R, Compston DAS. A double blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: 1. clinical effects. *J Neurol Neurosurg Psychiatry* 1987;50:511–6.

2 Soukop W, Tschabitscher H. Gammaglobulintherapie bei Multiplen Sklerose (MS): theoretische Überlegungen und erste klinische Erfahrungen mit 7S-Immunglobulin in der MS-Therapie. *Wien Med Wochenschr* 1986;136:477–80.

3 Yan J, Richert JR, Sirdofsky MD. High-dose intravenous immunoglobulin for multiple sclerosis. *Lancet* 1990;336:692.

4 Miller DH, Rudge P, Johnson G, *et al.* Serial

gadolinium enhanced magnetic resonance imaging in multiple sclerosis. *Brain* 1988; 111:927–39.

5 Miller DH, Thompson AJ, Morrissey SP, *et al.* High dose steroids in acute relapses of multiple sclerosis: MRI evidence for a possible mechanism of therapeutic effect. *J Neurol Neurosurg Psychiatry* 1992;55:450–3.

Hypothermia due to hypothalamic involvement in multiple sclerosis

Hypothermia can be caused by several different mechanisms, the most common being environment, neglect, drug overdose, and endocrine disturbance such as hypoglycaemia, hypothyroidism, and hypopituitarism. Disease affecting the hypothalamic regulatory centre can rarely cause hypothermia. We describe the first case of hypothermia in association with pathologically established hypothalamic damage due to multiple sclerosis.

A 53 year old woman with longstanding, severe, clinically definite multiple sclerosis presented with a five day history of dysphagia and lethargy. She was well cared for, in an adapted and centrally heated flat. Her skin was warm and well perfused. Although she was dysarthric with a severe spastic tetraparesis and bilateral optic atrophy, there were no new neurological signs. A relapse of multiple sclerosis was provisionally diagnosed and arrangements were made to admit her to the ward the next day.

Over the next 24 hours her conscious level deteriorated to a Glasgow coma scale score of 9. She developed a sinus bradycardia of 45/min with a blood pressure of 80/50 mm Hg. Her oral temperature was 35.5°C and her rectal temperature was 29°C. She was appropriately dressed for the ambient air temperature of 18°C. Her skin did not feel abnormally cool and there was no shivering. General examination disclosed a few coarse crepitations scattered throughout both lungs. There was no meningism. The pupils were constricted and the corneal reflexes depressed. The jaw was tightly clenched. There was a spastic tetraparesis with extensor plantars but the reflexes were now depressed.

Haematological investigations showed a picture consistent with mild disseminated intravascular coagulation (platelets 79; activated partial thromboplastin time 45 s (control 32 s); TCT 17 s (control 14 s); INR 1.0). Electrolytes and glucose were normal but the amylase concentration was slightly raised at 321 IU/l, suggesting mild pancreatitis. An ECG showed widespread J waves, the presence of which had led to the taking of the core temperature and thus the diagnosis. Chest radiography showed mild bilateral basal shadowing. Blood and urine toxin screens were negative.

The patient was slowly rewarmed and treated with intravenous atropine and antibiotics. However, she developed recurrent dysrhythmias, predominantly bradycardic in nature, and bronchopneumonia. She died three days later.

Postmortem examination confirmed the presence of bronchopneumonia and pancreatitis. The brain and spinal cord contained numerous plaques of demyelination typical of chronic multiple sclerosis. There was a large plaque involving the hypothalamus (figure). This had the grey, translucent appearance typical of a mature gliotic plaque. However, at the microscopic level there was evidence of current activity in a

Hypothalamus. Solochrome cyanin stain showing a plaque of demyelination, appearing pale (originally $\times 15$).

proportion of the plaques, including the one involving the hypothalamus. In addition to gliosis, lymphocytic cuffing of vessels and occasional macrophages containing lipid debris were seen, providing evidence of continuing demyelination. The corpus callosum appeared unremarkable.

The centre for temperature regulation is situated in the hypothalamus and commonly disorders in this region can cause hypothermia or hyperthermia, which can be continuous or paroxysmal.¹ Disrupted thermoregulation, secondary to hypothalamic damage, has been described with a wide range of pathological processes including tumour, trauma, infarct, haemorrhage, sarcoidosis, Wernicke's encephalopathy, ventricular shunt embolism, and fat embolism.² A combination of hypothermia, hyperhidrosis, and other autonomic abnormalities are occasionally seen in cases of concomitant hypothalamic damage with corpus callosal dysgenesis.¹ The precise anatomical lesion within the hypothalamus leading to hypothermia is unclear but may involve areas of the anterior hypothalamus (as in episodic hypothermia) or the posterior hypothalamus (as in Wernicke's encephalopathy).¹

There are few reported cases of hypothermia in multiple sclerosis.^{3–5} The disease process primarily affects white matter and, until now, hypothalamic disease has never been pathologically established. Sullivan *et al* described two patients with clinically definite multiple sclerosis who presented with acute hypothermia and on recovery developed chronic hypothermia. No pathological lesion was proved, but thermoregulatory studies suggested a central hypothalamic defect, presumably secondary to demyelination. Lammans *et al* described three patients with multiple sclerosis who presented with coma and hypothermia. Pathological examination in one case showed no abnormality. Finally, Ghawche *et al* reported a woman with multiple sclerosis who presented with three episodes of hypothermia. Hypothalamic disease was considered to be the likely cause, but repeated enhanced MRI failed to show a lesion in this region.