

Spinal MRI in patients with suspected multiple sclerosis and negative brain MRI

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Summary

Although MRI detects the white matter lesions of multiple sclerosis within the brain with high sensitivity, a minority of patients have normal brain MRI. We describe 20 patients, selected from over 170 who had undergone brain imaging with minimal ($n = 12$) or no ($n = 8$) abnormalities (median number of lesions = 1, range, 0–3) but in whom spinal MRI was abnormal. Twelve had clinically definite or laboratory supported definite multiple sclerosis according to the Poser criteria; one had clinically probable disease and seven, not fulfilling the Poser criteria, were classified as possible

multiple sclerosis. All had presented with symptoms and signs referable to the spinal cord or optic nerves. Eleven had a primary progressive course, eight relapsing–remitting and only one secondary progressive. Moderate or severe disability was the rule in the primary progressive cases; all the relapsing–remitting patients had minimal disability. All had at least one lesion visible in the spinal cord (median 2; range 1–6). In patients in whom the diagnosis of multiple sclerosis is not supported by abnormalities on brain MRI, imaging of the spinal cord can be of considerable value.

Key words: MRI; multiple sclerosis; myelopathy; spinal cord

Abbreviations: EDSS = expanded disability status scale

Introduction

MRI of the brain is established as a useful test in the diagnosis of multiple sclerosis (Young *et al.*, 1981; Lukes *et al.*, 1983; Runge *et al.*, 1984). Abnormalities are found in over 95% of patients with clinically definite disease (Runge *et al.*, 1984; Ormerod *et al.*, 1987). Although white matter abnormalities similar to those found in multiple sclerosis can be found in a variety of other conditions, the finding of a typical distribution of lesions, with a periventricular predominance, in conjunction with a suggestive clinical picture in a young adult, allows a confident diagnosis to be made. Prior to the advent of MRI, in patients presenting with progressive myelopathy, dissemination of lesions in space permitting a diagnosis of multiple sclerosis was usually sought by electrophysiological investigation or prolonged follow-up (Marshall, 1955; McAlpine, 1955; Hübbe and Mouritzen Dam, 1973; Bynke *et al.*, 1977; Paty *et al.*, 1979); examination of the CSF for locally synthesized oligoclonal immunoglobulin bands, implying inflammation within the CNS, could provide further support for the diagnosis (Link *et al.*, 1976; Bynke *et al.*, 1977; Paty *et al.*, 1979; Steiner

et al., 1988). Many authors have emphasized the value of brain MRI in such patients (Edwards *et al.*, 1986; Miller *et al.*, 1987; Miska *et al.*, 1987; Mauch *et al.*, 1988; Paty *et al.*, 1988; Marti-Fabregas *et al.*, 1989; Filippi *et al.*, 1990); according to the commonly used Poser criteria (Poser *et al.*, 1983), the finding of multiple lesions in the brain can permit a diagnosis of clinically probable multiple sclerosis (or laboratory supported definite multiple sclerosis if there are oligoclonal bands in the CSF) assuming the lesions can be shown to be disseminated in time on repeated study.

Nevertheless, in a minority of cases of multiple sclerosis the brain is not involved (Allen *et al.*, 1981). In the series of Ikuta and Zimmerman (1976) of 70 autopsies collected in the United States, nine cases (13%) showed disease limited to the spinal cord and optic nerves. Patients are also occasionally encountered who are found at autopsy (Weinshenker *et al.*, 1990) or biopsy (Meurice *et al.*, 1994) to have an isolated spinal cord lesion of the type typically found in multiple sclerosis. Several series report occasional patients, some of whom fulfil the criteria of definite multiple sclerosis, in

whom MRI reveals lesions typical of multiple sclerosis only in the spinal cord and not in the brain (DeLaPaz *et al.*, 1986; Nilsson *et al.*, 1987; Honig and Sheremata, 1989; Tippett *et al.*, 1991; Kidd *et al.*, 1993). Using recent technical developments which improve the quality of spinal cord images (Thorpe *et al.*, 1993), we have identified 20 such patients; their clinical and radiological characteristics are the basis of this report.

Patients and methods

Patients were selected from over 170 with possible, probable or definite multiple sclerosis who had undergone brain and spinal cord MRI between April 1992 and August 1994. This included 80 patients systematically recruited as part of a previous study (Kidd *et al.*, 1993). However, in addition patients presenting with predominantly spinal symptoms and those who had previously had normal brain MRI were specifically sought. Patients were included if they had one or more spinal cord lesion in the presence of normal or near normal brain MRI: this was defined as three or fewer lesions and not satisfying the criteria of Fazekas *et al.* (1988) for the diagnosis of multiple sclerosis. The Fazekas criteria require the presence of at least three cerebral white matter lesions and any two out of three of the following: (i) a lesion adjacent to the body of the lateral ventricles; (ii) an infratentorial lesion; (iii) a lesion ≥ 6 mm in diameter. During the study period no patients with definite or probable multiple sclerosis and only one patient with possible multiple sclerosis were identified who had both normal brain and spinal cord imaging. Brain and spinal imaging in all cases was performed on a 1.5 T Signa scanner (IGE Medical Systems, Milwaukee, Wisc., USA). Axial proton density and T₂-weighted brain images were acquired with a standard quadrature head coil using fast spin echo (FSE) or spin echo (SE) pulse sequences: typical parameters were FSE_{3100/19,95}, 192×256 matrix with a 24 cm field of view, 4 mm contiguous interleaved slices, one excitation. Contiguous, interleaved, 3 mm sagittal T₂-weighted FSE images of the spinal cord were acquired using a spinal multi-array coil (Roemer *et al.*, 1990). Moderately and more heavily T₂-weighted data sets (FSE_{2500/51} and _{2500/102}, respectively) were collected, using a 512×512 matrix and 48 cm field of view; in one case spin echo images (SE_{4000/80}) were acquired instead.

All images were reviewed by one of us (I.M.). Lesions were defined as areas of unequivocal high signal within the parenchyma of brain or spinal cord.

From the clinical history and the results of investigations patients were classified as definite (laboratory supported definite or clinically definite multiple sclerosis) or probable multiple sclerosis (laboratory supported probable or clinically probable multiple sclerosis) according to the Poser criteria (Poser *et al.*, 1983). Patients were classified both with and without the results of the spinal MRI taken into consideration. Those patients (without clinical or paraclinical evidence of dissemination in space) that could not be classified

were designated possible multiple sclerosis. Disease course was classified as (i) relapsing–remitting, in which there was a history of relapses and remission without progressive deterioration; (ii) primary progressive, in which there was progressive deterioration from outset with no relapses or remissions; or (iii) secondary progressive in which, after an initial relapsing–remitting course, there was progressive deterioration, with or without superimposed relapses.

Disability was graded according to the expanded disability status scale (EDSS) of Kurtzke (1983).

Results

The clinical and MRI details are summarized in Table 1. There were 10 men and 10 women aged 25–63 (median 42) years. Disease duration varied from 6 months to 18 years, with age at onset being from 23 to 55 (median 38) years. Including the results of spinal MRI in classification, eight patients were regarded as clinically definite, four as laboratory supported definite, one clinically probable and seven possible multiple sclerosis. Spinal MRI changed a classification of laboratory supported definite to clinically definite multiple sclerosis in three cases (6, 8 and 9). All the patients with possible multiple sclerosis had a clinically isolated myelopathy, one of whom had been suspected of having an intrinsic spinal cord tumour and had undergone biopsy of the cord. This had shown perivascular lymphocytic infiltration, with demyelination and gliosis. Eight patients had an relapsing–remitting disease course, 11 primary progressive and only one secondary progressive. Oligoclonal bands were found in the CSF in 13 out of the 15 patients in whom they were sought. Ten out of 18 patients tested had abnormal visual evoked potentials. Disability varied from none (minimal neurological signs only, EDSS 1) to restricted to a wheelchair with severe tetraparesis (EDSS 8.0). The median EDSS was 4.0.

Brain MRI

Eight patients (three relapsing–remitting, four primary progressive and one secondary progressive) had a completely normal brain MRI and six a solitary lesion only. Nearly all the lesions were small (under 5 mm), discrete (i.e. not periventricular) and supratentorial; hence the Fazekas criteria were not fulfilled in any case.

Spinal cord MRI

Five patients had a solitary cord lesion, nine had two and six more than two. The maximum number of lesions was six. There was no obvious relationship between disability and the number of cord lesions. For instance, Patient 17 had a solitary cord lesion despite an EDSS of 7.0, whereas Patient 9 had four lesions, with an EDSS of 2.0. There was no difference in the number of spinal cord lesions between relapsing–remitting and primary progressive subgroups.

Table 1 Clinical and MRI characteristics

Case	Sex	Age (years)	Duration (years)	Presentation	Course	EDSS	OCBS	VEP	BAEP	SEP	Poser*		No. brain lesions	No. spinal cord lesions
											(-MRI)	(+MRI)		
1	M	50	8	M	PP	3.5	+ve	Abn	-	Abn	LSDMS	LSDMS	1	6
2	F	39	8	S, Sph	PP	4.0	+ve	Abn	-	Abn	LSDMS	LSDMS	2	2
3	M	45	18	M	PP	7.0	+ve	Abn	-	N	LSDMS	LSDMS	2	2
4	M	42	4	M	PP	6.5	+ve	N	-	-	POSS	POSS	1	2
5	M	35	2	Sph, S	RR	2.0	+ve	Abn	-	Abn	CDMS	CDMS	1	1
6	F	37	12	S	RR	1.0	+ve	N	-	N	LSDMS	CDMS	2	2
7	F	42	18	S	RR	2.0	+ve	Abn	N	-	CDMS	CDMS	2	6
8	F	35	3	S	RR	3.0	+ve	N	N	Abn	LSDMS	CDMS	0	1
9	M	46	0.5	M, S	RR	2.0	+ve	N	N	-	LSDMS	CDMS	0	4
10	F	25	2	S	RR	2.0	+ve	Abn	-	N	CDMS	CDMS	2	2
11	F	26	0.5	ON	RR	3.0	-	Abn	-	-	CDMS	CDMS	1	2
12	F	63	8	S	SP	5.5	-ve	-	-	-	POSS	POSS	0	1
13	F	41	4	M	RR	2.0	-	N	N	Abn	CDMS	CDMS	0	2
14	M	56	12	M	PP	8.0	-	Abn	-	Abn	CPMS	CPMS	3	5
15	M	41	0.75	ON	PP	4.5	+ve	Abn	-	-	LSDMS	LSDMS	1	3
16	M	47	6	M	PP	2.0	-	Abn	N	Abn	POSS	POSS	1	3
17	F	55	14	M	PP	7.0	-	-	-	-	POSS	POSS	0	1
18	M	54	7	M	PP	7.5	+ve	N	N	Abn	POSS	POSS	0	4
19	F	39	1.5	M, S	PP	4.0	+ve	N	Abn	N	POSS	POSS	0	2
20	M	41	0.5	M	PP	7.5	-ve	N	N	N	POSS	POSS	0	1

OCBS = oligoclonal bands (+ve = positive, -ve = negative); VEP = visual evoked potentials; BAEP = brainstem auditory evoked potentials; SEP = sensory evoked potentials; M = motor; S = sensory; Sph = sphincter disturbance; ON = optic nerve; PP = primary progressive; RR = relapsing-remitting; SP = secondary progressive; Abn = abnormal; N = normal; LSDMS = laboratory supported definite multiple sclerosis; LSPMS = laboratory supported probable multiple sclerosis; POSS = possible multiple sclerosis (not defined in Poser criteria); CDMS = clinically definite multiple sclerosis; CPMS = clinically probable multiple sclerosis; - = not done or not available. *For the purposes of classification, the upper age limit specified in the Poser criteria (55 years), has been ignored: the results of classification both without and with the spinal MRI data are included (-MRI and +MRI, respectively).

Illustrative cases

Case 1

Eight years previously, a 50-year-old man first noticed dragging of the left foot. This gradually worsened over the ensuing years; 3 years later the left arm was also affected. He had never had sensory or bladder symptoms. On examination, the cranial nerves were normal. Tone was increased on the left side, with a moderate pyramidal weakness of the left arm and leg. Co-ordination was normal. Both plantar responses were extensor. There was some diminution of vibration sensation in both legs. Examination of the CSF showed locally synthesized oligoclonal bands. Visual evoked potentials were initially normal but subsequently showed latency prolongation, permitting classification as laboratory supported definite multiple sclerosis with a primary progressive course. MRI of the brain revealed one small lesion in the posterior frontal white matter only (Fig. 1A). Within the cord, however, were six lesions, three in the cervical and three in the thoracic region (Fig. 1B).

Case 13

A 41-year-old woman gave a 4-year history of relapsing and remitting sensorimotor dysfunction. She initially presented with loss of control of both legs, with a sensory level at the waist. This recovered completely in 6 weeks. Four months

later she experienced weakness and sensory disturbance in the left hand associated with Lhermitte's phenomenon. Four further episodes, implicating the spinal cord at different levels, had left her with little disability. On examination she had mild weakness of the left hand, and decreased light touch and pinprick sensation down the left side. Reflexes were brisk, but both plantars were flexor. Lumbar puncture was not performed. Visual and auditory evoked potentials were normal, somatosensory evoked potentials abnormal. Brain MRI was normal. Spinal cord MRI revealed two lesions within the cervical cord. On the basis of clinical and radiological evidence of disseminated lesions within the cord, a diagnosis of clinically definite multiple sclerosis was made.

Discussion

In patients in whom a diagnosis of multiple sclerosis is suspected, spinal cord MRI can fulfil three main functions. First and foremost, in patients presenting with symptoms referable to the spinal cord, MRI is the optimal way of excluding an alternative (particularly compressive) cause. Secondly, spinal cord MRI slightly increases the sensitivity with which multiple sclerosis lesions are detected. In the current study we found eight patients (three with definite multiple sclerosis) with completely normal brain MRI from over 170 patients who have undergone both brain and spinal

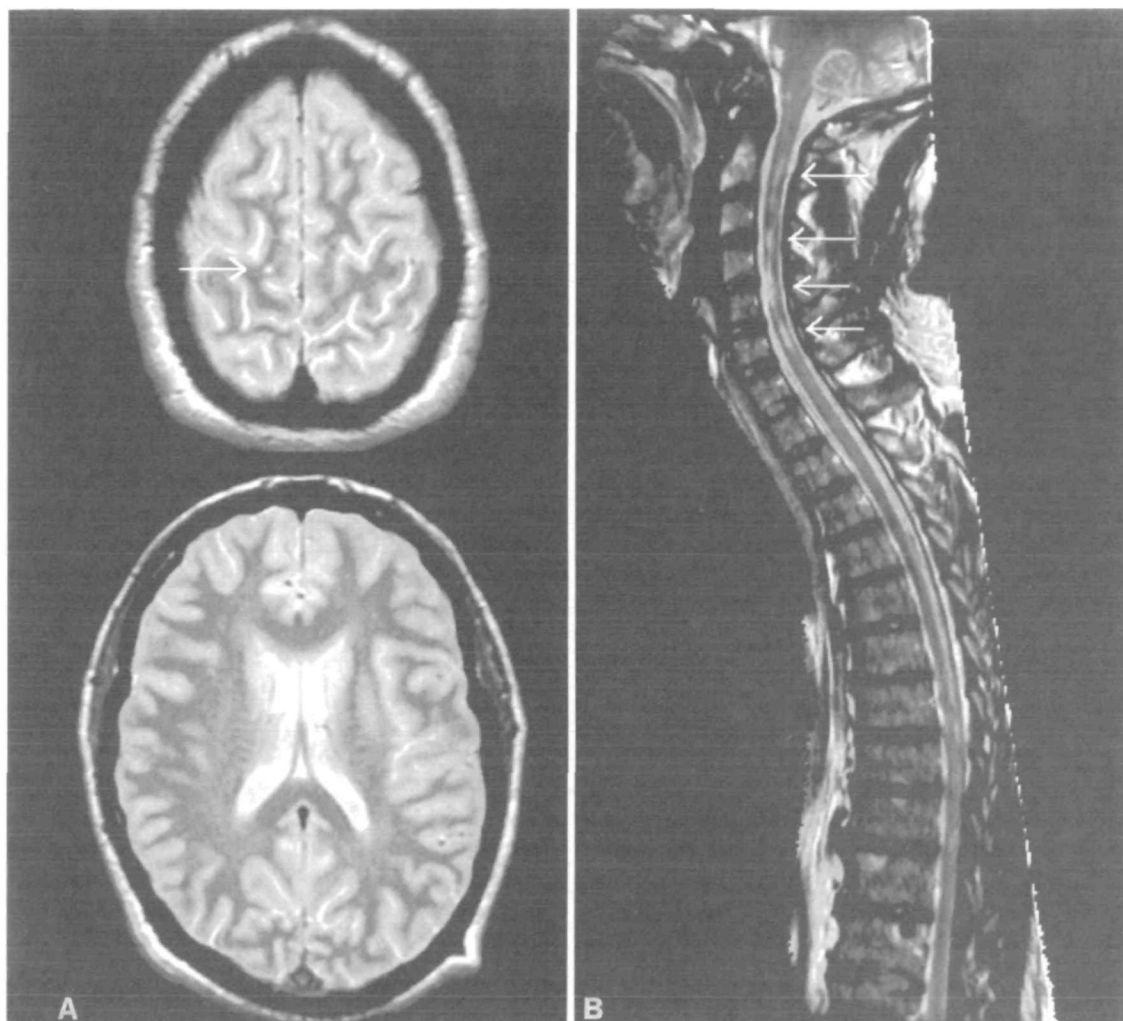


Fig. 1 Case 1. Laboratory supported definite multiple sclerosis with a primary progressive course. (A) There is a solitary subcortical white matter lesion (arrowed). No periventricular lesions are seen. (B) There is extensive disease within the cervical cord (arrowed). Additional lesions were also found within the thoracic cord but are not seen on this slice.

cord imaging: the denominator is slightly imprecise because of the difficulty in defining 'possible' multiple sclerosis. Despite this imprecision, and a degree of selection bias which would be expected to increase the proportion of patients with a normal brain MRI, our finding that brain MRI is abnormal in ~95% of multiple sclerosis patients differs little from previous reports in which there was a systematic survey of all available patients (Runge *et al.*, 1984; Ormerod *et al.*, 1987). Using current MR technology, our study suggests that the addition of spinal cord MRI may increase sensitivity to nearly 100%. Whereas other workers (Honig and Sheremata, 1989) at lower field strength and with conventional surface coils found 15 of 77 patients with definite multiple sclerosis to have normal brain and spinal cord imaging, we have yet to find a case of definite multiple sclerosis with completely normal imaging of brain and spinal cord using multi-array coils and fast spin echo pulse sequences for spinal imaging.

Finally, MRI of the spinal cord increases specificity. White matter lesions in the brain are common in health, especially

with advancing age (Brand-Zawadzki *et al.*, 1985; Awad *et al.*, 1986; George *et al.*, 1986; Gerard and Weisberg, 1986). In the older age group, even rigorous criteria such as those of Fazekas are less specific (Offenbacher *et al.*, 1993). Twelve patients in the current series were over the age of 40 years, and five aged over 50 years. The finding of one or two white matter brain lesions in these patients does little to support the diagnosis of multiple sclerosis. In this context, the finding of lesions in the cord is more specific, as previous work has suggested that these do not develop with age *per se*: Thorpe *et al.* (1993) found no abnormalities in 17 healthy individuals aged >50 years. The results of this study also shows the considerable diagnostic value of examination of the CSF and visual evoked potentials in patients with suspected multiple sclerosis but normal brain MRI. Oligoclonal bands were present in 87% of those tested and abnormal visual evoked potentials in 56%.

Eleven of the patients (55%) in the current series had a primary progressive course. In the general multiple sclerosis

population a primary progressive course only occurs in 5–10% (Weinshenker *et al.*, 1989). Patients with primary progressive multiple sclerosis have lower lesion burden in the brain than those with secondary progressive multiple sclerosis (Thompson *et al.*, 1990); consequently they have a higher proportion of their total lesion load within the spinal cord (Kidd *et al.*, 1993). It is therefore not surprising that this group of patients is over-represented in the current series. It is notable that many of the primary progressive cases were severely disabled.

All eight of the relapsing–remitting cases in this series had minimal disability (EDSS ≤ 3). In some patients within this subgroup the finding of a normal brain MRI may relate to short disease duration (especially Patients 9 and 11), as has been found by other authors (Mauch *et al.*, 1988; Honig and Sheremata, 1989); six of our patients had a disease duration of < 5 years. However, there were two patients who, despite long disease durations (12 and 18 years), also had essentially normal brain imaging.

It is of interest that we have found the same pattern of MRI abnormalities (i.e. predominantly or exclusively in the spinal cord) in two groups of patients with a distinctly different clinical course: one with primary progressive disease and often severe disability, the other with relapsing and remitting disease and minimal disability. This finding once again emphasizes the well documented discordance between brain and/or spinal cord lesion load on conventional MRI and locomotor disability. The possible explanations for this discrepancy are reviewed elsewhere (McDonald *et al.*, 1992; Miller, 1994).

All eight patients with a relapsing–remitting course had clinical, electrophysiological or spinal MRI evidence of more than one lesion and therefore could be classified as clinically definite multiple sclerosis. (NB We have made the assumption that two attacks implicating different parts of the spinal cord, as described in Patient 13, for instance, can be considered disseminated in space. If the spinal cord is considered a single site, then the diagnosis is less certain, although the Poser criteria do not specifically consider the case of recurrent episodes affecting the same site with evidence, clinical or paraclinical, of dissemination in space.) With a relapsing–remitting course implicating different sites, but clinical signs or paraclinical evidence of only one lesion, the Poser criteria permit a diagnosis of laboratory supported definite multiple sclerosis if oligoclonal bands are present or clinically probable multiple sclerosis if bands are absent or the CSF has not been examined. In the absence of the information from spinal MRI, Patients 6, 8 and 9 could only be classified as laboratory supported definite (rather than clinically definite) multiple sclerosis, and had the CSF not been examined they could only have been classified as clinically probable.

In patients with a progressive course from onset, even in the presence of oligoclonal bands in the CSF, the Poser criteria do not permit a diagnosis of definite multiple sclerosis unless there is clinical or paraclinical evidence of dissemination in space and time. If oligoclonal bands are absent but there is evidence of dissemination in space and time, the

diagnosis is clinically probable. In the present series, four of the primary progressive cases could be classified as laboratory supported definite multiple sclerosis and one as clinically probable multiple sclerosis. Six could only be classified as possible multiple sclerosis, despite multiple cord lesions being present in four and oligoclonal bands in three; in such patients serial imaging, by showing the development of new lesions, would allow a more certain diagnosis to be made. Given the relative specificity of cord lesions for demyelination, we suggest that any future revisions to the diagnostic classification of multiple sclerosis should take account of spinal MRI findings.

We conclude that the finding of a normal brain MRI, although rare, is nevertheless quite compatible with a diagnosis of multiple sclerosis. Such patients are likely to have either a primary progressive or relapsing–remitting course and, if the latter, are unlikely to be disabled. Spinal cord MRI in such patients frequently displays intrinsic cord lesions, the presence of which is of considerable diagnostic value.

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