



MRI only conversion to multiple sclerosis following a clinically isolated syndrome

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ABSTRACT

Objectives Using current diagnostic criteria, patients who present with a clinically isolated syndrome (CIS) may develop multiple sclerosis (MS) by subsequently exhibiting dissemination in space and time on clinical (clinically definite (CD) MS) or radiological (MRI) grounds. This study investigated the frequency of radiological without clinical conversion to MS after long term follow-up as this has not previously been defined.

Methods Two cohorts who underwent serial clinical and MRI studies from presentation with a CIS and who were followed-up over a mean of 6 and 20 years were investigated. The distribution and formation of lesions visible on brain MRI were assessed using the revised McDonald criteria (2005). Radiologically defined (RD) MS was determined by fulfilment of the MRI but not the CDMS criteria.

Results 105 people were followed-up for 6 years after a CIS, of whom 51% developed CDMS, 15% RDMS and the remainder were classified as still having had a CIS. 70 people were followed-up at 20 years, of whom 61% and 11% had developed CDMS and RDMS, respectively.

Conclusion About 10–15% of CIS patients may develop MS on MRI criteria only, without further clinical events for up to two decades.

INTRODUCTION

For most patients who develop multiple sclerosis (MS), the initial clinical event is a clinically isolated syndrome (CIS) suggestive of demyelination. About two-thirds of young adults presenting with a CIS exhibit clinically silent lesions on MRI that suggest demyelination. Long term (15–20 year) follow-up studies have revealed that subsequent further clinical relapses leading to a diagnosis of clinically definite (CD) MS¹ occur in 70–80% with an abnormal scan and 20–25% with normal imaging^{2,3}; the majority of those who convert do so within the first 5 years.^{4,5}

Since 2001, diagnostic criteria for MS allow for MRI evidence of dissemination in space and time alone to diagnose MS following a CIS,^{6,7} and follow-up studies have shown that MRI conversion is often associated with developing CDMS.^{8–10} Although it is known that people with CIS develop clinically silent new lesions during follow-up,^{11,12} the frequency with which patients develop MS on MRI criteria only after prolonged follow-up has not been studied.

The work we report here sought to address the question: in the longer term, how many people could be diagnosed as having MS based on the current MRI criteria only?⁷

METHODS

Participants

We retrospectively interrogated data from two cohorts who underwent serial clinical and MRI studies following a CIS. The first cohort was recruited between May 1984 and July 1987 and had clinical and MRI follow-up at (means) 1, 5, 10, 14 and 20 years.² The second cohort was recruited between June 1995 and November 2002 and had clinical and MRI follow-up at 3 months and 1, 3 and 6 years.¹³ Clinical and MRI data were missing at some time points in some patients; to be included in the present study, subjects must have had both a clinical and MRI follow-up study at the final scheduled 6 year or 20 year time point.

These studies were approved by the National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology Joint Research Ethics Committee. All participants gave written informed consent.

MRI

The 20 year cohort had baseline MRI and 5 year follow-up scanning undertaken using a Picker (Cleveland, USA) 0.5 T system, and all other scanning performed using a General Electric (Milwaukee, USA) Signa 1.5 T system. Contiguous 5 mm axial slices were obtained at all time points except for a minority of baseline images that were acquired with a slice thickness of 10 mm. At baseline and 5 years, spin echo scans (repetition time (TR)=2000 ms, echo time (TE)=60 ms) were acquired; at 10 years, conventional spin echo scans were obtained (TR=2000 ms, TE=30/90 ms); at 14 years, fast spin echo (FSE) sequences was acquired (TR=2000 ms, TE=14/98 ms); and at 20 years an FSE sequence was obtained (TR=2000 ms, TE=17/102 ms).

For the 6 year cohort, all scanning was undertaken using a General Electric Signa 1.5 T system. Contiguous 3 mm axial slices were obtained at all time points. An FSE sequences (TR=3200 ms, TE=15/90 ms) was acquired during each scanning session, and at baseline a T1 weighted (TR=600 ms, TE=17 ms) post-gadolinium (Gd) (0.1 mmol/kg body weight) image was also obtained.

Brain T2 weighted lesion counts and volumes were determined from baseline images in both the 20 and 6 year cohorts.¹⁴ Baseline brain Gd enhancing lesion counts were obtained in the 6 year cohort.

Clinical assessment

Patients were classified into four subgroups at the last follow-up.

1. Clinically definite (CD) MS: those people who had at least one new clinical relapse with documented new symptoms and signs, or who developed progressive neurological deficits.¹
2. Radiologically defined (RD) MS: fulfilling the McDonald MRI⁷ criteria for dissemination in space and time, but not the CDMS criteria.
3. Evolving (E) CIS: not fulfilling CDMS or McDonald MRI criteria for MS while still accruing new MRI lesions.
4. Stable (S) CIS: with neither clinical nor MRI evidence for new disease.

Expanded Disability Status Scale (EDSS)¹⁵ scores are reported from the baseline and 6 year follow-up visits for the 6 year cohort and from the 5 and 20 year follow-up visits for the 20 year cohort (a baseline EDSS was not obtained in this group). Disease modifying treatments were prescribed only to patients with CDMS who had experienced two or more relapses in the previous 2 years.

Statistical analyses

Fisher's exact tests were used to assess group wide differences in gender ratios; all other measures were compared using Mann-Whitney U tests. Analyses were performed using SPSS 11 (SPSS Inc).

RESULTS

Six year CIS group

The 6 year CIS group were first reviewed an average of 47 days after their first clinical event (median 45, range 2–106). They were followed-up for a mean of 6.3 years (median 5.6, range 4.7–10.2 years), at which time ~51% had CDMS, ~15% RDMS, ~12% ECIS and ~20% SCIS. Comparing baseline observations between CDMS and RDMS, except for a greater proportion of males in the RDMS group ($p=0.005$) and a trend towards the RDMS group being older at the time of their first episode ($p=0.068$), no significant differences were detected (baseline T2 lesion volumes and numbers, Gd enhancing lesion counts and EDSS scores). Comparing CDMS with the ECIS and SCIS groups, there were significant differences in T2 lesion volume ($p<0.001$), T2 lesion number ($p<0.001$) and Gd enhancing lesion number (CDMS with ECIS, $p=0.026$ and with SCIS, $p<0.001$) (table 1).

Twenty year CIS group

The 20 year CIS group were first reviewed an average of 63.3 days after their first clinical event (median 26, range

1–361). They were followed-up for a mean of 19.9 years (median 20, range 18.0–23.1 years), at which time ~61% had CDMS, ~11% had RDMS, ~11% ECIS and ~16% SCIS. Comparing baseline observations between CDMS and RDMS, no significant differences were detected (gender, age at first episode, baseline T2 lesion numbers and 5 year EDSS scores), although a slight trend to a lower baseline T2 lesion volume was noted ($p=0.073$, with the caveat that T2 lesion volumes were only available in a subset of patients, as per table 2). Comparing CDMS with ECIS and SCIS, baseline T2 lesion counts were lower ($p=0.001$ and $p<0.001$, respectively), as were T2 lesion volumes ($p=0.002$ and <0.001 , respectively); 5 year EDSS scores were lower in the SCIS compared with the CDMS group ($p=0.048$).

DISCUSSION

The main finding of our study was that some CIS patients (11–15%) developed MS using current imaging but not clinical criteria after prolonged follow-up (6–20 years), so identifying a group of patients who exhibit a clinically silent disease course over a long period.

Although the length of follow-up of the two cohorts is very different, conversion to CDMS following a CIS occurs most commonly during the first 5 years. Our findings are consistent with this, showing similar proportions with CDMS in the 6 year and 20 year cohorts (51% and 61%, respectively). They also suggest that those classified as having RDMS at 5 years are more likely than not to remain so in the longer term (with 15% and 11% classified as having RDMS in the 6 year and 20 year cohorts, respectively) although some will still convert to CDMS.

With the available data, we also investigated whether there were MRI features at presentation that could help distinguish RDMS from CDMS evolution. However, like CDMS, most RDMS subjects had abnormal brain MRI at presentation with similar T2 lesion loads and, in the 6 year cohort, a similar number of gadolinium enhancing lesions. We found that the 6 year RDMS group were more often male and had a slightly older age at CIS presentation compared with the CDMS group. These clinical features tend to be over-represented in progressive forms of MS,^{16 17} and their presence in the 6 year but not the 20 year RDMS group might suggest that the former cohort includes subjects who in the longer term will evolve to a secondary progressive form of disease.

It is well established that the presence of brain MRI lesions in CIS patients is associated with a relatively high likelihood of

Table 1 Clinical and MRI baseline observations, and last review EDSS scores, in the cohort followed-up over 6 years from their index clinical event

	Subtype			
	CDMS	RDMS	ECIS	SCIS
Further clinical events	Yes	No	No	No
New MRI lesions	Not required	Yes	Yes	No
Gender (F/M)	42/12	6/10	8/5	15/7
Age at first event (years) (mean (SD))	33.0 (7.7)	36.6 (6.3)	34.3 (7.5)	32.3 (7.5)
T2 lesion volume (ml) (median (range))	1.3 (0.0–25.1)	1.2 (0.3–9.6)	0.1 (0.0–0.5)	0.0 (0.0–0.8)
T2 lesion number (median (range))	12 (0–142)	13.5 (3–57)	1 (0–6)	0 (0–5)
Gd enhancing lesion number (median (range))	0 (0–21)	0 (0–13)	0 (0–3)	0 (0–0)
First review EDSS (median (range))	1.0 (0.0–6.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	1.0 (0.0–4.0)
6 year EDSS (median (range))	2.0 (0.0–7.5)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–2.5)

N=105, except for baseline EDSS, where N=103 (N=53 for CDMS and N=21 for SCIS) and 6-year EDSS scores, where N=104 (N=15 for RDMS).

CDMS, clinically definite multiple sclerosis; ECIS, evolving clinically isolated syndrome; EDSS, expanded disability status scale; RDMS, radiologically defined multiple sclerosis; SCIS, stable clinically isolated syndrome.

Table 2 Clinical and MRI baseline observations, and last review EDSS scores, in the cohort followed-up over 20 years from their index clinical event

	Subtype			
	CDMS	RDMS	ECIS	SCIS
Further clinical events	Yes	No	No	No
New MRI lesions	Not required	Yes	Yes	No
Gender (F/M)	31/12	5/3	6/2	7/4
Age at first event (years) (mean (SD))	31.5 (6.4)	32.6 (8.5)	28.5 (7.6)	33.3 (8.4)
T2 lesion volume (ml) (median (range))	0.8 (0.0–13.7)	0.0 (0.0–2.3)	0.0 (0.0–0.4)	0.0 (0.0–0.0)
T2 lesion number (median (range))	14 (0–74)	6 (0–26)	0 (0–5)	0 (0–32)
5-year EDSS (median (range))	1.5 (0.0–6.5)	1.5 (0.0–6.5)	0.0 (0.0–2.0)	0.0 (0.0–5.0)
20-year EDSS (median (range))	3.5 (1.0–8.0)	2.0 (0.0–6.5)	0.5 (0.0–2.5)	1.0 (0.0–5.0)

N=70, except for baseline T2 lesion volume, where N=53 (N=33 for CDMS, N=4 for RDMS, N=6 for ECIS and N=10 for SCIS) and 5-year EDSS, where N=55 (N=37 for CDMS, N=5 for RDMS, N=6 for E-CIS and N=7 for SCIS).

CDMS, clinically definite multiple sclerosis; ECIS, evolving clinically isolated syndrome; EDSS, expanded disability status scale; RDMS, radiologically defined multiple sclerosis; SCIS, stable clinically isolated syndrome.

conversion to CDMS, and disease modifying treatments such as β interferon and glatiramer acetate delay the time to developing CDMS^{18–21} and are sometimes initiated in CIS patients with abnormal MRI. Our present study nevertheless highlights the fact that conversion to CDMS is not invariable and awareness of the possibility of a long term RDMS course may be useful in counselling and managing CIS patients.

In addition to the RDMS group, there was a group who accrued new lesions but did not fulfil current diagnostic criteria (ECIS). This group is likely to include subjects with a mild form of MS and some with other causes of white matter lesions, and raises the issue of the specificity of MRI findings. In this regard, the present McDonald imaging criteria for MS may beneficially reduce the chance of a false positive diagnosis of MS, albeit at the expense of diagnostic sensitivity. It has been noted that some patients who develop CDMS do not fulfil the current MRI criteria for MS, and recent work supports expanding the imaging criteria for MS in patients with a typical CIS.^{10 22 23} Further research to improve prediction of outcomes following a CIS is needed, and could include newer genetic, immunological and imaging measures.

There are several limitations to the study. Firstly, cognitive testing was not included in the 20 year follow-up cohort and the possibility that some of the RDMS cases developed cognitive impairment cannot be excluded. Neuropsychological testing was performed at follow-up of the 6 year cohort²⁴ and cognitive impairment when present was mild with no clear differences between those who developed MS and those who did not. Secondly, it is possible that some MRI lesions were not due to demyelination; particularly in the older 20 year follow-up cohort, some of the new white matter lesions may represent vascular disease. However, the proportion with RDMS in this group was not higher (it was actually slightly lower) than in the younger 6 year cohort, suggesting that the contribution from superadded vascular disease is probably small. Thirdly, some subjects originally recruited could not be followed-up with the required clinical and MRI evaluation at the final study time point; this was more often the case for the 20 year cohort in whom it was also not possible to scan some more disabled MS patients. Finally, there were differences between the CIS cohorts with respect to imaging protocols, frequency of scanning, type of scanner and type of CIS. Notwithstanding these factors, the two CIS cohorts exhibited many similarities (eg, age, gender and frequency of MRI abnormalities at presentation and of evolution to clinically definite MS) and the baseline clinical and imaging features of both groups are typical for CIS.

Overall, the similarity of findings in both CIS cohorts confirms that a long term RDMS course occurs, albeit less commonly than CDMS. Awareness of an RDMS course may be relevant when counselling and treating CIS patients. Further prospective follow-up studies are warranted to better characterise and understand this evolution of MS.

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