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Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis

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Summary

We compared MRI criteria used to predict conversion of suspected multiple sclerosis to clinically definte multiple sclerosis. Seventy-four patients with clinically isolated neurological symptoms suggestive of multiple sclerosis were studied with MRI. Logistic regression analysis was used to remove redundant information, and a diagnostic model was built after each MRI parameter was dichotomized according to maximum accuracy using receiver operating characteristic analysis. Clinically definite multiple sclerosis developed in 33 patients (prevalence 45%). The optimum cut-off point (number of lesions) was one for most MRI criteria (including gadolinium-enhancement and juxta-cortical lesions), but three for periventricular lesions, and nine for the total number of T_2-lesions. Only gadolinium-enhancement and juxta-cortical lesions provided independent information. A final model which, in addition, included infratentorial and periventricular lesions, had an accuracy of 80%, and having more abnormal criteria, predicted conversion to clinically definite multiple sclerosis strongly. The model performed better than the criteria of Paty et al. *(Neurology 1988; 38: 180–5) and of Fazekas* et al. *(Neurology 1988; 38: 1822–5). We concluded that a four-parameter dichotomized MRI model including gadolinium-enhancement, juxtacortical, infratentorial and periventricular lesions best predicts conversion to clinically definite multiple sclerosis.*

Keywords: brain; multiple sclerosis; diagnosis; MRI; gadolinium

Abbreviations: FLAIR = fluid attenuated inversion recovery; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive

Introduction

Multiple sclerosis ultimately is a histopathological diagnosis, and clinical criteria have been developed for the diagnosis of multiple sclerosis during life. Clinical criteria essentially require fulfilment of two prerequisites, i.e. dissociation of the disease progress in time and in space (Schumacher *et al*., 1965). In the most recent and commonly applied clinical criteria (Poser *et al*., 1983), paraclinical evidence can be used in making a diagnosis of clinically definite or laboratory supported definite multiple sclerosis. Paraclinical support for multiple sclerosis can consist of abnormalities detected with evoked potentials, cerebrospinal fluid analysis, or imaging techniques (Poser *et al*., 1983). The most sensitive paraclinical test is MRI, showing abnormalities in ~95% of patients with clinically definite multiple sclerosis (Paty *et al*., 1988). As with any medical test showing a high sensitivity, the specificity (in this context conversion from suspected to clinically definite multiple sclerosis) of MRI for multiple sclerosis is usually considerably lower, reaching 57% after a follow-up of 2 years (Lee *et al*., 1991). Likewise, based on a 5-year follow-up study, the positive predictive value (PPV)

Table 1 *Diagnostic MRI criteria commonly used for multiple sclerosis*

Criteria (reference)	Definition	Study design	Sensitivity (%)	Specificity (%)
Paty's (Paty *et al*., 1988)	⩾4 lesions, or 3 lesions, of which 1 is periventricular*	Prospective, at first presentation	94	57
Fazekas' (Fazekas *et al*., 1988)	⩾3 lesions with 2 of the properties: (i) an infratentorial lesion (ii) an periventricular lesion (iii) a lesions > 6 mm	Retrospective, in established multiple sclerosis and controls with white matter lesion(s) on MRI	88	100
Abnormal callosal-septal interface (Gean-Marton *et al*., 1991)	Any lesion at the callosal-septal interface	Prospective, in established multiple sclerosis and patients with white matter lesion(s) on MRI	93	98
Gadolinium-enhancement (Tas *et al*., 1995)	⩾1 enhancing lesion and ⩾1 non-enhancing lesion	Prospective, at first presentation	59	80
Ovoid lesions (Horowitz *et al*., 1989)	Major axis larger than minor axis	Retrospective, in established multiple sclerosis with abnormal MRI	86	NA

*Only the criteria which are 'strongly suggestive' of multiple sclerosis were used in the present study. NA = not applicable.

of an abnormal brain MRI scan (minimum four lesions) in patients presenting with isolated syndromes suspected of multiple sclerosis is 65%, while the negative predictive value (NPV) of a normal brain MRI scan at presentation is 97% (Morissey *et al*., 1993).

Since comparable MRI abnormalities may be found in a variety of other diseases and in healthy volunteers, criteria have been developed by which MRIs can be classified as suggestive of multiple sclerosis or not. Initially, studies relied on the presence of more than three lesions >3 mm (Gebrarski *et al*., 1985), sometimes reinforced by the presence of a 'lumpy-bumpy' periventricular border (Runge *et al*., 1984). Those features were later incorporated by Paty *et al*. (1988) into the MRI criteria now commonly used (Table 1). The criteria of Paty have been evaluated prospectively in patients presenting with isolated syndromes suggestive of multiple sclerosis, showing high sensitivity but relatively low specificity (Paty *et al*., 1988; Lee *et al*., 1991). Several other diagnostic criteria have been proposed (Table 1), of which the most extensively used ones are those by Fazekas *et al*. (1988). In a retrospective study of patients with established multiple sclerosis, the criteria of Fazekas showed both high sensitivity and a high specificity (Offenbacher *et al*., 1993), but the criteria of Fazekas *et al*. (1988) perform less well in a prospective fashion when applied to patients presenting with an isolated syndrome suggestive of multiple sclerosis (Tas *et al*., 1995).

The typical MRI findings in multiple sclerosis are a reflection of the histopathology of the disease. The periventricular location, especially in the corpus callosum, and the characteristic ovoid nature of the lesions with extensions (Dawson fingers) into the adjacent white matter (Dawson, 1916) are dictated by the perivenular distribution of multiple sclerosis plaques (Fog, 1965). It is therefore not surprising that the criteria of both Paty and Fazekas incorporate periventricular lesions (Fazekas *et al*., 1988; Paty *et al*., 1988), and that ovoid and callosal/subcallosal MRI abnormalities are a frequent finding (Simon *et al*., 1986; Horowitz *et al*., 1989; Gean-Marton *et al*., 1991). However, the reason for choosing certain MRI parameters to be used as diagnostic criteria is not always explicitly described (Fazekas *et al*., 1988; Paty *et al*., 1988). Only one study (Namer *et al*., 1993) addressed the relative significance of various MRI findings using a multiple linear regression analysis; they found that temporal and occipital lesions were good predictors of multiple sclerosis. However, this study was carried out in patients with established multiple sclerosis, and the results can not be simply applied to patients presenting with a first symptom of what might become multiple sclerosis.

Gadolinium-enhancement depicts the early inflammatory phase of multiple sclerosis lesions (Grossman *et al*., 1986; Katz *et al*., 1990; Nesbit *et al*., 1991). It has therefore been speculated that presence of both enhancing and non-enhancing MRI lesions is the radiological counterpart of dissociation in space and in time (Heun *et al*., 1988). One study (Tas *et al*., 1995) showed that gadolinium-enhancement was more specific for diagnosing multiple sclerosis than abnormalities revealed on T_2-weighted imaging. In that study gadolinium-enhancement was compared with the composite criteria of Paty and Fazekas, but not with other individual diagnostic MRI criteria.

The purpose of the present study was to evaluate the importance of several individual brain MRI criteria at first presentation to predict the conversion to clinically definite multiple sclerosis. We combine data from three groups of patients with isolated syndromes suggestive of multiple sclerosis who were studied prospectively for a minimum of 2 years. We aimed to compare individual MRI criteria, including gadolinium-enhancement, in patients followed from the onset of symptoms, to determine up-to-date criteria with

high predictive value for conversion to clinically definite multiple sclerosis.

Patients and methods

Patients with clinically isolated syndromes suggestive of multiple sclerosis which could not be attributed to other diseases had been identified prospectively in three centres. In Amsterdam, 42 patients with a variety of symptomatology suggestive of multiple sclerosis were identified during a 12-month period in 1992 by alerting neurologists and ophthalmologists in neighbouring hospitals. The patients are part of a larger cohort ($n = 59$), of which the early findings have been previously reported (Tas *et al*., 1995). Of the original cohort, seven patients were lost to follow-up, while 10 patients were subsequently given a definitive diagnosis other than multiple sclerosis and were excluded from the present analysis. In Milan, 19 patients were identified mainly with spinal cord symptomatology in 1992–3; the early findings of some of these have been reported on previously (Campi *et al*., 1995). In London, 13 patients with optic neuritis had been identified in 1986–90 from the Physicians Unit at Moorfields' Eye Hospital; the early findings on some of those have been reported previously (Youl *et al*., 1991). In Milan and London, patients with diagnoses other than multiple sclerosis had been excluded already in earlier reports.

The follow-up period was extended beyond that reported previously, and all patients were reassessed for the occurrence of new symptoms. This was done by a single neurologist at each centre, who personally reviewed all available medical data and contacted patients when insufficient clinical data were documented. Clinically definite multiple sclerosis was diagnosed when new symptoms or signs had occurred in other parts of the central nervous system, after an interval of at least 1 month (Poser *et al*., 1983), and when other diagnoses had been ruled out by appropriate tests, such as serological testing or spinal cord imaging, according to local standards. MRI (and other paraclinical evidence) was not used in the final assessment of the diagnosis of clinically definite multiple sclerosis.

MRI was performed at 0.6 T in Amsterdam (Technicare, Solon, Ohio, USA), at 1.5 T in Milan (Siemens SP63 and GBS III, Erlangen, Germany) and at 0.5 T in London (Picker, Cleveland, Ohio, USA). In all three centres the scanning protocol included axial slices through the brain with a 192 × 256 or 256 × 256 pixel matrix, and included double echo T_2-weighted spin-echo images and T_1-weighted spin-echo images after intravenous injection of 0.1 mmol/kg gadolinium–DTPA. The slice thickness was 5 mm (1.25-mm gap) in Amsterdam, 6 mm (1.2-mm gap) in Milan and 5 or 10 mm (contiguous) in London.

The MRIs were analysed by consensus during a single session by two observers (F.B. and M.F.) who were unaware of the clinical findings. From the T_2-weighted images the following items were scored: number of frontal, parietal, temporal, occipital, infratentorial, basal ganglia (including internal capsule) and total number of T_2 lesions; number of periventricular lesions, number of callosal/subcallosal lesions, number of juxtacortical (contiguous with the cortex) lesions, number of lesions >6 mm, and the presence/absence of at least one ovoid lesion. The gadolinium-enhanced T_1-weighted images were analysed for the number of enhancing lesions, the number of enhancing lesions >6 mm and the number of hypointense lesions. Typical examples are presented in Figs 1–4. Based on a combination of imaging findings, patients were classified as not compatible with multiple sclerosis, or compatible with multiple sclerosis, according to the criteria of Paty and Fazekas (Figs 2 and 4; Table 1).

Based on the clinical outcome at follow-up (multiple sclerosis or not multiple sclerosis) the imaging findings were classified as true positive (TP, test abnormal and diagnosis multiple sclerosis), true negative (TN, test normal, no multiple sclerosis), false positive (FP, test abnormal, no multiple sclerosis), or false negative (FN, test normal, but diagnosis multiple sclerosis). Sensitivity was determined by the ratio TP/(TP + FN); specificity by TN/(TN + FP); and accuracy by (TP + TN)/(TP + TN + FP + FN). PPV was defined as TP/(TP + FP), NPV as TN/(TN + FN). Logistic regression analysis was performed to assess the relative contribution of the individual imaging parameters (all MRI parameters considered as independents) in predicting the diagnosis at follow-up (dependent). Both forward and backward stepwise analyses were conducted (using Wald's statistic as a criterion), with a *P*-value for entry of 0.05, and a *P*-value for removal of 0.1 (Altman *et al*., 1991). Based on these findings several MRI criteria were selected, and a regression model was built with these terms to predict the diagnosis and calculate the chance of having clinically definite multiple sclerosis with any combination of these parameters. This was done after the continuous parameters were dichotomized according to maximum accuracy to determine the best cut-off point for that particular parameter using ROC (receiver operating characteristic) curves (curves not shown).

Results

At the time of the MRI, the duration of symptoms varied from 1 to 20 weeks, with a median of 4 weeks. The presenting symptoms of the patients are detailed in Table 2. During follow-up, clinically definite multiple sclerosis was diagnosed in 33 patients (prevalence 45%) after a median period of 9 months (range 1–48, interquartile range 5.5–23 months). Multiple sclerosis had not been diagnosed in the remaining 41 patients after a median follow-up of 39 months (range 23–96 months). Figure 5 displays the cumulative percentage of patients converting to clinically definite multiple sclerosis over the duration of the follow-up. The MRI scan showed no abnormalities in 13 patients, of whom only one developed clinically definite multiple sclerosis (NPV 92%). T_2 abnormalities were found in the remaining 61 patients (range 1–145, median 4.5 lesions). In those patients converting to clinically definite multiple sclerosis, the

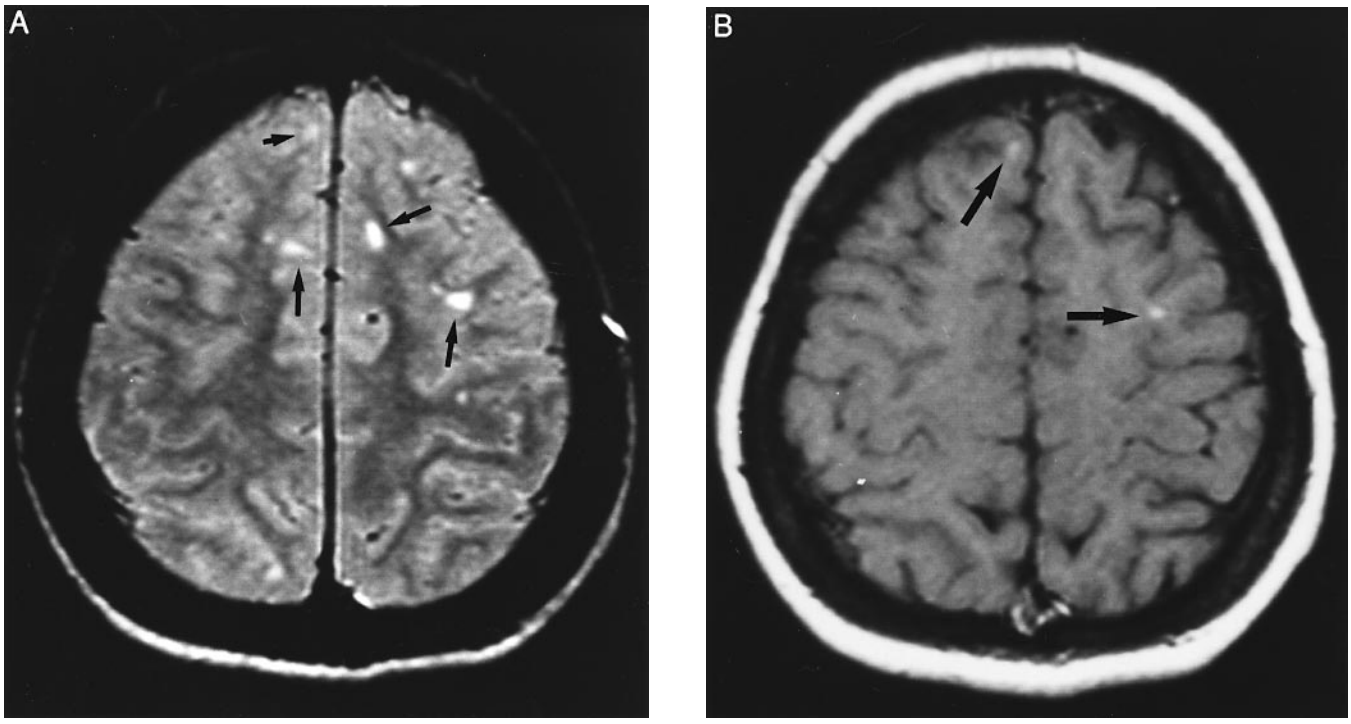

Fig. 1 Juxtacortical lesions in the frontal and parietal lobes. (**A**) T_2-weighted image shows multiple lesions contiguous with the cortex, four of which are indicated with arrows, and two of which enhanced with gadolinium (arrows) on the T_1-weighted image (**B**).

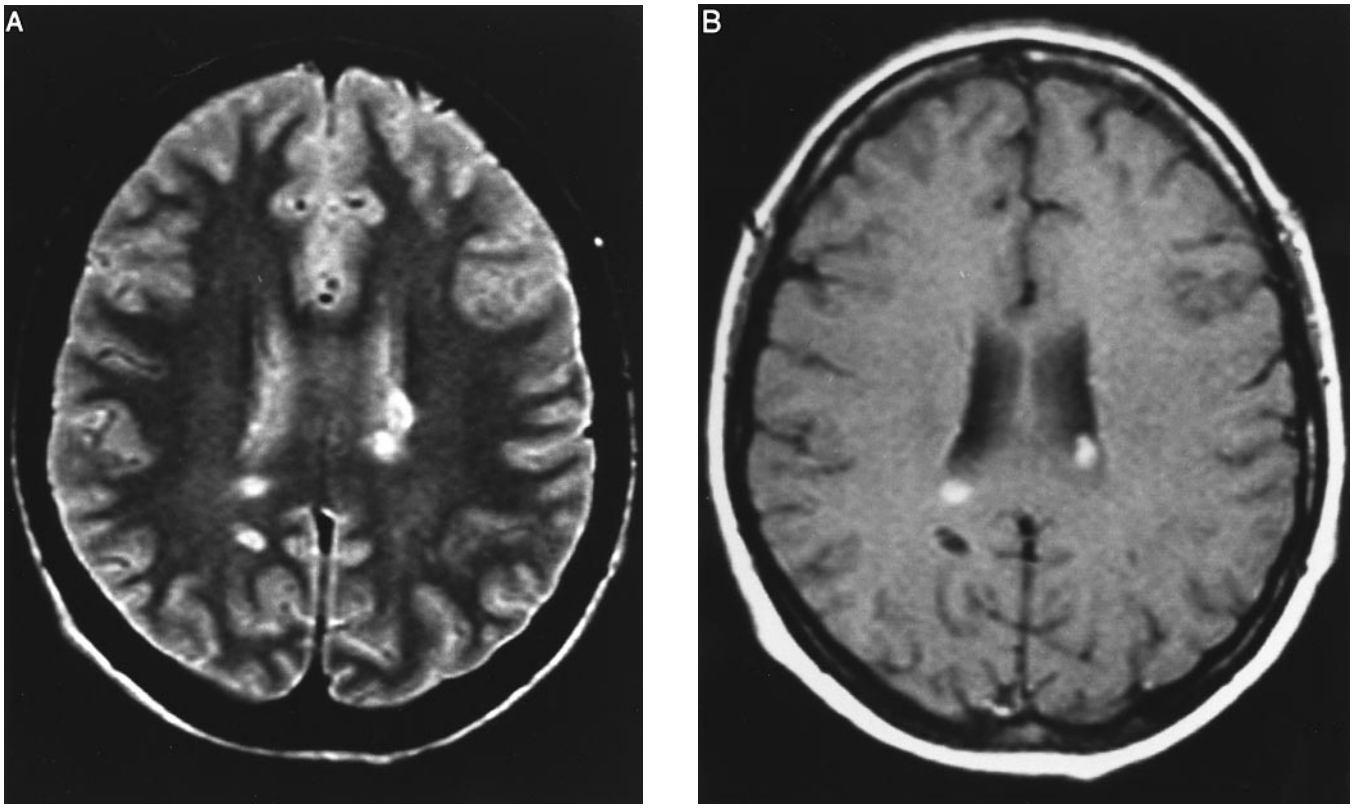

Fig. 2 Periventricular, callosal/subcallosal, and ovoid lesions. The T_2-weighted image (**A**) shows four hyperintense lesions, three of which display an ovoid shape. The two lesions that enhance with gadolinium on the T_1-weighted image (**B**) are in a callosal/subcallosal location, while one of the non-enhancing lesions is located around the border of the left lateral ventricle and is >6 mm in diameter. Note that the right-sided non-enhancing lesion has a hypointense appearance in **B**. The presence of four lesions, with one being periventricularly located fulfils the criteria of Paty *et al*. (1988).

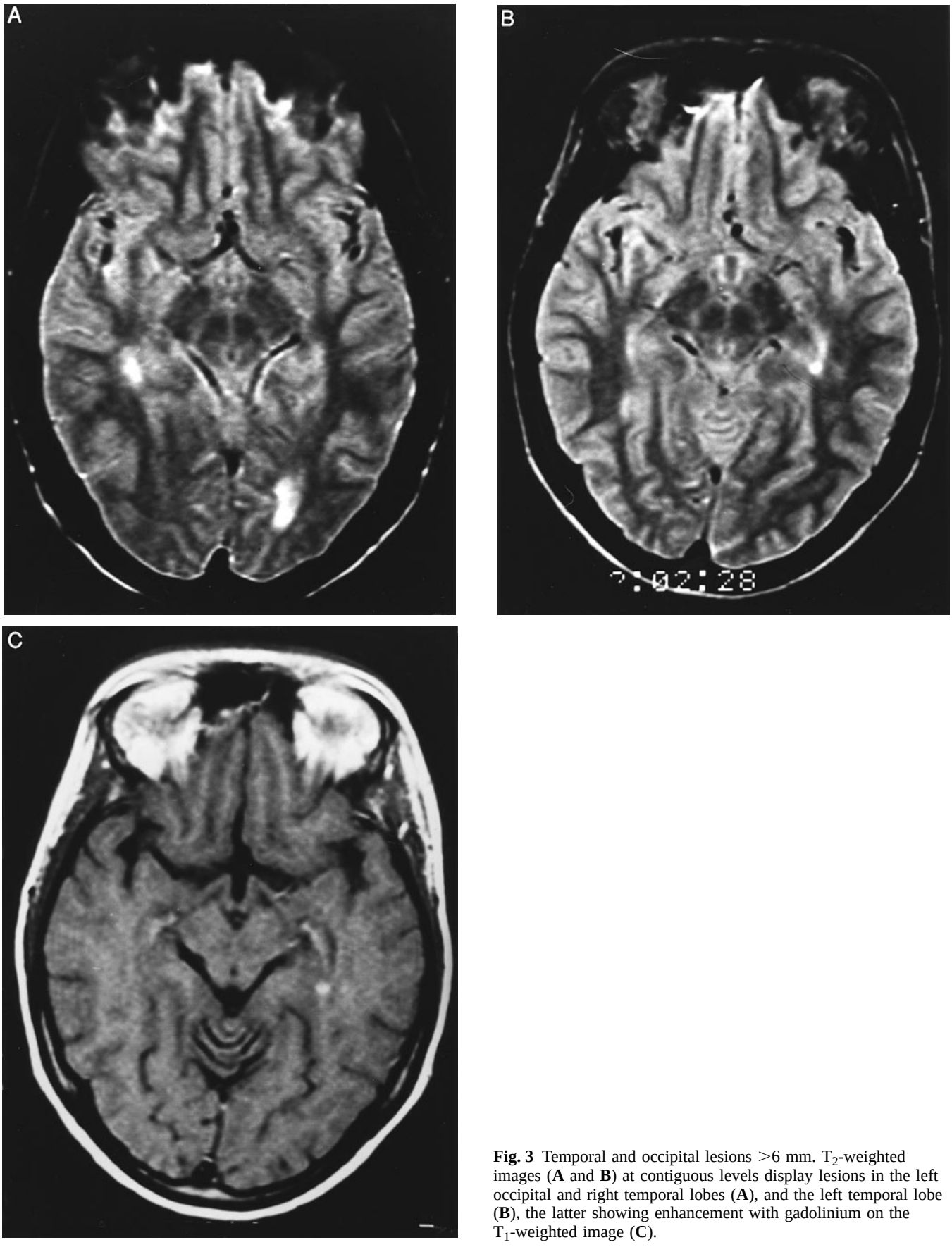

Fig. 3 Temporal and occipital lesions >6 mm. T_2-weighted images (**A** and **B**) at contiguous levels display lesions in the left occipital and right temporal lobes (**A**), and the left temporal lobe (**B**), the latter showing enhancement with gadolinium on the T_1-weighted image (**C**).

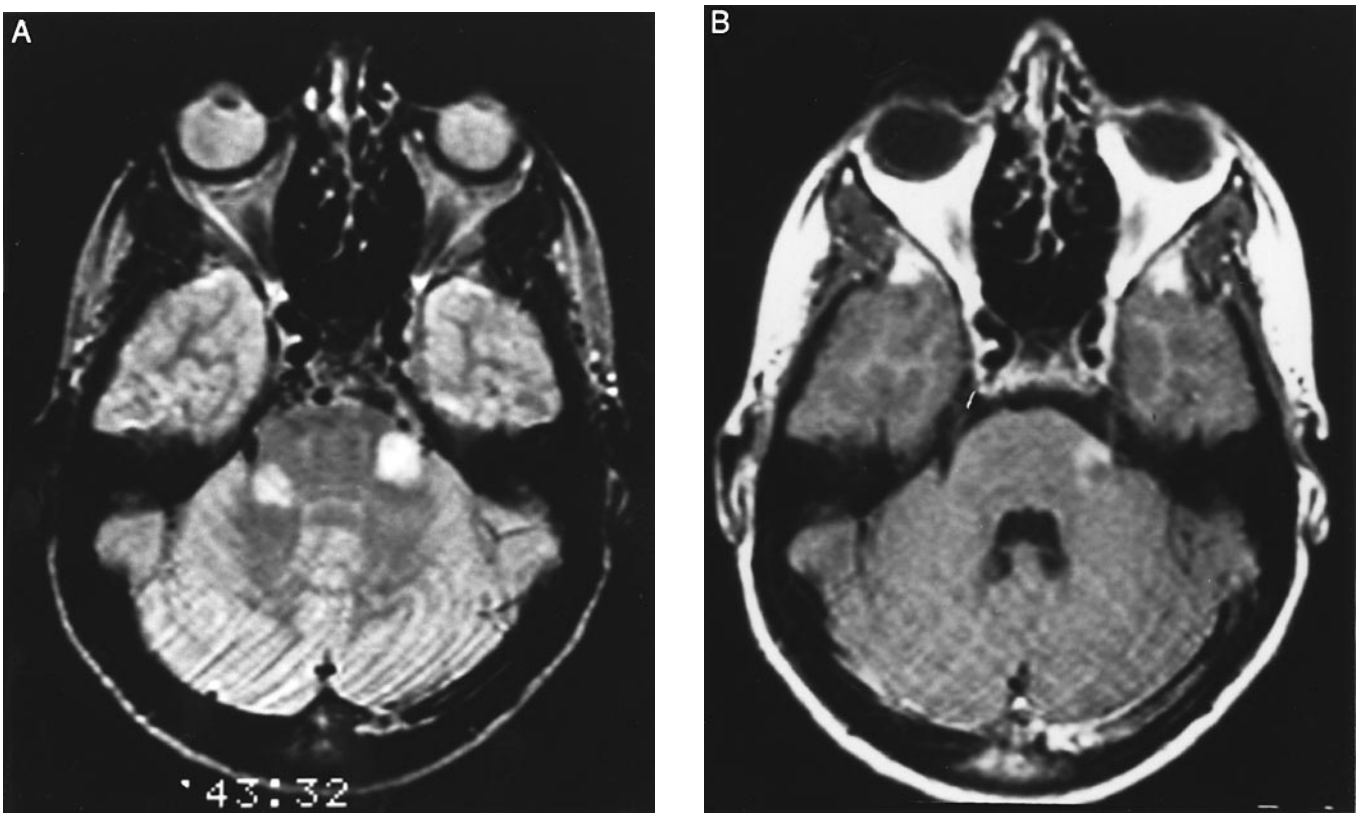

Fig. 4 Infratentorial lesions >6 mm. T_2-weighted image (**A**) shows large lesions in the left side of the pons and the right middle cerebellar peduncle, both >6 mm, thus fulfilling the criteria of Fazekas *et al*. (1988); the lesion on the left side enhances with gadolinium on the T_1-weighted image (**B**).

Table 2 *Presenting symptoms according to centre*

Symptom	Amsterdam	Milan	London	Total no. (%)
Optic neuritis	22	5	13	40 (54)
Brainstem and cerebellum	9	3	0	12 (16)
Spinal	11	11	0	22 (30)

median number of lesions was 16 (in patients without conversion, the median was 2).

Using the continuous MRI parameters, the forward stepwise method revealed significant contributions from only gadolinium-enhancement (coefficient, $B = 0.96$; standard error, SE = 0.36; $P = 0.0081$) and juxta-cortical lesions ($B = 0.49$; SE = 0.23; $P = 0.028$). Although the criterion of oval lesions was initially included in the first step of the analysis, it was removed later when gadolinium-enhancement had been added. The backward method confirmed that gadolinium-enhancement and juxtacortical lesions provided the most important information, and, in addition, revealed (less) significant contributions from periventricular lesions, hypointense T_1 lesions, infratentorial lesions, large enhancing lesions, and the total number of T_2 lesions. Several parameters, including the total number of T_2 lesions had negative *B*-values; since adding such parameters with negative prediction is confusing, only parameters with positive *B*-values are considered interesting. Following gadolinium-enhancement and juxtacortical lesions, the strongest positive *B*-values were found for infratentorial and periventricular lesions, which have also been included in other diagnostic criteria (Fazekas *et al*., 1988).

Although the presence of any T_2 abnormality provided high sensitivity for conversion to clinically definite multiple sclerosis, specificity was poor. By increasing the minimum number of lesions in order to classify a scan as abnormal, specificity increased, while sensitivity decreased (Fig. 6). Accuracy was found to be optimal at a minimum of nine T_2 lesions. Similar curves were also constructed for al the other continuous MRI criteria (graphs not shown); following the optimization of cut-off points, prevalence, PPV, sensitivity, specificity and accuracy were determined (Table 3).

Based on the results of the logistic regression analysis, four dichotomized MRI parameters (gadolinium-enhancement, infratentorial, juxtacortical and periventricular lesions)

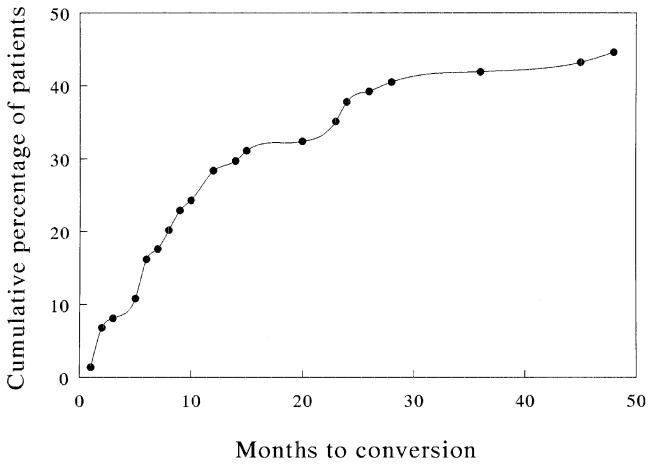

Fig. 5 Cumulative percentage of patients converting to clinically definite multiple sclerosis. Note that one dot can represent more than one patient, and that the rate of accumulation flattens off after 2 years (median time to conversion 9 months).

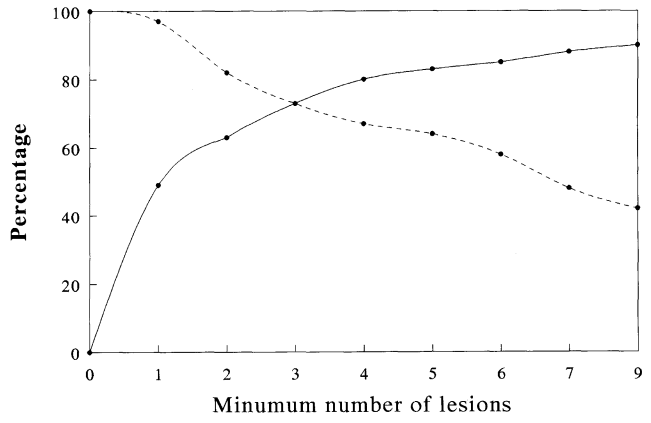

Fig. 6 Curves of sensitivity and specificity versus the total number of hyperintense lesions on T_2-weighted images. With an increasing number of lesions required to classify a scan as abnormal sensitivity (dashed line) decreases, while specificity (solid line) increases. The fact that accuracy is optimal at a minimum of nine lesions, and not at the intercept of the two lines between seven and eight, is related to the fact that the prevalence is >50%.

were used to build a final regression model, which had a sensitivity of 82%, a specificity of 78%, and an accuracy of 80%. Using this model (PPV 75%, NPV 84%), the chance of developing multiple sclerosis during the follow-up period was calculated for each individual patient, and the effect of the number of abnormal parameters on calculated risk and observed outcome is shown in Table 4. The predicted chance of converting to clinically definite multiple sclerosis based on the model fitted well with the clinical outcome (goodness-of-fit 75.96).

Discussion

In this study we investigated the relative contribution of several MRI criteria derived from T_2-weighted and gadolinium-enhanced T_1-weighted images in making a diagnosis of multiple sclerosis in a large cohort of patients presenting with a first episode of symptoms suggestive of multiple sclerosis. The 'gold standard' in the present study was conversion to clinically definite multiple sclerosis. In autopsy studies, the diagnosis of multiple sclerosis is supported by neuropathological findings in ~95% of cases, and can be considered as a reliable reference (Herndon and Brooks, 1985). One might argue that with longer follow-up the rate of conversion to clinically definite multiple sclerosis will increase and the diagnostic performance of the paraclinical test will change. In this study, the median duration of follow-up in those patients who had not converted to clinically definite multiple sclerosis (39 months) was relatively long in comparison with the median duration of the time to conversion to clinically definite multiple sclerosis in those patients that did convert (9 months). Of those patients who converted to clinically definite multiple sclerosis, 50% had done so by 9 months, while 90% had done so by 30 months of follow-up. Figure 5 suggests that the results of the present study are not likely to change dramatically with longer periods of follow-up. As in many other studies, the prevalence of multiple sclerosis at follow-up was lower than 50%, which determines that specificity is more important than sensitivity. The stepwise logistic regression analysis therefore identifies as the most significant predictors gadolinium-enhancement and juxtacortical lesions, both of which are relatively specific (and prevalent).

The currently most commonly used diagnostic MRI criteria for multiple sclerosis are those by Paty *et al.* (1988) (Table 1), which were established in a prospective study. Our results confirm that those criteria are quite sensitive, but not very specific (Table 3). We found that the diagnostic accuracy would increase from 69 to 80% by requiring a minimum of nine lesions instead of four, as in the criteria of Paty. Interestingly, this number approximates with the number of 'average sized' lesions making up the area of 1.23 cm^2, which was the cut-off point in a study which investigated the minimum area predicting future disability in patients with isolated syndromes suggestive of multiple sclerosis (Filippi *et al.*, 1994). Completely normal brain MRI scans were acquired in a low percentage of cases (18%) and, as in previous studies (Filippi *et al.*, 1994), had a very high NPV. It should be noted that a negative brain MRI does not rule out definitively the diagnosis of multiple sclerosis, which is ultimately made on clinical grounds. Recently, Thorpe *et al.* (1996) described a series of 20 patients with suspected multiple sclerosis with a negative brain scan, in whom MRI of the spinal cord revealed lesions in all of them, suggesting that spinal imaging further increases sensitivity and NPV.

In order to increase specificity, Fazekas *et al.* (1988) developed composite criteria (Table 1) which showed high specificity in two retrospective studies involving patients with established multiple sclerosis compared with patients with other neurological diseases (Fazekas *et al.*, 1988; Offenbacher *et al.*, 1993). In this prospective study of cases

Table 3 *Cut-off (minimum number of lesions), prevalence, positive predictive value, sensitivity and specificity of MRI parameters using optimized cut-off point*

MRI criterion	Cut-off point	Prevalence (*n*)	CDMS (*n*)	PPV (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
Periventricular lesions	3	35	24	69	73	73	73
Basal ganglia and internal capsule lesions	1	15	10	67	30	89	62
Hypointense lesions on T1	1	20	14	70	44	85	65
Callosal/subcallosal lesions	1	38	26	69	79	71	74
Juxtacortical lesions	1	38	24	63	73	66	74
Gadolinium-enhancement	1	28	20	71	61	80	72
Infratentorial lesion	1	28	19	68	58	78	69
Lesions > 6 mm	2	30	21	70	64	78	72
Large gadolinium-enhancing lesion	1	10	6	60	18	90	58
Occipital lesions	1	30	12	40	64	78	72
Parietal lesions	3	33	23	70	70	76	73
Temporal lesions	1	39	26	67	79	68	73
Frontal lesions	3	35	24	69	77	73	73
Oval	NA	39	25	64	76	66	70
Total number of lesions	9	30	24	80	73	80	77

See text for optimization of cut-off points. CDMS = clinically definite multiple sclerosis; PPV = positive predictive value; NA = not applicable.

Table 4 *Relationship between number of abnormal MRI criteria, calculated risk and observed risk*

No. of abnormal MRI criteria*	Prevalence in 74 patients (%)	Observed risk (% with CDMS)	Calculated risk (%), median (range)†
0	24 (32)	16	14
1	9 (12)	11	28 (20–32)
2	16 (22)	54	55 (39–57)
3	12 (16)	75	64 (64–77)
4	13 (18)	87	84

*Presence of gadolinium enhancement, juxtacortical lesions, periventricular lesions or infratentorial lesions. †Based on the logistic regression model (*see* text for details). CDMS = clinically definite multiple sclerosis.

Table 5 *Diagnostic performance of final model compared with Paty's and Fazekas' criteria**

Criteria	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Paty's	88	54	85	60	69
Fazekas'	88	54	85	60	69
This study	82	78	84	75	80

*Paty *et al*. (1988) and Fazekas *et al*. (1988). PPV = positive predictive value; NPV = negative predictive value.

with clinically isolated syndromes suggestive of multiple sclerosis, such criteria do not perform as well (sensitivity 88%; specificity 54%), underlining the need of testing criteria in a prospective fashion. For the individual elements making up the criteria of Fazekas, the optimum cut-off point is not always just simply 1, but 2 for lesions >6 mm, and 3 for periventricular lesions. By taking these cut-off points, each of the elements making up the Fazekas criteria had an accuracy equal to or better than the composite measure (Table 3). The same holds true for the criteria of Paty, i.e. the optimized individual elements perform better than the composite measure they lead up to (Table 3). In fact, it is more realistic to assess the number of lesions and apply the corresponding sensitivity/specificity (Fig. 6). Likewise, one can better predict the chance of developing clinically definite multiple sclerosis based on the number of abnormal MRI criteria, than to be forced to make a two-choice decision (compatible with multiple sclerosis or not).

Many of the individual MRI criteria show reasonably high accuracy once the cut-off point is optimized (Table 3), which already indicates that the various parameters must be strongly associated. Logistic regression analysis was therefore used

to reduce redundancy in information and to identify those parameters best predicting conversion to clinically definite multiple sclerosis. The forward stepwise method (which is the most strict) revealed juxtacortical and enhancing lesions as the only significant contributors. Using a backwards analysis (which is less rigid) a more complex model was found with a higher accuracy, but several MRI parameters were assigned negative *B*-values; this indicates that in the presence of several other good predictors, an increasing number of T_2 lesions now harbours an NPV, indicating a tendency for over fitting. The backwards analysis, however, confirms the relevance of enhancing and juxtacortical lesions and, in addition, reveals significant contributions from (amongst others) infratentorial and periventricular lesions. Since the latter two have been considered to be relevant in multiple sclerosis in many studies already, they were included in our final model. This model has an overall accuracy of 80% and the predictive value of the cumulative number of criteria being positive correlates very closely with final outcome (Table 4), illustrating an appropriate fit to the data. The simplicity of using only four variables in a dichotomized fashion is attractive, since they can be quickly assessed, and the number of criteria being positive translated into a chance of developing multiple sclerosis is much more realistic than a forced yes-or-no answer.

Interestingly, our final model does not include the total number of lesions any more. This result coincides with the common-sense that it is not merely the number of lesions that counts, but rather (i) what sort of lesions are found and (ii) where they are found. Periventricular lesions (Fig. 2) were implicated early on (Runge *et al*., 1984), and were incorporated in the criteria of both Paty *et al*. (1988) and Fazekas *et al*. (1988). It relates to the fact that multiple sclerosis lesions are located around venules, with the majority of medullary veins draining into the subependymal veins in the lateral ventricles (Dawson, 1916). Infratentorial lesions (Fig. 4) were incorporated into the criteria of Fazekas. Apparently multiple sclerosis lesions occur throughout the brain, while lesions occurring in other diseases tend to be confined more frequently to the supratentorial compartment, although this is not universally true: sarcoid (Sherman and Stern, 1990), acute disseminated encephalomyelopathy (Caldemeyer *et al*., 1994), Behçet's disease (Kazui *et al*., 1991), systemic lupus erythemathosis (Miller *et al*., 1987), and many other diseases may all produce brainstem lesions. Lesion in the cortex (Fig. 1) make up a substantial percentage of lesions in histopathological studies, up to 59% in one series (Lumsden, 1970). Using fluid attenuated inversion recovery (FLAIR), the percentage of juxtacortical lesions in multiple sclerosis was 30% (Filippi *et al*., 1995). Their presence is related to myelinated axons extending well into the cortex, and contrasts with hypoxic/ischaemic diseases where the direct subcortical zone, containing the U-fibres, is typically spared (van der Knaap and Valk, 1995). Not included in our model was the presence of callosal/subcallosal lesions. Their significance has been stressed by several authors (Simon *et al*., 1986; Gean-Marton *et al*., 1991), but their prevalence at first presentation has not been studied. Apparently their presence does not harbour independent information. One can argue that such lesions would be seen to advantage on sagittal images and using FLAIR, both of which were not at our disposal.

In the present study, gadolinium-enhancement (Figs 1 4) was identified as the most predictive MRI parameter. Gadolinium-enhancement reveals a phase of inflammation and active demyelination in experimental allergic encephalomyelitis (Hawkins *et al*., 1990; Morrissey *et al*., 1996) and multiple sclerosis (Katz *et al*., 1990; Nesbit *et al*., 1991), and is initially seen in new multiple sclerosis lesions (Grossman *et al*., 1986; Barkhof *et al*., 1992). Kappos *et al*. (1991) already indicated the value of simultaneous demonstration of enhancing and non-enhancing lesions during a single examination at first presentation. In that series of 14 patients with enhancement, 11 converted to clinically definite multiple sclerosis within 12 months; the PPV in that open study (79%) compares well with the one reported here (75%). Although the final diagnosis remains a clinical one, simultaneous demonstration of enhancing and non-enhancing lesions is the radiological counterpart of clinical dissemination in time and space. In case gadolinium-enhanced images are not available, using the presence of $\geqslant 9$ T_2 lesions provides an alternative with an accuracy (77%), similar to our final model.

The hypointense lesions that can sometimes be observed on the (gadolinium-enhanced) T_1-weighted images, have been shown to be more prevalent in multiple sclerosis than in subcortical arteriosclerotic encephalopathy (Uhlenbrock *et al*., 1989) and to correlate better with changes in disability in more advanced multiple sclerosis (van Walderveen *et al*., 1995), but the prevalence of such lesions at first presentation is relatively low (Table 3), and therefore probably not diagnostically useful.

Recently, 3D fast FLAIR has been used to obtain 1-mm sagittal sections through the brain, revealing many periventricular and subcallosal lesions which went undetected on conventional axial T_2-weighted sequences (Hashemi *et al*., 1995). Perhaps the results of the present analysis would have been different, had this technique been used. The time needed to collect a new sample and obtain the necessary follow-up, precluded such an analysis in the present study. By the same token, the results from such a new study using 3D FLAIR will be challenged by still newer techniques, which almost certainly will be developed within the 5-year period needed to conduct a study like the current one. Currently, however, conventional T_2-weighted 5-mm axial slices are still widely used, and the results of our study are therefore of considerable practical value. Another potential limitation of our study is the fact that most studies were done at 0.5-T and 0.6-T machines, but the authors of a recent report were unable to confirm the hypothesis that a higher field strength improves the accuracy of MRI in the initial diagnosis of multiple sclerosis (Lee *et al*., 1995).

In conclusion, many MRI parameters can be optimized to predict conversion to clinically definite multiple sclerosis

at first presentation. Our study shows that the diagnostic performance of such criteria are best tested in a prospective fashion in patients with isolated clinical syndromes. Our results indicate that gadolinium-enhancement and juxtacortical lesions are the most relevant MRI criteria. Adding infratentorial and periventricular lesions increases the number of abnormal criteria to creating a simple model with increased probability of developing multiple sclerosis. The use of only four dichotomized variables ensures that the model can be applied easily in daily practice, and that the PPV can be inferred from the number of abnormal criteria in a straight forward fashion (Table 4). The fact that this model has a higher specificity (and PPV) than other currently available criteria is fortunate, at a time when the introduction of more effective therapies require the emphasis to be shifted, from excluding multiple sclerosis, towards predicting the development of multiple sclerosis (Table 5).

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