*Brain* (1998), **121,** 495–503

# The prognostic value of brain MRI in clinically isolated syndromes of the CNS
## A 10-year follow-up

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## Summary
*A definitive diagnosis of multiple sclerosis cannot be made at presentation on patients with a clinically isolated syndrome of the optic nerve, spinal cord or brainstem suggestive of demyelination, as dissemination in time is not established. To determine the long-term risk of abnormalities on brain MRI for the development of multiple sclerosis and disability we performed a 10-year follow-up on 81 such patients who had $T_2$-weighted brain MRI at presentation. Initial brain MRI was abnormal in 54 (67%). Follow up of those patients with an abnormal MRI revealed progression to clinically definite multiple sclerosis in 45 out of 54 (83%), of whom 11 (20%) had relapsing/remitting disease (EDSS $> 3$), 13 (24%) secondary progressive and 21 (39%) benign (relapsing/remitting with EDSS $\leqslant 3$) disease. For those with a normal MRI progression to clinically definite multiple sclerosis occurred in only three out of 27 (11%), all benign. There was a significant relationship between the number of lesions at presentation and both EDSS ($r = 0.45$, $P < 0.001$) and the type of disease at follow-up ($P < 0.0001$). Brain MRI at presentation with a clinically isolated syndrome is predictive of the long-term risk of subsequent development of multiple sclerosis, the type of disease and extent of disability.*

**Keywords**: clinically isolated syndromes; multiple sclerosis

**Abbreviations**: ANOVA = analysis of variance; EDSS = extended disability status scale (Kurtzke)

## Introduction
Multiple sclerosis is a disorder of the CNS which results in abnormalities disseminated in time and place. In ~90% of patients the first presentation is an acute, usually reversible, episode of CNS dysfunction. In most instances the symptoms and signs indicate a lesion of the spinal cord (50%), optic nerve (25%) or brainstem (15%). However, not all patients with these symptoms progress to develop further episodes consistent with a clinical diagnosis of multiple sclerosis. These syndromes sometimes have an alternative cause including, rarely, the monophasic demyelinating disorder acute disseminated encephalomyelitis. It is therefore desirable that, on presentation with an isolated syndrome, (i) the correct diagnosis is made and (ii) the prognosis for the future risk of developing clinically definite multiple sclerosis and disability can be estimated, once the clinician is satisfied that the event is compatible with demyelination.

Prior to the advent of MRI a number of clinical studies looked at the risk of developing clinically definite multiple sclerosis following an isolated syndrome, particularly optic neuritis. These studies revealed a risk of progression of between 30 and 75% with a higher risk in the UK than in the USA (Bradley and Whitty, 1968; Compston *et al*., 1978; Cohen *et al*., 1979; Landy, 1983; Francis *et al*., 1987; Rizzo and Lessell, 1988; Sandberg-Wolheim *et al*., 1990). Francis *et al*. (1987) reported on 101 patients from the UK with acute optic neuritis, followed for 15 years, and from this they projected a life-time risk of progressing to clinically definite multiple sclerosis of 75%. Around the same time

Rizzo and Lessell (1988) reported on 60 patients from the USA followed for a similar period of time and found a risk of 74% in females and 34% in male patients. Subsequently, Sandberg-Wolhein *et al.* (1990) reported on a truly prospective study of 86 patients and estimated a risk of progression over 15 years of 45%. This latter group found a higher likelihood of developing multiple sclerosis with the presence of oligoclonal bands in the CSF, younger age at presentation and early recurrence of the optic neuritis. Prospective clinical studies on isolated spinal cord or brainstem syndromes are limited. Lipton and Teasdall (1973) reported that only one patient out of 29 patients with a complete transverse myelitis subsequently progressed to clinically definite multiple sclerosis after 5 years. Morrissey *et al.* (1993) found that eight out of 17 (47%) of those with a brainstem syndrome and 11 out of 28 (39%) with a spinal cord syndrome progressed to clinically definite multiple sclerosis over 5 years. The same group found a slightly higher risk of progression for those with an isolated optic neuritis, i.e. 24 out of 44 (56%). Allowing for slight differences in length of follow-up it appears the risks of progression are broadly similar.

When patients present with a clinically isolated syndrome it is apparent that they are at risk of developing further episodes; however, it is also clear that a substantial proportion do not do so. It is important for two reasons that more definitive risk factors are established: (i) to give patients a more accurate prognosis and (ii) to select appropriate patients with a high risk of developing multiple sclerosis to include in treatment trials aimed at preventing or delaying the development of clinically definite disease.

The prognostic value of human leucocyte antigen tests, CSF examinations and MRI have all been evaluated. The presence of the human leucocyte antigen DR2 increases the risk of progression to clinically definite multiple sclerosis over the next 5 years (Compston *et al*., 1978; Morrissey *et al*., 1993). However, this increased risk disappears on longer-term follow-up (Francis *et al*., 1987; Sandberg-Wolheim *et al.*, 1990). Oligoclonal IgG [and, in one study, oligoclonal IgM (Sharief and Thompson, 1991)] in the CSF also confers an increased risk of progression (Sandberg-Wolheim *et al.*, 1990; Lee *et al.*, 1991). However, the predictive value is only moderate, and, because lumbar puncture is invasive, many patients with a clinically isolated syndrome, particularly optic neuritis, do not routinely have this examination.

There have been numerous MRI studies using conventional $T_2$-weighted brain imaging in patients at presentation with a clinically isolated syndrome. These studies consistently demonstrate multiple asymptomatic abnormalities compatible with demyelination in 50–80% (Jacobs *et al.*, 1986; Ormerod *et al.*, 1986*a*, *b*; Miller *et al.*, 1987; Frederiksen *et al.*, 1991; Martinelli *et al.*, 1991; Ford *et al.*, 1992). Even when such abnormalities are present, it is not possible to diagnose clinically definite multiple sclerosis, as the criterion for dissemination in time is not met. It is possible that some of these patients may have the multifocal but monophasic disorder, acute disseminated encephalomyelitis, in which the MRI findings may be indistinguishable from multiple sclerosis (Atlas *et al.*, 1986; Kesserling *et al.*, 1990).

Short-term follow-up of between 1 and 5 years (Frederiksen *et al.*, 1991; Jacobs *et al.*, 1991, 1997; Lee *et al.*, 1991; Martinelli *et al*., 1991; Ford *et al.*, 1992; Beck *et al.*, 1993; Morrissey *et al.*, 1993; Soderstrom *et al*., 1994; Campi *et al.*, 1995; Tas *et al.*, 1995) have shown that, for those patients who present with a normal brain scan, the risk of progressing to clinically definite multiple sclerosis is low (at ~5%), whereas, for those patients with an abnormal cerebral scan the risk is much higher (43% when all studies are combined). Morrissey *et al.* (1993) and Beck *et al.* (1993) also showed that the number or grade of MRI abnormalities influenced the risk of developing clinically definite multiple sclerosis. In the former study progression to multiple sclerosis after 5 years was seen in 13 out of 24 (54%) with one to three lesions and in 28 out of 33 (85%) with four or more lesions (Morrissey *et al.*, 1993). In the latter study, for those who did not receive methylprednisolone, i.e. the placebo group of the North American Optic Neuritis Trial, progression to clinically definite multiple sclerosis after 2 years occurred in two out of 12 (17%) with grade 2 MRI abnormalities (one periventricular or ovoid lesion $\geqslant$3 mm in size) and in 14 out of 39 (36%) with grade 3 or 4 MRI abnormalities (two or more periventricular or ovoid lesions $\geqslant$3 mm in size).

These relatively short-term studies confirm that MRI has a predictive role in the development of clinically definite multiple sclerosis following a clinically isolated syndrome, and that the greater the extent of abnormalities the greater the risk. Longer-term follow-up studies are nevertheless required to elucidate the relationship between the initial MRI findings and (i) the longer-term risk for developing multiple sclerosis (after $\geqslant$10 years), (ii) the type of multiple sclerosis patients may develop, (iii) the extent of disability that develops, and (iv) the amount of asymptomatic MRI activity. For this reason, a clinical and MRI follow-up was performed on our group of patients, who had all had a $T_2$-weighted brain MRI at presentation with a clinically isolated syndrome ~10 years previously. Results at 1 and 5 years have been reported previously (Miller *et al.*, 1988, 1989; Morrissey *et al.*, 1993).

## Patients

All patients presenting with a clinically isolated syndrome to the wards and clinics of The National Hospital, Queen Square, London or the Physicians Clinic at Moorfields Eye Hospital, London between May 1984 and July 1987 were considered for inclusion in the study. The study was approved by the Medical Ethics Committees of both hospitals and informed consent was obtained from each patient prior to entry into the study. A clinically isolated syndrome was defined as an acute or subacute episode suggestive of demyelination affecting the optic nerves, brainstem or spinal cord. Male and female patients aged between 10 and 50

years at presentation were included (the upper limit was made in order to minimize the effect of non-specific age-related MRI changes) and appropriate investigations, including the initial brain MRI, had not revealed an alternative diagnosis; patients with clinically isolated cord syndromes always underwent either spinal MRI or myelography, and some patients with optic neuritis had an orbital CT scan. During the recruitment period, 135 patients were seen. Four were subsequently excluded because follow-up revealed an alternative diagnosis: myasthenia gravis, cerebrovascular disease, HIV-related complications and systemic lupus erythematosus. In retrospect, for these four patients there were no clinical or laboratory features at presentation which alerted the clinician to the possibility of an alternative diagnosis. Two further patients died from problems unrelated to multiple sclerosis. This left an initial cohort of 129 patients. An early clinical and MRI follow-up was performed after a mean of 1.3 years from the initial scan in 109 patients (Miller *et al.*, 1988, 1989). Subsequently, after a mean of 5.3 years, 89 patients were re-examined and re-scanned (Morrissey *et al.*, 1993; Filippi *et al.*, 1994). The present follow-up concerns 81 patients who were seen at ~10 years.

The original cohort was representative of the general population because: (i) patients with optic neuritis were predominantly seen in a Central London Eye Hospital with a casualty department where patients with acute visual loss readily attended, (ii) few MRI scanners were available in central London at the time, and there was an enthusiastic pattern of referral by physicians at our hospitals and neighbouring institutions of patients with isolated brainstem/spinal cord syndromes for diagnostic evaluation. Patients were located after 10 years from reference to our previous records, or when the patient had moved by using the NHS central register at The Office for National Statistics. Ethical approval was obtained for release of information regarding the health authority in which each patient was registered. The health authority subsequently released the name and address of the patients' general practitioner. The general practitioner was then contacted for information regarding the patient's current address and telephone number. Finally, the patient was contacted, first by letter (sent on two occasions if no reply to the original) and subsequently by telephone. All patients of the original cohort were considered whether or not they had reached an exact 10-year follow-up point.

At 10 years, progression to multiple sclerosis was defined using Poser criteria solely on clinical grounds (Poser *et al.*, 1983). The additional information on MRI was not used for the diagnosis. Clinically definite multiple sclerosis was defined as two separate attacks disseminated in time and place and clinical evidence of two separate lesions. Clinically probable multiple sclerosis was defined as either two separate attacks disseminated in time and clinical evidence of one lesion, or one attack (i.e. the original episode) and clinical evidence of two separate lesions, the second having developed later than the first, i.e. a new sign noted at a follow-up examination. It was required that there be an interval of $\geqslant$6 months between the first and last clinical episode, in order to minimize the chance of including a case of slowly evolving acute disseminated encephalomyelitis. Assessment of disability was made using Kurtzke's extended disability status scale (EDSS) (Kurtzke, 1983). In those with clinically definite multiple sclerosis, disease subtype at 10 years was defined as: (i) benign, if the patient had a typical relapsing/remitting course but with an EDSS of $\leqslant$3; (ii) relapsing/remitting, if patients had a typical relapsing/remitting course but with an EDSS of $>$3; or (iii) secondary progressive, if, after a period of relapsing/remitting disease, the patient entered a phase of gradual deterioration of $\geqslant$6 months duration, with or without superimposed relapses.

## Methods

### *MRI*

All baseline MRI scans, early follow-up and 5-year follow-up studies, were performed on a Picker 0.5-T superconducting scanner. At 10 years a General Electric Signa 1.5-T scanner was used. An SE 2000/60 sequence was used for the baseline, and early and 5-year follow-up, with contiguous axial slices throughout the whole brain. In some early baseline scans (1984/1985) slices were 10 mm thick; in all subsequent scans 5 mm slices were obtained. At 10 years a conventional dual echo spin echo sequence (2000/30/90) was used, again with 5 mm slice thickness. The MRI scans were reported by two experienced neuroradiologists (D.P.E.K. and B.E.K.) blinded to the clinical findings. Scans were reported as normal if they were completely normal or, in the case of a brainstem syndrome, if only the symptomatic lesion was seen. Scans were reported as abnormal if one or more asymptomatic lesions, compatible with demyelination, were seen; only lesions considered to be unequivocal by the experienced observers were counted. The number of brain lesions compatible with demyelination was recorded. All scans were re-read with the baseline, and 5- and 10-year scans side-by-side. The development of new lesions at 10 years was determined on the short echo with reference to the long echo when clarification was needed.

Statistical analysis was performed using the 'SPSS for Windows 6.1' statistical package (SPSS Inc., Chicago, Ill., USA). The Spearman rank correlation coefficient was calculated and a Kruskal–Wallis one-way ANOVA (analysis of variance), where appropriate.

## Results

Eighty-one patients were seen for clinical review after 10 years. There were 28 male and 53 females; the mean age at presentation was 32.3 years (range 17–49 years) and at latest follow-up 42 years (range 2–60 years), giving a mean follow-up period of 9.7 years. Forty-two patients presented with an isolated optic neuritis, which was bilateral in four. Sixteen patients had a brainstem syndrome and 23 a spinal cord

**Table 1** *Relationship between number of asymptomatic lesions at baseline and outcome*

| | Asymptomatic lesions detected on MRI at baseline | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2–3 | 4–10 | >10 |
| Number of patients | 27 | 3 | 16 | 15 | 20 |
| Clinical outcome at 10-year follow-up | | | | | |
| Progression to CDMS | 3 (11%) | 1 (33%) | 14 (87%) | 13 (87%) | 17 (85%) |
| EDSS > 3 (due to MS) | 0 | 0 | 5 (31%) | 4 (27%) | 14 (75%) |
| EDSS > 3 (non-MS) | 5 (19%) | | | | |
| EDSS > 5.5 | 1 (4%) | 0 | 2 (13%) | 3 (20%) | 7 (35%) |
| New MRI lesions (median number) | | | | | |
| Between 0 and 5 years (72 patients) | 0 (0–10) | 8 (6–11) | 5 (0–27) | 9 (0–55) | 17 (0–40) |
| Between 5 and 10 years (61 patients) | 0 (0–12) | 0 | 1 (0–15) | 2 (0–10) | 3 (0–22) |

CDMS = clinically definite multiple sclerosis; MS = multiple sclerosis.

**Table 2** *Clinical subtype at 10 years and MRI status at baseline*

| Clinical subtype | Normal MRI ($n$ = 27) | Abnormal MRI ($n$ = 54) |
|---|---|---|
| Clinically isolated syndrome | 22 (82%) | 7 (13%) |
| Clinically probable MS | 2 (7%) | 2 (4%) |
| Clinically definite MS | | |
| Benign MS | 3 (11%) | 21 (39%) |
| Relapsing/remitting MS | 0 | 11 (20%) |
| Secondary progressive MS* | 0 | 13 (24%) |

MS = multiple sclerosis. *Includes one death from severe multiple sclerosis.

syndrome. Fifty-four patients (66.7%) had had an abnormal brain MRI at presentation. This percentage is similar to that of the original cohort (80 out of 132; 62%), and at the earlier 5-year assessment (57 out of 89; 64%) suggesting that the present cohort is representative of the original groups. Seventy-three patients were reviewed clinically at all three visits. A 10-year follow-up MRI scan was performed on 64 patients, and 61 of these had a 5-year scan.

For those patients not followed-up at 10 years, six were contacted directly, but declined to have either a clinical examination or MRI scan, and two had emigrated and were unavailable. Of the remainder, either the general practitioner declined to release patient details (10 cases) or, when these details were available, the patient did not reply to the original or second letter and no telephone number was known.

## *Normal baseline MRI cohort (***n** *= 27)*

For those patients with a normal brain MRI at presentation, only three patients (11%) had progressed to clinically definite multiple sclerosis, all of whom had benign disease (see Tables 1 and 2). Two further patients (7%) had clinically probable multiple sclerosis. All four patients with clinically definite or clinically probable multiple sclerosis who had a 10-year follow-up scan developed new brain lesions. In one patient with benign disease, follow-up MRI was not possible at 10 years due to obesity; however, there was evidence of abnormalities on the 5-year MRI scan. Twenty-two patients (82%) were still classified as having a clinically isolated syndrome at follow-up. In 17 of them there were no new clinical events and the MRI remained normal at follow-up. Five patients, who had all presented with an isolated optic neuritis, went on to develop new MRI abnormalities. In three of these there were no further clinical problems. However, two patients had recurrent episodes of optic neuritis, one with subsequent progressive visual failure. This latter patient exhibited a single lesion on the frontal horn of the left lateral ventricle on both follow-up studies. Despite evolution of recurrent or progressive optic nerve disease, these patients are still classified as having a clinically isolated syndrome according to the Poser criteria.

There were five patients with a clinically isolated syndrome at 10 years who had an EDSS of >3. Three had an optic neuropathy, one a brainstem syndrome and one a complete transverse myelitis without recovery.

## *Abnormal baseline MRI cohort (***n** *= 54)*

For those patients with an abnormal baseline MRI the outcome was very different. After 10 years, only seven patients (13%) still had a diagnosis of a clinically isolated syndrome, whereas two patients (4%) had clinically probable multiple sclerosis and 45 (83%) had progressed to clinically definite disease. Of those with clinically definite multiple sclerosis, 21 (39%) had benign multiple sclerosis, 11 (20%) relapsing/remitting disease with an EDSS of >3 and 13 (24%) had developed secondary progressive multiple sclerosis; one of these latter patients had died from severe disability as a result of multiple sclerosis 8 years after presenting with a brainstem syndrome. For those patients with an abnormal baseline MRI, the presence of infra-tentorial lesions did not confer any greater risk for the subsequent development of clinically definite multiple sclerosis; 17 out of 20 with infratentorial lesions versus 28 out of 34 without ($P$ = 0.35).

**Table 3** *Clinical subtype and EDSS at 10 years, and lesion load at baseline*

| Clinical subtype at 10 years | Lesions at baseline (median) | EDSS at 10 years (median) |
|---|---|---|
| Clinically isolated syndrome (29) | 0 (0–26) | 1 (0–6.5) |
| Clinically probable MS (4) | 4 (0–11) | 2 (1–2) |
| Benign MS (24) | 3 (0–74) | 2 (0–3) |
| Relapsing/remitting MS (11) | 13 (2–31) | 4 (3.5–6) |
| Secondary progressive MS (13) | 18 (2–29) | 6.5 (4–10) |

MS = multiple sclerosis.

In order to estimate the minimal rate of progression to multiple sclerosis for the original cohort of 129, an assumption could be made that none of those lost to follow-up developed clinically definite multiple sclerosis. In this scenario, the minimal rate of progression to multiple sclerosis for those with an abnormal scan would be 56% (45 out of 80) and only 6% (three out of 49) for those with a normal scan.

### *MRI–clinical correlation*

When the baseline lesion number was analysed, there was a strong correlation with the number of new lesions over the first 5 years ($n = 72$; $r = 0.65$; $P < 0.001$), the number of new lesions between 5 and 10 years ($n = 61$; $r = 0.38$; $P = 0.002$), and the overall number of new lesions over 10 years ($n = 61$; $r = 0.66$; $P < 0.001$). There was also a significant correlation between the lesion number at baseline and EDSS at 5 years ($n = 73$; $r = 0.56$; $P < 0.001$) and 10 years ($n = 81$; $r = 0.45$; $P < 0.001$). The number of new lesions over the first 5 years correlated with the change in EDSS over that time period ($n = 72$; $r = 0.52$; $P < 0.001$) (see also Table 1). There was a weaker, but still significant, correlation between the number of new lesions between 5 and 10 years and the change in EDSS over that time ($n = 61$; $r = 0.29$; $P = 0.03$) and between the number of new lesions over 10 years and change in EDSS ($n = 61$; $r = 0.34$; $P = 0.007$). Using Kruskal–Wallis one-way ANOVA there was a significant correlation between baseline lesion number and clinical subtype at 10 years ($P < 0.0001$; Table 3). Patients without clinical conversion over the first 5 years were subdivided into those who subsequently converted to clinically definite multiple sclerosis between 5 and 10 years and those who did not. We compared the two groups, but no significant association was found between the change in lesion load over the first 5 years and clinical outcome ($P = 0.13$). There was no relationship between sex, age or syndrome type at presentation and baseline lesion number.

Sixty-one patients underwent MRI scans at all three visits. Table 4 outlines the number of patients developing new lesions and clinically definite multiple sclerosis at each visit. A clear relationship is apparent between the development of further clinical episodes and new lesions on MRI. Table 5 shows the relationship between MRI and EDSS changes at each 5-year period for this subgroup. Although the correlation is significant in both periods, it is rather weaker for the second 5 years. When those who developed secondary progressive multiple sclerosis alone are analysed, the comparison over the 10 years is non-significant ($n = 7$; $r = 0.15$; $P = 0.75$), whereas there is a weak but significant correlation for those who developed clinically definite multiple sclerosis but without secondary progression, i.e. for those with benign and relapsing/remitting multiple sclerosis ($n = 35$; $r = 0.38$; $P < 0.05$). The median baseline lesion load for those patients who converted between 5 and 10 years was lower (median 3.5, range 0–11 lesions) than for those who converted earlier (median 5, range 0–74 lesions).

For each of the three clinical syndromes, progression to clinically definite multiple sclerosis was always greater in those with an abnormal baseline MRI, with slightly higher rates in those presenting with either an optic neuritis (89%) or brainstem syndrome (91%) than those with a spinal cord syndrome (67%) (Table 6).

## Discussion

This follow-up study has demonstrated that $T_2$-weighted brain MRI at presentation with a clinically isolated syndrome is strongly predictive of the risk of developing clinically definite multiple sclerosis, and of the type of disease course and the extent of disability over the next 10 years. The baseline MRI scans of the present cohort revealed disseminated abnormalities compatible with demyelination in 54 (67%). This was slightly greater than in the whole original cohort (80 out of 129; 62%) so there may be a minimal bias in follow-up in favour of patients with abnormal MRIs. These asymptomatic abnormalities could potentially represent one of two things: (i) disseminated presentation of a monophasic illness (acute disseminated encephalomyelitis) or (ii) clinically silent multiple sclerosis. However, 45 out of 54 (83%) patients with an abnormal baseline scan, developed clinically definite multiple sclerosis, and another two have clinically probable multiple sclerosis. Of the 40 with an abnormal initial scan who were reviewed at 5 and 10 years, only three (8%) had no new evidence of clinical or MRI activity (Table 4). This indicates that the MRI abnormalities at presentation were indeed due to clinically silent multiple sclerosis in the large majority of cases. Pathological activity due to multiple sclerosis may indeed be clinically silent. A number of studies have reported pathological changes compatible with multiple sclerosis in patients without clinical symptoms during life (Gilbert and Sadler, 1983; Engell, 1989). Also, frequent MRI scanning reveals new lesions about five to 10 times more often than clinical relapses in early relapsing remitting disease (Isaac *et al*., 1988; McFarland *et al*., 1992; Thompson *et al*., 1992).

The correlation between change in EDSS and change in lesion number merits close attention; there is a greater correlation over the first 5 years than when the time period of 5–10 years, or the whole 10 years is considered. This

**Table 4** *Number of patients developing clinically definite multiple sclerosis according to baseline, 5-year and 10-year MRI findings**

| Baseline | Normal MRI [21] | | | | Abnormal MRI [40] | | | |
|---|---|---|---|---|---|---|---|---|
| Follow-up at 5 years | Normal MRI [0/14] | | Abnormal MRI [1/7] | | Same [3/6] | | New lesions [22/34] | |
| Follow-up 10 years | Normal MRI [0/12] | New lesions [1/2] | Same [0/2] | New lesions [1/5] | Same [1/4] | New lesions [2/2] | Same [10/13] | New lesions [19/21] |

*The denominator defines the number of patients in the particular subgroup, while the numerator defines the number of patients who progressed to clinically definite multiple sclerosis in that subgroup.

**Table 5** *Change in EDSS and lesion number over time*

| | 0–5 years | 5–10 years | 0–10 years |
|---|---|---|---|
| Median change in EDSS (range) | 1 (0–6.5) | 0.5 (0–6) | 2 (0–6.5) |
| Median number of new $T_2$ lesions (range) | 5 (0–40) | 1 (0–22) | 7 (0–60) |
| Correlation between change in EDSS and number of new $T_2$ lesions | | | |
| *r* | 0.45 | 0.29 | 0.34 |
| *P* | $< 0.0001$ | 0.03 | 0.007 |

**Table 6** *The rate of progression to clinically definite multiple sclerosis overall and for each clinical syndrome according to the baseline MRI*

| | Normal MRI | Abnormal MRI |
|---|---|---|
| All cases | 3/27 (11%) | 45/54 (83%) |
| Optic neuritis | 1/14 (7%) | 25/28 (89%) |
| Brainstem syndrome | 0/5 (0%) | 10/11 (91%) |
| Spinal cord syndrome | 2/8 (25%) | 10/15 (67%) |

difference may be as a result of biological mechanisms and/or measurement sensitivity.

(i) *Biological mechanisms.* When one considers the group of patients who continue to experience relapses, but with a stable baseline between the relapses, i.e. relapsing/remitting and benign patients, disability arises from new lesions which result in inflammation and demyelination. This causes associated changes on MRI. In secondary progressive patients, the other factors such as axonal degeneration and progressive atrophy may play a more significant role (Davie *et al*., 1995; Losseff *et al*., 1996*a, b*). We found a greater correlation over time between change in lesion number and the EDSS in the relapsing/remitting groups than in those patients who entered secondary progression, and the latter group contribute to the weaker correlation in the second quinquennium.

(ii) *Measurement sensitivity.* There is less change in both EDSS and lesion number between 5 and 10 years than over the first 5 years, so there is less opportunity to demonstrate a correlation. Also the number of patients with secondary progressive disease who underwent all three scans is small, so firm long-term conclusions on this group are not possible. Nevertheless, the weaker correlations between new lesion number and EDSS change for the whole 10-year period than for the first 5 years suggests that a dissociation of these outcomes is becoming more apparent over time.

The risk of progression to clinically definite multiple sclerosis appears to be greatest in the first 5 years. Overall, by this time 49% of patients had progressed, whereas between 5 and 10 years a further 10% had progressed. When one considers all the available evidence it is quite clear that the presence of brain MRI abnormalities at presentation with a clinically isolated syndrome is predictive not only of the risk of developing clinically definite multiple sclerosis but also the extent of disability and type of disease over the next 10 years. This has obvious implications for patient and physician alike.

Patients with a normal scan may be given an optimistic prognosis not only for the long-term risk of developing multiple sclerosis, which is low, but also for the development of disability. Only three out of 27 (11%) have progressed to clinically definite multiple sclerosis in each case with minimal disability. For those with an abnormal scan the prognosis is less certain but not necessarily poor; 21 out of 45 (47%) of those developing multiple sclerosis had only minimal disabilities at follow-up.

The data also have implications for patient-selection for therapeutic trials aimed at preventing or delaying the development of multiple sclerosis and disability (Miller *et al.*, 1996). Recent studies using interferon β have shown a modest disease-modifying effect in relapsing/remitting multiple sclerosis (IFNB Multiple Sclerosis Study Group, 1993, 1995; Jacobs *et al*., 1996). The main issue is the selection of patients with high risk of progression over 2–5 years. The risk of progression in the first 2–5 years appears to be greatest for those with either four or more lesions, or three lesions, one of which is periventricular (Beck *et al.*, 1993; Morrissey *et al*., 1993). These MRI entry-criteria are currently being used in phase III treatment trial to determine whether the use of interferon β in patients with a clinically isolated syndrome delays the development of clinically definite multiple sclerosis. Our present data are consistent with those of previous studies but the risk is increased on longer-term follow-up in that >85% of patients with two or more MRI

lesions progressed to multiple sclerosis. A more selective appraisal of different MRI criteria has been developed by Barkhof *et al*. (1997). A model based on four variables (gadolinium enhancement, juxtacortical, infratentorial and periventricular lesions) has a high predictive value for the development of clinically definite multiple sclerosis.

The long-term outlook in relation to disability is somewhat different. For patients with >10 lesions at presentation, three-quarters had significant functional impairment 10 years later, i.e. an EDSS of >3. For those with <10 lesions, however, approximately three-quarters were minimally impaired (EDSS ⩽3). The use of possible disease-modifying treatments must be a balance between (i) the risk of developing not only multiple sclerosis but also disability and (ii) the long-term, and as yet unknown, side effects of the agent. It seems prudent therefore to follow strict guidelines for the inclusion of these patients in treatment trials for multiple sclerosis; a more conservative selection approach, e.g. ⩾10 lesions, may be appropriate.

There are some limitations to be considered in interpreting our data: (i) the initial images were performed on a 0.5-T machine using 5-mm slices which is slightly less sensitive than more modern 1.5-T machines and 3-mm slices; (ii) $T_1$-weighted post-gadolinium images were not performed: gadolinium enhancement at presentation confers an even higher risk of early conversion to multiple sclerosis (Tas *et al*., 1995); (iii) change in hypointense areas on $T_1$-weighted images (not available in our study) has been shown to correlate more closely with disability than hyperintensities on $T_2$-weighted scans (van Walderveen *et al*., 1995); and (iv) the spinal cord was not imaged [sagittal fast spin echo imaging of the spinal cord shows lesions in approximately one-third of patients with a clinically isolated syndrome (O'Riordan *et al.*, 1996), and in established multiple sclerosis occasionally abnormalities may only be evident in the spinal cord (Kidd *et al*., 1993)]. For all these reasons we are recruiting a new cohort of patients with clinically isolated syndromes, who are being followed prospectively with high resolution brain and spinal cord imaging, utilizing multiple sequences.

Despite these limitations there is no doubt that conventional $T_2$-weighted brain MRI at presentation with a clinically isolated syndrome is predictive of the long-term risk of developing multiple sclerosis, the type of disease and the extent of disability. As such, it has a major role in assigning prognosis for individual patients and in selecting those most appropriate to enter trials of putative disease-modifying therapies.

## Acknowledgement

The two scanners were provided by the Multiple Sclerosis Society of Great Britain and Northern Ireland.

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*Received June 6, 1997. Revised September 14, 1997. Accepted October 20, 1997*