Asymptomatic spinal cord lesions in clinically isolated optic nerve, brain stem, and spinal cord syndromes suggestive of demyelination

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Abstract

Objectives—Conventional T2 weighted MRI studies have highlighted the fact that the presence of clinically silent brain lesions increases the risk of developing clinically definite multiple sclerosis after an isolated syndrome of the optic nerve, brain stem, or spinal cord. The objectives of the present study are: (1) to show whether or not these patients also have asymptomatic abnormalities of the spinal cord, and (2) to recruit a new cohort of such patients using high resolution MRI of both brain and spinal cord.

Methods—The brain was imaged in the axial plane with 3 mm thick contiguous slices using a proton density and T2 weighted fast spin echo (FSE) sequence; a T1 weighted sequence after the injection of gadolinium-DTPA; and a fast fluid attenuated inversion recovery (fFLAIR) sequence. The spinal cord was imaged in the sagittal plane with 3 mm thick slices using a T2 weighted FSE and a T1 weighted gadolinium enhanced sequence.

Results—Thirty three patients, mean age 31 (16–46) were recruited. There were 14 men and 19 women. Brain MRI was abnormal in 22 (67%); no patient was seen with abnormalities on *only* one or other sequence. Six patients (18%) displayed one or more gadolinium enhancing lesions on brain MRI. In the spinal cord, nine (27%) patients displayed one or more clinically silent lesions on FSE. Two patients showed one and two gadolinium enhancing lesions in the spinal cord respectively.

Conclusion—This high incidence of spinal cord lesions emphasises that asymptomatic demyelinating lesions may also involve clinically eloquent pathways. Follow up studies are required to determine their prognostic importance.

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Keywords: isolated syndrome; spinal cord

Adults presenting with a clinically isolated syndrome of the CNS which is suggestive of demyelination have a substantial risk of developing clinically definite multiple sclerosis.¹⁻⁷ Some clinical studies have shown that for patients presenting with an isolated optic neuritis the overall risk of developing clinically

definite multiple sclerosis is between 34% and 75%. A definitive diagnosis cannot be made at presentation, however, as dissemination in time and place has not occurred.⁸

There have been numerous MRI related studies using T2 weighted brain imaging in patients with isolated optic neuritis or clinically isolated syndromes of the brain stem and spinal cord. After short term follow up of one to five years, the overall risk of developing clinically definite multiple sclerosis is much greater for those patients with an abnormal brain MRI (mean 44% (range 23%-93%)) than for those with a normal scan at presentation (mean 4% (range 0%-33%)).⁹⁻²⁰ Furthermore, there is a correlation between the number of lesions at presentation and the subsequent risk of progression to multiple sclerosis over two to five years.^{16 17}

These brain MRI findings are of major importance in the counselling of individual patients with regard to their prognosis and in selecting the most appropriate candidates for inclusion into therapeutic trials aimed at delaying the evolution from an isolated syndrome to definite multiple sclerosis.²¹ However, there are as yet no data on spinal cord MRI findings in such cohorts. The importance of spinal cord lesions lies in their presumed greater potential to result in clinical symptoms and disability than white matter lesions, involving as they do clinically eloquent pathways (pyramidal tracts, spinothalamic tracts, and posterior columns). Cord lesions are also potentially more specific for demyelination than cerebral white matter lesions, especially in older adults.²² It is thus important to determine the frequency of asymptomatic cord lesions at presentation with a clinically isolated syndrome and to assess whether their presence and extent is predictive of the future clinical course. The present study describes the frequency of such abnormalities in a prospectively recruited cohort of patients with clinically isolated syndromes.

Materials and methods

Patients were recruited from the wards and clinics at the National Hospital for Neurology and Neurosurgery, Queen Square and from the physicians' clinic at Moorfields Eye Hospital, London, UK. Inclusion criteria were (1) a clinically isolated syndrome suggestive of demyelination, involving the optic nerve, brain stem, or spinal cord; the syndrome had to be of acute (less than 14 days to peak severity) or subacute onset (14 to 28 days to peak severity);

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Table 1 Syndrome type, age at presentation, sex, and MRI findings of each patient

Patient	Syndrome	Age	Sex	MRI brain*			MRI cord*	
				T2	fFLAIR	Gd	T2	Gd
1	ON	21	F	-	-	-	-	-
2	ON	28	M	-	-	-	-	-
3	BS	40	F	+	+	-	-	-
4	BS	22	M	+	+	-	-	-
5	BS	30	M	-	-	-	-	-
6	ON	45	F	+	+	-	+	-
7	ON	46	F	+	+	-	+	-
8	ON	33	F	+	+	-	+	+
9	ON	35	M	+	+	-	-	-
10	BS	33	F	+	+	-	-	-
11	BS	33	M	-	-	-	-	-
12	ON	24	F	+	+	-	+	-
13	ON	40	M	+	+	-	+	-
14	BS	32	F	+	+	+	+	-
15	ON	42	F	+	+	-	+	-
16	ON	33	M	-	-	-	-	-
17	ON	27	F	+	+	+	+	-
18	ON	37	M	-	-	-	-	-
19	ON	36	M	+	+	+	-	-
20	ON	32	F	+	+	+	-	-
21	BS	34	F	-	-	-	-	-
22	SC	26	F	+	ND	-	-	-
23	SC	25	F	-	-	-	-	-
24	SC	33	M	+	+	+	+	+
25	SC	28	F	-	-	-	-	-
26	ON	22	F	-	-	-	-	-
27	ON	31	F	+	+	-	-	-
28	ON	35	M	+	+	-	-	-
29	ON	25	F	+	+	+	-	-
30	ON	16	M	+	+	-	-	-
31	BS	30	F	+	+	-	-	-
32	BS	37	M	+	+	-	-	-
33	BS	28	M	-	-	-	-	-
Total				22	21	6	9	2

ON = optic neuritis; BS = brain stem syndrome; SC = spinal cord syndrome; M = male, F = female; ND = not done; * Asymptomatic abnormalities present (+) or absent (-).

(2) male or female patients aged 16 to 50 years; (3) the onset of the syndrome was within three months of the examination; and (4) appropriate investigations did not disclose an alternative diagnosis to that of suspected demyelination. Informed consent was obtained from all patients before inclusion into the study. All patients underwent a full neurological examination and disability was rated using Kurtzke's extended disability status scale (EDSS).²³

Magnetic resonance imaging was performed on a 1.5T Signa (General Electric, Milwaukee, WI, USA) scanner provided by the Multiple Sclerosis Society of Great Britain and Northern Ireland. The brain was imaged in the axial plane with 3 mm thick contiguous slices using a proton density and T2 weighted fast spin

echo (FSE) sequence (TR=3200 ms, effective TE=15/95 ms); a T1 weighted sequence (TR=600 ms, TE=14 ms) after the injection of gadolinium-DTPA (0.1 mmol/kg); and a fast fluid attenuated inversion recovery (fFLAIR) sequence (TI=2600 ms, TR=11000 ms, effective TE=143 ms, ETL=8). In each case the field of view was 25 cm, matrix 256², and NEX 1. The spinal cord was imaged in the sagittal plane with 3 mm thick slices using a T2 weighted FSE (TR=2500 ms, effective TE=56/98 ms) and a T1 weighted gadolinium enhanced sequence (TR=500, TE=19).

The images were reported by a single observer blinded to the clinical state. They were reported as normal if there were no focal abnormalities compatible with demyelination, or, in the case of a brain stem or spinal cord syndrome, when only the symptomatic lesions were seen. Images were reported as abnormal if there were one or more asymptomatic lesions compatible with demyelination. Four sites were identified in the brain: (1) posterior fossa, (2) discrete—cerebral white matter or basal ganglia discrete from cortex or ventricles, (3) subcortical/cortical—lesions in the subcortical white matter adjacent to the cortex, or in the cortex, and (4) periventricular. Lesions were graded according to their largest diameter as small (<5 mm), medium (5–10), large (>10), or confluent. Intrinsic spinal cord lesions were identified only if areas of high signal intensity were seen on both the proton density (TE=56 ms) and T2 weighted (TE=98 ms) images. The high signal areas were located on sagittal images as being anterior, posterior, central (a margin of normal cord is visible both anterior

Table 2 Number of patients with an abnormal brain and spinal cord MRI (symptomatic lesions excluded) overall and for each clinical subgroup

	No	(+) Brain MRI	(+) Spinal cord MRI
Optic nerve	19	14 (74)	7 (37)
Brainstem	10	6 (60)	1 (10)
Spinal cord	4	2 (50)	1 (25)
Total	33	22 (67)	9 (27)

Table 3 The mean number of brain lesions on each sequence in patients (n=22) with abnormal brain MRI

Site	FSE	fFLAIR	T1 Post-Gd
Discrete	3 (0-19)	4 (0-19)	0.1 (0-1)
Subcortical	2.6 (0-2)	3 (0-22)	0.1 (0-2)
Posterior fossa	1.4 (0-6)	0.4 (0-2)	0.1 (0-1)
Periventricular	3.4 (0-14)	3.8 (0-18)	0.1 (0-1)
Total	11 (1-33)	11 (1-37)	0.45 (0-2)

Table 4 Mean number and site of spinal cord lesions in patients ($n=9$) with an abnormal spinal cord MRI (symptomatic lesion excluded)

Site	FSE	Gd
Cervical	1.11 (0-2)	0.3 (0-2)
Thoracic	0.78 (0-4)	0
Lumbar	0	0
Total	1.89 (1-4)	0.3 (0-2)

and posterior to the lesion), or full thickness (in the anteroposterior direction). Lesion size was scored according to maximum length along the cord in the sagittal image as small (<5 mm), medium (5–10 mm), or large (>10). Lesion number and load were calculated for the cervical, thoracic, and lumbar cord individually, as well as for the whole cord.

Results

Thirty three patients were recruited (table 1). Their mean age was 31 (range 16–46). There were 14 male and 19 female patients; mean EDSS (as a result of the clinically isolated syndrome) 1.95 (range 0–8). Nineteen patients presented with optic neuritis, 10 with a brain stem syndrome, and four with a spinal cord syndrome (table 2). Brain MRI was abnormal in 22 (67%) patients, with one or more asymptomatic, focal lesions compatible with demyelination (table 3). For those patients with an abnormal scan, abnormalities were seen on both fast FLAIR and FSE sequences and never on a single sequence alone. A larger number of cerebral hemispheric lesions was seen with fast FLAIR than FSE; the reverse applied in the posterior cranial fossa. Six patients (18%) displayed one or more gadolinium enhancing lesions on brain MRI.

In the spinal cord, nine (27%) patients displayed one or more clinically silent lesions on FSE (table 4). Lesions were seen with a similar frequency in the cervical and thoracic cord; no lumbar cord lesions were found. Most lesions were <1 cm in length (12 out of 17 lesions (70%)). Two patients showed one and two gadolinium enhancing lesions in the spinal cord respectively.

OPTIC NEURITIS

Nineteen patients, eight male and 11 female, mean age 32 (range 16–46), presented with optic neuritis, unilateral in 18 and bilateral (consecutive) in one. Brain MRI was abnormal in 14 (74%) whereas spinal cord abnormalities were identified in seven (37%) (figure).

BRAIN STEM SYNDROME

Ten patients, five male and five female, mean age 29 (range 18–41) presented with a brain stem syndrome. The symptomatic lesion was seen in only four instances. Cerebral hemispheric abnormalities were present in six (60%) and the spinal cord showed additional lesions in one (10%).

SPINAL CORD

Four patients, one man and three women, mean age 28 (range 25–32) presented with a spinal cord syndrome, partial in two and com-

Contiguous, sagittal, 3 mm thick, T2 weighted images of the spinal cord in a patient with clinically isolated optic neuritis. Asymptomatic cord lesions are visible at C3 and T8.

plete transverse in two. The symptomatic lesion was seen in two. Brain MRI was positive in two and one showed additional abnormalities in the spinal cord.

Discussion

This study, utilising high resolution MRI and multiple imaging indices, has shown a high frequency of asymptomatic lesions not only in the brain but also in the spinal cord in patients presenting with a clinically isolated syndrome of the optic nerve, brain stem, or spinal cord. There are two particular points of interest;

Firstly, the detection of asymptomatic brain abnormalities. Previous studies, using conventional T2 weighted brain imaging in patients at presentation with a clinically isolated syndrome have generally reported multiple asymptomatic abnormalities compatible with demyelination in 50%–70% of patients.^{11 12 24–27} Our present findings using a T2 weighted FSE sequence are similar. The addition of fFLAIR did not alter the overall results—that is, no patient had abnormalities only on fFLAIR. However, consistent with previous experience, fFLAIR detected a greater number of discrete and subcortical lesions than FSE but fewer in the posterior fossa.^{28–30} It was also helpful in providing additional information in occasional lesions unclear on FSE. High signal on FSE due to

demyelination may occasionally be confused with that due to vascular causes—for example, perivascular spaces or flow. Clarification of this issue is aided with the addition of fFLAIR when the last phenomena result in a low signal.

We also found six of 33 (18%) patients with gadolinium enhancing lesions in the brain and only two with enhancing lesions in the spinal cord. The proportion with enhancing brain lesions is rather lower than those reported in other series and may reflect a longer interval between the onset of the syndrome and MRI.^{19–31} One group of investigators has reported that the risk of early progression to multiple sclerosis is higher in those with enhancing lesions than in those with non-enhancing T2 abnormalities alone. Further follow up of the present and other series is needed to clarify the longer term risks for progression to multiple sclerosis and disability.¹⁹

Secondly, the importance of asymptomatic spinal cord lesions needs to be considered. The occurrence of these abnormalities was not totally unexpected. Previous studies using somatosensory evoked potentials (SEPs) have shown that between 0% and 34% of patients with isolated optic neuritis will have some abnormality. Although all 12 patients with isolated optic neuritis studied by Hume *et al* had normal SEPs, Matthews reported a 10% incidence, and Paty *et al* a 34% incidence of abnormalities.^{32–34} Frederiksen *et al* found a greater frequency of abnormalities in SEPs taken from the tibial rather than the median nerve, presumably because of the greater length of spinal cord surveyed.¹² The precise location of any abnormality was not generally reported in these studies and it may therefore have been anywhere along a path from the spinal cord to the brain stem and cerebral cortex—that is, brain lesions may result in some of the abnormalities. In those studies in which additional brain MRI was performed, there was an increase in the sensitivity of MRI over SEPs of almost 50%.^{12–34} It is therefore clear that patients presenting in this manner may have had clinically silent episodes affecting the spinal cord as evidenced by a delay in conduction time, although their frequency is uncertain.

What is the relevance of our finding that a quarter of the patients had asymptomatic spinal cord lesions? A pathological diagnosis cannot be made with certainty as hyperintense cord lesions on T2 weighted images are non-specific, the differential diagnosis including multiple sclerosis, acute disseminated encephalomyelitis, systemic lupus erythematosus, Behçet's disease, sarcoidosis, and spinal cord infarction.^{35–39} Spinal cord lesions, however, are common in multiple sclerosis. In one series of 80 patients with clinically definite multiple sclerosis, 74% had intrinsic spinal cord abnormalities.⁴⁰ Two patients in that study had normal brain scans but multiple lesions in the spinal cord. This is by contrast with normal controls in whom intrinsic spinal cord lesions are extremely rare.²² In particular in older patients (>50 years) spinal cord lesions are more specific for demyelination than brain

lesions as they do not appear with age alone in the way that cerebral white matter lesions do.

One area of concern is the possibility of acute disseminated encephalomyelitis in which spinal cord lesions may be evident. In the context of a truly monophasic illness, the presence of spinal cord abnormalities may not differentiate between acute disseminated encephalomyelitis and multiple sclerosis. In multiple sclerosis, demyelinating lesions usually affect one or two segments only (as was the case for most of the lesions we saw in this study) and may or may not be associated with cord swelling.^{20–40} This contrasts with Devic's neuromyelitis optica in which the acute lesions are extensive involving many segments and with associated cord swelling.⁴¹ The MRI features of spinal cord abnormalities in acute disseminated encephalomyelitis are not as well characterised, although we have seen patients with postinfectious acute disseminated encephalomyelitis or transverse myelitis who had extensive lesions.⁴² That demyelinating lesions may be clinically silent even if they occur in clinically eloquent pathways is well known. Thus persistently delayed visual evoked responses are often seen after full recovery from an attack of optic neuritis, or in patients with clinically definite multiple sclerosis who have never had an attack of optic neuritis.⁴³ Taking all the evidence together we think it likely that the cord lesions seen in our study represent areas of demyelination.

What is the role of spinal MRI in patients with clinically isolated syndromes? It is clearly important in those with isolated cord syndromes, where it has a primary diagnostic role. Although the situation is less clear in patients with isolated optic neuritis or brain stem syndromes, several potentially valuable roles emerge. Firstly, in subjects older than 50 intrinsic cord lesions are more specific for demyelination than cerebral white matter lesions, which in this age group are often due to small vessel disease. In cases in which diagnostic difficulty arises imaging of the spinal cord may help clarify the issue. Secondly, asymptomatic cord lesions might have a predictive value for the development of multiple sclerosis in the way that brain lesions do. Follow up studies are continuing on the present cohort to determine their relevance. Until this prognostic value is clarified we do not routinely image the spinal cord in all those patients with a isolated brain stem syndrome or optic neuritis. Thirdly, it would be useful to show cord lesions in those with a normal brain MRI. Although no cord lesions were found in the patients with normal brain imaging in our study, it is well documented that patients with established multiple sclerosis may have a normal brain scan but multiple cord lesions; the detection of such lesions in patients with a clinically isolated syndrome would point to a demyelinating aetiology.⁴⁴ The very low frequency of gadolinium enhancing cord lesions (only one of 29 patients with optic neuritis or a brain stem syndrome) suggests a limited role for enhanced cord imaging in the diagnostic evaluation of isolated optic neuritis or brain stem

syndromes, although we cannot exclude the possibility that more enhancing lesions would have been seen if patients had been scanned closer to the onset of their syndrome.

In conclusion, asymptomatic lesions consistent with demyelination are often seen not only in the brain but also in the spinal cord of patients presenting with a clinically isolated syndrome. Such lesions may thus be present even in clinically eloquent pathways. Whereas abnormalities in the brain confer a certain risk to the development of clinically definite multiple sclerosis and disability, it is unclear at present whether associated spinal cord abnormalities represent a similar or increased risk. Follow up studies are continuing to determine their importance.

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