

Disability and T₂ MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis

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Clinically isolated syndromes (CIS), such as optic neuritis, brainstem or spinal cord syndromes are frequently the first clinical presentations of multiple sclerosis. However, not all CIS patients develop multiple sclerosis and in those who do, disability is highly variable. In previous follow-up studies, brain lesions on T₂-weighted MRI are associated with increased risk of multiple sclerosis and to an extent disability. We evaluated the longitudinal relationships between the MRI lesions and clinical course over a period of 20 years. CIS patients were recruited between 1984 and 1987 and previously followed up after 1, 5, 10 and 14 years. Of the 140 subjects who were initially recruited with a CIS for a baseline MRI study, we followed up 107 patients after a mean of 20.2 years (range 18–27.7). Multiple sclerosis was diagnosed as clinically definite on clinical grounds only and disability determined using the Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) score. Clinically definite multiple sclerosis developed in 67 out of 107 (63%) overall: 60 out of 73 (82%) with abnormal and 7 out of 34 (21%) with normal baseline MRI. Multiple sclerosis was still relapsing-remitting in 39 (58%)—including 26 (39%) with a ‘benign’ course (EDSS ≤ 3)—whilst 28 (42%) had developed secondary progression. T₂ lesion volume at all time-points correlated moderately with 20-year EDSS (r_s values 0.48 to 0.67; $P < 0.001$) and MSFC z-score [r_s values (–0.50) to (–0.61); $P < 0.001$]. In those developing multiple sclerosis, a concurrent correlation of change in T₂ lesion volume with change in EDSS was most evident in years 0–5 ($r_s = 0.69$, $P < 0.001$). The estimated rate of lesion growth over 20 years was 0.80 cm³/year in those who retained a relapsing remitting multiple sclerosis course, and 2.89 cm³/year in those who developed secondary progressive multiple sclerosis, a difference of 2.09 cm³/year (95% CI: 0.77, 2.96; $P < 0.001$). This study extends previous follow-up of CIS patients and sheds new light on how the lesions evolve according to the natural history. Baseline MRI findings are predictive for development of clinically definite multiple sclerosis. Lesion volume and its change at earlier time points are correlated with disability after 20 years. Lesion volume increases for at least 20 years in relapse-onset multiple sclerosis and the rate of lesion growth is three times higher in those who develop secondary progressive than in those who remain relapsing remitting multiple sclerosis.

Keywords: clinically isolated syndromes; longitudinal study; lesion volume; MRI

Abbreviations: CD = clinically definite; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; MSFC = Multiple Sclerosis Functional Composite Score.

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Introduction

Clinically isolated syndromes (CIS), such as optic neuritis, brainstem or spinal cord syndromes are frequently the first clinical presentation of multiple sclerosis. However, not all CIS patients convert to multiple sclerosis and

in those who do, disability is highly variable (Weinshenker *et al.*, 1989; Runmarker and Andersen 1993; Boiko *et al.*, 2002; Nilsson *et al.*, 2005; Confavreux and Vukusic 2006; Kremenchutzky *et al.*, 2006) and limited prognostic information is provided by early clinical features such as

the type of CIS, frequency of early relapses and disability status 5 years after onset.

Numerous studies have investigated the prognostic role of MRI in CIS patients, most with follow-up of a few years only. Clinically silent T₂-weighted brain white matter lesions are present in 50–70% of CIS patients (Jacobs *et al.*, 1986; Ormerod *et al.*, 1986a; Miller *et al.*, 1987; O’Riordan *et al.*, 1998b) and their presence indicates a higher likelihood of developing clinically definite (CD) multiple sclerosis (Morrissey *et al.*, 1993; Soderstrom *et al.*, 1994; Jacobs *et al.*, 1997; O’Riordan *et al.*, 1998a; Brex *et al.*, 2002; Beck *et al.*, 2003; Minneboo *et al.*, 2004).

To assess the potential of MRI to predict disability due to multiple sclerosis requires prolonged follow-up, since on average disability accrues only slowly in multiple sclerosis. Tintore *et al.* (2006) followed up 156 patients with CIS after a mean of 7 years and they found that baseline brain MRI findings helped to differentiate patients with low, medium and high risk for conversion to multiple sclerosis. The number of brain lesions best predicted 5-year disability (Tintore *et al.*, 2006). Minneboo *et al.* (2004) reported on 42 CIS patients followed up 8.7 years later and showed that two or more infratentorial lesions best predicted long-term disability (Minneboo *et al.*, 2004). Another long-term follow-up study of 30 patients with relapsing remitting multiple sclerosis reported that T₂ lesion volume correlated strongly with brain tissue loss and clinical disease severity 13 years later (Rudick *et al.*, 2006).

In a previous report based on data from 14-year follow-up of a prospectively recruited CIS cohort, Expanded Disability Status Scale (EDSS) score at 14 years correlated moderately with lesion volume in MRI at 5 years ($r_s = 0.60$) and with increase of lesion volume over the first 5 years ($r_s = 0.61$) (Brex *et al.*, 2002). We followed up this same CIS cohort and now report the findings after 20 years. Our overall aim was to investigate whether the longitudinal relationships between the MRI and clinical course were maintained over a uniquely long period of 20 years and to assess how lesions evolve in relation to natural history. This investigation includes a comparison of the rate of lesion volume change over time in three distinct subgroups classified according to their clinical status at last follow-up; CIS, relapsing remitting multiple sclerosis or secondary progressive multiple sclerosis.

Methods

Subjects

One hundred and forty CIS patients were recruited between May 1984 and July 1987 and had a clinical assessment and brain MRI performed (Ormerod *et al.*, 1986a, b; Miller *et al.*, 1987; Ormerod *et al.*, 1987; Miller *et al.*, 1988, 1989). A follow-up was performed ~1 year later in 109 patients (53 optic neuritis; 23 brainstem syndrome and 33 spinal cord syndrome), who had a clinical examination and brain MRI scan repeated at this time (Miller *et al.*, 1988, 1989). Subsequent follow-ups were performed after 5 (89 patients) (Morrissey *et al.*, 1993), 10

(81 patients) (O’Riordan *et al.*, 1998a) and 14 years (71 patients) (Brex *et al.*, 2002).

We wanted to follow-up—after 20 years—those patients in whom the baseline scans and adequate clinical information of the first clinical episode were still available. The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee. The NHS (National Health Service) Strategic Tracing System, which is a database of people, places and organizations in England and Wales, was used in those cases where the contact details were missing or found to be incorrect. Approval for access to this database for research purposes was obtained from the Security Confidentiality Advisory Group of the NHS Information Authority (the Research Ethics Committee also approved the use of the NHS Strategic Tracing System for research purposes).

Special precaution was needed when approaching those who had been seen at baseline and Years 1 and 5 but not at Years 10 or 14. During the period covering the earliest time-points in this study (i.e. the baseline, Year 1 and Year 5 assessments that were performed from the mid-1980s to the early 1990s), it was not a routine practice to provide patients with information about the link between CIS and multiple sclerosis nor was there a standard patient information sheet for recruitment which contained this information. Some participant in the study might therefore still have been unaware of the association of their symptoms with multiple sclerosis. It was also uncertain whether subjects would expect, or be sympathetic to, contact from us some 15 or more years after the last time they had been seen. Thus with the Research Ethics Committee approval, the initial contact with such individuals was by a letter which did not provide full details of the project, or mention multiple sclerosis, but simply asked them to get in touch if they were interested in being followed up. Those people who replied positively to this initial approach were invited for clinical examination and brain MRI at which point further information was provided, including the relevance of the study to multiple sclerosis. With those patients who did not reply either positively or negatively to two letters of invitation, we made an attempt to contact them either by phone or through their general practitioner.

Of the 140 subjects who were identified and had been initially recruited with a CIS for a baseline MRI study, eight were excluded because they had (at baseline) or developed (subsequently) another non-multiple sclerosis diagnosis: three at baseline—pontine arteriovenous malformation, pontine haematoma and Leigh’s disease; three at 5 years—myasthenia gravis, cerebrovascular disease and HIV-related complications; one at 10 years—systemic lupus erythematosus and one at 14 years—cerebrovascular disease. Six other patients had died from non-multiple sclerosis related disease (three between Years 1 and 5 and three between Years 14 and 20) and there was insufficient information to determine their prior neurological status. Of the remaining 126 subjects, three were abroad and could not be traced; two did not reply to a second letter of invitation and no contact number was available; one was contacted but did not wish to be followed up; the contact details were unobtainable in nine; and either the baseline scan could not be located or adequate clinical information on the first presentation was not available in four subjects.

The remaining 107 patients were included in the study: 104 who were living at the time of the 20-year assessment, and three who were known to have died from the complications of severe multiple sclerosis at an earlier time-point. Of these 107 subjects,

the first follow-up was after 1 year for 92, 5 years for seven, 10 years for three and 20 years for five subjects. The disease duration (from CIS onset) at the 20-year follow-up was a mean of 20.2 years (range 18 to 27.7 years).

CD multiple sclerosis was diagnosed by using Poser criteria and was based solely on clinical evidence (Poser *et al.*, 1983). This required a second clinical episode with objective new neurological signs *i.e.* clear evidence for dissemination in time and space. Patients who did not develop CD multiple sclerosis were classified as remaining CIS at the 20-year follow up. Because the primary focus was to explore the relationship of MRI findings with the clinical course and natural history, MRI evidence only for dissemination in space and time (Polman *et al.*, 2005) was not used to diagnose multiple sclerosis. In those who developed multiple sclerosis, the clinical course, either relapsing remitting or secondary progressive, was determined by Lublin and Reingold criteria (Lublin and Reingold, 1996). Disability status was determined for all subjects by using Kurtzke's EDSS (Kurtzke, 1983) and Multiple Sclerosis Functional Composite Score (MSFC) (Fischer *et al.*, 1999). Relapsing remitting multiple sclerosis with EDSS ≤ 3 was defined as benign.

MRI protocol

Baseline and 5-year MRI scans were obtained on a 0.5-T scanner (Picker, Cleveland) and on a 1.5 Tesla GE Signa Echospeed scanner (General Electric Signa, Milwaukee) at 10, 14 and 20 years. Contiguous, axial slices covering the whole brain were obtained at all visits. In a minority of early baseline scans (1984–85), slice thickness was 10 mm; it was 5 mm for all subsequent scans. At 20 years, T₂-weighted, dual-echo fast spin-echo sequences of the brain were obtained on 75 patients [TR 2000 ms; TE 17/102 ms; 28 × 5 mm (matrix 256 × 256, FOV 24 × 18 cm, 1 NEX)]. Of the remaining 32 subjects included in the 20-year clinical follow-up, three had died of severe multiple sclerosis; one had become claustrophobic and the remainder could not be scanned either because of severe disability (eight subjects) or because lived too far away (20 subjects). In these patients, phone EDSS was obtained. Identification of the lesions on the hard copies was performed by an experienced neuroradiologist (K.M.) who was blinded to the clinical details. Marking of the lesions was done on the short echo sequence with the long echo used as a reference. Baseline MRI was classified as abnormal if it displayed one or more clinically silent lesions compatible with demyelination. A normal scan might include the CIS symptomatic lesion only. T₂ lesion volume was measured from electronic images using a semi-automated contouring technique to outline lesions, previously described (Sailer *et al.*, 1999). The 20-year T₂ lesion volume was not measured in one patient in whom cerebrovascular disease developed as a second pathology.

Statistical analysis

The data were analysed using the standard statistical software package (SPSS 12, Chicago, IL) and Stata 9.2 (Stata Corporation, College Station, TX, USA). Spearman rank-correlation was used to evaluate the correlation of the lesion volume or change of lesion volume, on brain MRI, with the EDSS and MSFC score. Because of the skewed (non-normal) nature of T₂ lesion volume data, a non-parametric test, Cuzick's test, was used to look for a linear trend across the three groups of patients (defined as CIS, relapsing remitting or secondary progressive multiple sclerosis at 20 years),

to assess whether the lesion variable is associated with these different clinical courses; and Wilcoxon rank-sum test was used to compare the rate of lesion volume increase between these groups. Longitudinal linear mixed models were used to compare rates of change in lesion volume, with T₂ lesion volume as response variable and time and patient group terms as covariate, using all available data points for the T₂ lesion volume. A quadratic term was fitted in addition to the linear term in the model for the T₂ lesion volume over time to assess if there was non-linearity in lesion growth. Bootstrap confidence intervals were obtained where residuals showed signs of non-normality. Bootstrap derived *P*-values are given as ranges, or to fewer decimal places, due to the computer-intensive nature of the method.

Results

The cohort followed up at 20 years was similar to that seen at baseline in terms of mean age, gender, type of syndrome and frequency of abnormalities on MRI at presentation (Table 1). Disability was assessed by examination on 77 patients. EDSS only was assessed by telephone on 27 patients who were unable to attend the hospital for a clinical examination (Lechner-Scott *et al.*, 2003). Three who had already died from severe complications of multiple sclerosis [already reported at the 14-year follow-up (Brex *et al.*, 2002)] were assigned an EDSS of 10. Three patients were on disease-modifying treatment (two had relapsing remitting multiple sclerosis and one had secondary progressive multiple sclerosis). Another patient had stopped medication 3 years before the time of examination, after entering secondary progressive stage.

The 75 patients who had MRI at 20 years were compared with the 29 who were not scanned in terms of the baseline demographic features: the groups were similar with regard to age, gender and frequency of baseline MRI abnormalities, while the baseline group had a high percentage with optic neuritis (55% versus 41%) and a lower percentage with brainstem presentations (19% versus 31%). The median EDSS at Year 20 was 2.5 in the scanned group and 5.5 in the non-scanned group, higher disability in the latter group reflecting the fact that disability precluded scanning a number of patients.

Conversion to CD multiple sclerosis and disability status

After 20 years, CD multiple sclerosis developed in 67 out of 107 patients (63%). The remaining 40 patients were classified as still CIS—this included five with 'clinically probable' multiple sclerosis by the Poser criteria who had experienced new neurological symptoms but with no new signs or disability. CD multiple sclerosis developed in 35 out of 54 (65%) who initially presented with optic neuritis, 15 out of 25 (60%) with a brainstem syndrome and 17 out of 28 (61%) with a spinal cord syndrome. The median EDSS score of the multiple sclerosis group was 4.0 (range 0–10): 39 (58%) had relapsing remitting multiple

Table 1 Characteristics of the cohort at each follow-up time point

Characteristic	Baseline	1 year	5.3 year	9.7 year	14.1 year	20.2 year
Patients who underwent clinical assessment—no	140	109	89	81	71	107
Exclusion due to alternative diagnosis—no	3	0	3	1	1	0
Deaths not related to MS—no	0	0	3	0	0	3
Female sex—no (%)	80 (60) ^a	68 (62)	53 (60)	53 (65)	49 (69)	71 (66)
Mean age at presentation.	32 ^a	32	31	32	32	32
Range	13–49	13–49	13–49	17–49	19–49	13–49
Optic neuritis—no (%)	69 (50)	53 (49)	44 (49)	42 (52)	36 (51)	54 (51)
Brain stem syndrome—no (%)	33 (24) ^b	23 (21)	17 (19)	16 (20)	14 (20)	25 (23)
Spinal cord syndrome—no (%)	38 (28)	33 (30)	28 (31)	23 (28)	21 (30)	28 (26)
MRI examinations—no	140	109	89	64	55	75
Electronic data for lesion volume quantification—no	74	— ^c	69	63	55	75
Abnormal results—baseline MRI—no (%)	85 (64) ^a	69 (63)	57 (64)	54 (67)	50 (70)	73 (68)
Optic neuritis—no (%)	42 (64)	—	—	—	—	36 (67)
Brain stem syndrome—no (%)	23 (77)	—	—	—	—	20 (80)
Spinal cord syndrome—no (%)	20 (54)	—	—	—	—	17 (61)
Conversion to clinically definite MS—all patients—no (%)	—	21 (19)	38 (43)	48 (59)	48 (68)	67 (63)
Abnormal scan at baseline	0	21 (30)	37 (65)	45 (83)	44 (88)	60 (82)
Normal scan at baseline	—	0	1 (3)	3 (11)	4 (19)	7 (21)
Lesion volume on MRI—cm ³						
Median	0.43	—	1.9	4.3	6.01	7.2
Range	0–55	—	0–114.3	0–88.6	0–70.2	0–60.8
Median EDSS score						
All patients	0 ^d	—	1.5	2	2	3
Clinically definite MS	—	—	2.5	3.25	3.25	4.0

^aBased on 133 patients (Apart from CIS type, demographic data was no longer available in five patients who were excluded at an earlier time point due to an alternative non-MS diagnosis and 2 who died of non-MS cause before five years follow-up). ^bIncludes three patients excluded after baseline MRI revealed a non-MS diagnosis. ^cLesion volume measures not available at year 1. ^dAs EDSS was not measured during the CIS presentation, 0 represents the presumed EDSS immediately prior to CIS. This value was used to evaluate change of EDSS from baseline to year 5.

sclerosis and 28 (42%) had secondary progressive multiple sclerosis. Twenty-six out of 67 (39%) patients with CD multiple sclerosis had an EDSS score of 6 or more and 26 out of 67 (39%) had an EDSS score of 3 or less. The median EDSS score of the secondary progressive multiple sclerosis group was 6.5 (this includes three patients who died of severe complications of disease in whom an EDSS of 10 was assigned). The median EDSS of the optic neuritis onset multiple sclerosis group was 4.0 and in the non-optic neuritis multiple sclerosis group was 5.0 ($P=0.28$, Wilcoxon rank-sum test).

Normal brain MRI scans at baseline

CD multiple sclerosis developed in 7 out of 34 (21%) patients with normal brain MRI scan at baseline, (four presented with optic neuritis and three with spinal cord syndrome). The median EDSS of this multiple sclerosis group was 3.5 (range 1.5 to 7.5) and the median time to converting to multiple sclerosis was 6.0 years (range 1 to 11).

Abnormal brain MRI scans at baseline

CD multiple sclerosis developed in 60 out of 73 (82%) patients with an abnormal brain MRI scan. Their median EDSS was 4.25 (range 0 to 10) and median time to

Table 2 Baseline MRI lesion number and clinical status at 20 years

	No of Brain T2 lesions at baseline			
	0 (N=34)	1–3 (N=22)	4–9 (N=20)	10+ (N=31)
No of CIS at 20 years	27 (79%)	4 (18%)	3 (15%)	6 (19%)
No of clinically definite MS at 20 years	7 (21%)	18 (82%)	17 (85%)	25 (81%)
No of patients with EDSS >3 at 20 years	9 (26%)	8 (36%)	10 (50%)	20 (65%)
No of patients with EDSS ≥6 at 20 years	2 (6%)	4 (18%)	7 (35%)	14 (45%)

converting to multiple sclerosis was 2 years (range 0.5 to 14 years).

Baseline MRI lesion number and clinical outcome

Table 2 shows the relationship between baseline lesion number (grouped as 0, 1–3, 4–9 and ≥10) and clinical outcome at 20 years (CIS or CD multiple sclerosis; those with EDSS >3 or ≥6).

Table 3 MRI lesion volumes at each study time-point (baseline, 5, 10, 14 and 20 years) displayed according to clinical subgroup classification at 20-year follow up

Clinical outcome	Baseline	5 years	10 years	14 years	20 years
CIS—no	27	21	18	15	30
Median volume (cm ³)	0	0	0.07	0.18	0.5
Range (cm ³)	0–2.2	0–10.8	0–16.3	0–15.1	0–13.8
RRMS (All)—no	26	26	28	25	33
Median volume (cm ³)	0.7	2.06	5.1	6.09	12.7
Range (cm ³)	0–13.7	0.1–36.5	0.55–40.6	0.97–37.8	0.2–60.8
RRMS (EDSS ≤3)—no	18	18	20	17	22
Median volume (cm ³)	0.7	1.8	4.5	5.8	8.7
Range (cm ³)	0–13.7	0.5–36.5	0.5–40.6	0.9–37.8	0.2–60.8
RRMS (EDSS >3)—no	8	8	8	8	11
Median volume (cm ³)	0.5	2.7	6.2	9.7	17.5
Range (cm ³)	0–4.07	0.1–12.4	0.5–19.9	1.5–23.1	4.7–47.6
SPMS—no	20 ^a	17 ^a	14 ^b	13	11
Median volume (cm ³)	2.5	17	18.9	27.7	34.4
Range (cm ³)	0–55	0–114	0.4–88.6	0.5–70.2	0.5–56.4

SPMS = secondary progressive MS; RRMS = relapsing remitting MS.

^aIncludes three patients who died of MS. ^bIncluded one patient who died of MS.

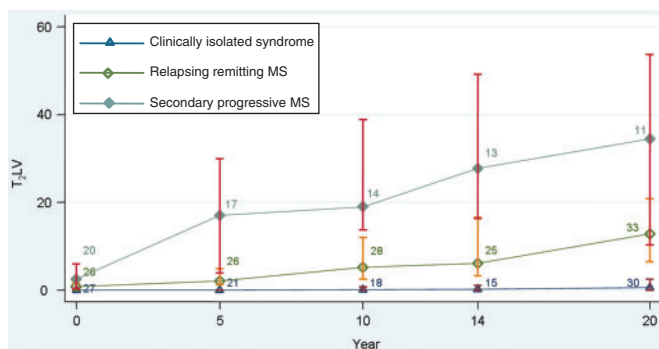


Fig. 1 Median T₂ lesion volume (T₂LV) (cm³) over time for patients groups. Bars show Inter-quartile range; Numbers of patients with clinically isolated syndrome shown by open triangles, with relapsing remitting MS shown by open diamond and secondary progressive MS by filled diamond.

Longitudinal changes

Patients who developed secondary progressive multiple sclerosis tended to have larger baseline T₂ lesion volumes and a greater increase of lesion volume especially over the first 5 years—this was even more evident for those patients who died of complications of multiple sclerosis (Table 3 and Fig. 1). Observing the pattern of median T₂ lesion volume change over 20 years showed that although at baseline there was some overlap, from 5 years onwards the groups of patients (CIS, relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis) were well distinguished. The secondary progressive multiple sclerosis group showed a steeper rate of lesion volume increase than relapsing remitting multiple sclerosis. The increase in secondary progressive multiple sclerosis was higher than in relapsing remitting multiple sclerosis over

the first 5 years of the disease ($P=0.008$, Wilcoxon rank-sum test).

Cuzick's test was used to look for a linear trend across the three multiple sclerosis subgroups—benign and non-benign relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis—for those patients in whom the baseline and 20 years T₂ lesion volume was available. It showed an increase in lesion growth from the benign group, through the non-benign relapsing remitting group (EDSS > 3), to the secondary progressive multiple sclerosis group ($P=0.08$). Lesion growth over 20 years showed a trend to be higher in secondary progressive than relapsing remitting multiple sclerosis (for the latter, benign and non-benign subgroups were combined; $P=0.07$, Wilcoxon rank-sum test) and in benign versus non-benign relapsing remitting multiple sclerosis ($P=0.08$).

A longitudinal analysis of the gradients, using all available data points, estimated the rate of growth in the relapsing remitting multiple sclerosis group as 0.80 cm³ per year (bootstrap 95% CI: 0.63, 0.99; $P<0.001$) while in the secondary progressive multiple sclerosis group it was estimated as 2.89 cm³ per year (bootstrap 95% CI: 1.78, 4.01; $P<0.001$). This is a difference of 2.09 cm³ per year (95% CI: 0.77, 2.96; $P<0.001$). Comparing non-benign versus benign relapsing remitting multiple sclerosis, the rate of lesion growth per year were 0.66 and 1.08 cm³, respectively, a difference of 0.42 cm³ per year (bootstrap 95% CI: -0.01, 0.90; $0.05<P<0.07$).

To assess if there was a levelling off or alternatively acceleration in lesion growth, a quadratic term in time was added to the longitudinal models to test for curvature: significant negative or positive quadratic terms indicate, respectively, reducing or accelerating rates of growth. However, there is less power in any one group to detect curvature than to detect a difference in curvature between

Table 4 Correlation of MRI lesion volumes and changes in lesion volumes at various time points during the study with disability (EDSS & MSFC) measured at the 20 years follow up for the whole cohort

EDSS				MSFC		
P-value	r_s (95% CI)	Patients number	Time point	Patients number	r_s (95% CI)	P-value
< 0.001	0.48 (0.28–0.64)	73	0 year	49	–0.49 (–0.68 to [–0.24])	0.0003
< 0.001	0.62 (0.45–0.75)	64	5 years	48	–0.61 (–0.76 to [–0.40])	< 0.001
< 0.001	0.61 (0.43–0.74)	64	0–5 years	48	–0.56 (–0.73 to [–0.33])	< 0.001
< 0.001	0.55 (0.35–0.71)	60	10 years	50	–0.50 (–0.68 to [–0.25])	0.0002
0.001	0.45 (0.20–0.64)	53	5–10 years	45	–0.49 (–0.68 to [–0.23])	0.0005
< 0.001	0.67 (0.49–0.80)	53	14 years	44	–0.59 (–0.75 to [–0.36])	< 0.001
0.004	0.40 (0.13–0.61)	48	10–14 years	42	–0.42 (–0.64 to [–0.13])	0.005
< 0.001	0.50 (0.30–0.65)	74	20 years	62	–0.53 (–0.68 to [–0.33])	< 0.001
< 0.001	0.49 (0.24–0.68)	47	14–20 years	44	–0.51 (–0.70 to [–0.25])	0.0004

Table 5 Correlation of MRI lesion volumes and changes in lesion volumes at various time points during the study with disability (EDSS & MSFC) measured at the 20 years follow up for the clinically definite MS cohort

EDSS				MSFC		
P-value	r_s (95% CI)	Patients number	Time point	Patients number	r_s (95% CI)	P-value
0.036	0.31 (0.02–0.55)	46	0 year	30	–0.41 (–0.67 to [–0.06])	0.024
< 0.001	0.53 (0.27–0.71)	43	5 years	30	–0.51 (–0.73 to [–0.18])	0.003
< 0.001	0.53 (0.28–0.72)	43	0–5 years	30	–0.45 (–0.70 to [–0.11])	0.011
0.005	0.42 (0.13–0.64)	42	10 years	34	–0.38 (–0.63 to [–0.05])	0.025
0.026	0.37 (0.05–0.62)	36	5–10 years	29	–0.39 (–0.66 to [–0.03])	0.033
< 0.001	0.57 (0.30–0.75)	38	14 years	30	–0.50 (–0.73 to [–0.17])	0.004
0.020	0.22 (–0.12–0.52)	34	10–14 years	29	–0.42 (–0.68 to [–0.07])	0.020
0.009	0.38 (0.10–0.61)	44	20 years	39	–0.47 (–0.69 to [–0.19])	0.002
0.003	0.50 (0.18–0.72)	32	14–20 years	30	–0.54 (–0.75 to [–0.22])	0.002

The larger patient cohort with EDSS measures includes those who had a telephone EDSS only.

groups. In the whole group, there was neither evidence of a curved trajectory (bootstrap $P > 0.9$) nor was there evidence at 5% level for curvature in any of the three groups, though the quadratic terms for both the secondary progressive multiple sclerosis (with bootstrap $0.1 < P < 0.2$) and CIS (bootstrap $0.2 < P < 0.3$) subgroups were negative, consistent with a levelling off, and positive for relapsing remitting multiple sclerosis (bootstrap $0.1 < P < 0.2$), consistent with accelerated growth. There was a borderline significant decelerating curvature in both CIS (bootstrap $P = 0.08$) and secondary progressive multiple sclerosis (bootstrap $P = 0.09$) compared to relapsing remitting multiple sclerosis.

T_2 lesion volumes at all time-points were strongly correlated with T_2 lesion volume at 20 years: T_2 lesion volume at baseline versus 20 years ($n = 55$, $r_s = 0.76$, $P < 0.001$); 5 years versus 20 years ($n = 52$, $r_s = 0.83$, $P < 0.001$); 10 years versus 20 years ($n = 53$, $r_s = 0.89$, $P < 0.001$); 14 years versus 20 years ($n = 47$, $r_s = 0.94$, $P < 0.001$).

For the whole cohort, T_2 lesion volume at all time-points (0, 5, 10, 14 and 20 years) was significantly correlated with 20-year EDSS (r_s values 0.48 to 0.67, $P < 0.001$) and MSFC z-scores [r_s values (–0.50) to (–0.61); $P < 0.001$]

(Table 4). There were similar correlations in those patients who developed CD multiple sclerosis only (Table 5).

For the whole cohort, a significant correlation was found between the change in T_2 lesion volume over the first 5 years and concurrent change of EDSS [$r_s = 0.59$ (95% CI 0.41–0.72); $P < 0.001$]. There were significant but weaker concurrent correlations for Years 5–10 and 10–14 and no significant correlation for Years 14–20. These correlations were similar for those who developed CD multiple sclerosis only (Table 6).

Discussion

This report provides prospectively acquired, longitudinal MRI and clinical data over a period averaging 20 years from CIS onset. By comparison, long-term follow-up of MRI findings and clinical course in other CIS cohorts has ranged from 7 to 10 years (Beck *et al.*, 2004; Minneboo *et al.*, 2004; Tintore *et al.*, 2006). Our cohort at 20 years has similar demographic features to the original cohort in terms of mean age, gender, clinical presentation and frequency of baseline MRI abnormalities (Table 1). The number of the cases ascertained at 20-year follow-up was about 50%

Table 6 Correlations between concurrent changes in MRI lesion volumes and changes in EDSS score

P-value	All patients			Clinically definite MS only		
	r_s (95% CI)	Number of patients	Interval	Number of patients	r_s (95% CI)	P-value
<0.001	0.59 (0.41–0.72)	62	0–5	43	0.69 (0.49–0.82)	< 0.001
0.002	0.40 (0.15–0.60)	53	5–10	36	0.43 (0.12–0.66)	0.008
0.002	0.41 (0.15–0.62)	48	10–14	34	0.46 (0.14–0.69)	0.006
0.165	0.20 (–0.08–0.46)	47	14–20	32	–0.03 (–0.37–0.31)	0.853

higher when compared with the 14-year follow-up, and provides a robust long-term assessment of the MRI–clinical relationship in relapse-onset multiple sclerosis. The 20-year follow-up with clinical and MRI data is the longest study of the CIS patients. It also reflects the unmodified natural history of MRI lesion load in CIS and multiple sclerosis: only 4 out of 107 patients were treated with disease-modifying therapies, all four after developing CD multiple sclerosis. Other long-term studies have often included substantial proportions of patients who received disease-modifying therapies, which may modify the relationships between MRI and disability (Rudick *et al.*, 2006).

Baseline MRI and long-term clinical outcome

The present report confirms and extends the findings of the previous follow-up studies of this cohort (Morrissey *et al.*, 1993; O’Riordan *et al.*, 1998a; Brex *et al.*, 2002). It shows that after 20 years, CIS patients with an abnormal MRI scan at presentation are far more likely to convert to CD multiple sclerosis than those with a normal scan (82% versus 21%; Table 2). It is however noteworthy that 18% of those with an abnormal scan at presentation did ‘not’ develop CD multiple sclerosis. This proportion is higher than that reported at 14-year follow-up (12%), which likely reflects more complete ascertainment of cases in our latest follow-up. The detection of such ‘non-converting’ cases after 20 years supports the approach of the new multiple sclerosis diagnostic criteria that do not allow a diagnosis of multiple sclerosis in CIS patients with a single abnormal MRI scan without evidence for dissemination in time (Polman *et al.*, 2005). On the other hand, it appears that the higher risk for multiple sclerosis that is associated with an abnormal scan is evident whether there are few or many lesions.

Brain T₂ lesion detection, as several studies have shown, is resolution and slice-thickness dependent (Bradley and Glenn 1987; Sicotte *et al.*, 2003; Nielsen *et al.*, 2006). While it is possible that with contemporary MR imaging acquiring thinner slices on higher-field strength magnets, the proportion of people with normal baseline MRI scan converting to multiple sclerosis might be lower than that reported in the present study (21%), recent CIS studies also report conversion to multiple sclerosis of patients with a normal brain MRI (Swanton *et al.*, 2007).

The CD multiple sclerosis group in our study exhibited a wide spectrum of disability at Year 20. Whilst 42% had developed secondary progression, 39% had a benign course with minimal disability (EDSS ≤ 3). The percentage of people with benign multiple sclerosis in our cohort is higher than that reported on other cohorts of patients (Eriksson *et al.*, 2003; Nilsson *et al.*, 2005). Optic neuritis presentation has been associated with better outcome in several reports (Beck *et al.*, 2003, 2004; Confavreux *et al.*, 2003; Nilsson *et al.*, 2005) and nearly half of our cohort presented with optic neuritis. However, their rate of conversion to CD multiple sclerosis was high (67%) and the 20-year disability status of the optic neuritis group did not differ significantly from the non-optic neuritis group, so this does not appear to explain the high proportion of minimally disabled multiple sclerosis patients in our cohort. However, our patients were followed up prospectively from their first episode, before a diagnosis of multiple sclerosis was established, and efforts were made to follow up all patients, whether or not they had developed multiple sclerosis at an earlier time-point. Some of those with mild/benign multiple sclerosis may not be followed up at a routine multiple sclerosis or general neurology clinics and may not be detected in prevalence studies.

Patients with a higher number of lesions at baseline were somewhat more likely to be disabled after 20 years: an EDSS of 6 or more, indicating that assistance is required for walking, was seen in 45% with ≥ 10 lesions, 35% with 4–9 lesions, 18% with 1–3 lesions and 6% with no lesions, suggesting that lesion number has some predictive effect for disability (Table 2). Conversely, about one-third (35%) of patients with ≥ 10 lesions had minimal disability after 20 years (EDSS ≤ 3) and 18% had not developed CD multiple sclerosis. Such a wide spectrum of outcomes indicates that MRI lesion number at CIS presentation provides limited prediction for long-term disability.

MRI lesion volume evolution over 20 years

This study sheds new light on lesion load evolution and the natural history of CIS and multiple sclerosis. The rate of lesion volume growth over 20 years was clearly higher in those developing secondary progressive multiple sclerosis than in those who retained a relapsing remitting course, and this difference became clearly evident 5 years after the

first CIS presentation (Fig. 1). These findings should be investigated in other cohorts of patients with more frequent follow-ups to determine whether an earlier than 5-year time-point might show these differences (lesion volume measures were not available at the 1-year follow-up in the present cohort). Reliable early identification of patients at high risk for secondary progression is important: for such individuals there is a high priority to develop disease-modifying treatments that delay or prevent secondary progression.

Immunomodulatory treatment with beta interferon in CIS patients with abnormal MRI for up to over 3 years decreases the number of new MRI lesions, delays development of CD multiple sclerosis (Jacobs *et al.*, 2000; Comi *et al.*, 2001; Kappos *et al.*, 2006), and possibly slows development of early disability (Kappos *et al.*, 2007). While our natural history cohort data suggest that slowing of lesion volume increase might delay or prevent secondary progression, an alternative consideration is that the white matter T₂ lesion volumes seen in our study may have increased in parallel with anatomically and mechanistically separate pathological changes that are more directly responsible for long-term disability e.g. pathology in normal-appearing brain white and grey matter or spinal cord disease. It is plausible that if a therapy prevents new T₂ lesions but not abnormalities in normal-appearing white and grey matter, secondary progression and disability will still evolve. There is a need to investigate the long-term relationship of other MRI measures that are abnormal in CIS and early relapsing remitting multiple sclerosis e.g. brain volume and quantitative measures of normal-appearing white and grey matter (Filippi *et al.*, 2003, Dalton *et al.*, 2004; Fernando *et al.*, 2004, 2005) with the long-term clinical course both in untreated patients and those on disease-modifying treatment.

Despite the loss of some subjects to clinical and/or MRI examination and changes in MRI technology, a robust long-term relationship of lesion volume and EDSS was observed, albeit of a moderate strength only. The lesion volumes at all time-points were correlated with the 20-year EDSS suggesting that the moderate predictive value of T₂ lesion volume appears early in the disease.

Several reasons might explain why white matter lesion volume and disability are only moderately—rather than strongly—correlated. First, not all patients were followed up with MRI. Secondly, the detection of the T₂ hyperintense lesions and lesion load is resolution dependent (Filippi *et al.*, 1995; Erskine *et al.*, 2005) and the use of 5-mm thick slices (or 10 mm in few scans at baseline) will have limited detection of smaller lesions. In addition, changes in scanner hardware and software, during the follow-up period could have had some effect on a lesion measurement precision (earlier measurements less sensitive than the later ones). However, it should not have affected the relative ranking of patients with regard to lesion volumes, and hence the strength of clinical correlations observed.

Furthermore, there was no evidence of a step increase in T₂ lesion volume between Years 5 and 10 when the change in scanner and field strength (from 0.5 to 1.5) Tesla occurred. Thirdly, with current MRI resolution, intra-cortical lesions remain largely undetected (Kidd *et al.*, 1999; Geurts *et al.*, 2005a, b). Fourthly, demyelinating lesions also occur in the spinal cord in CIS and multiple sclerosis patients (O’Riordan *et al.*, 1998a, Swanton *et al.*, 2007). It is possible that some patients in our cohort had more severe spinal disease with less abnormality in the brain. Multiple sclerosis cord pathology may be independent of concomitant brain changes, develop at different rates according to the disease phenotypes and be associated to medium-term disability accrual (Agosta *et al.*, 2007). Fifthly, despite a high sensitivity to global tissue damage, the T₂ lesion volume measure lacks pathological specificity—it is collectively sensitive to inflammation, oedema, demyelination and axonal loss as well as re-myelination and is therefore not specific for the irreversible damage to myelin and axons that underpin irreversible disability in multiple sclerosis (Guttmann *et al.*, 1995).

Sixthly, abnormalities in normal-appearing white and grey matter are also detected early on the disease (Fernando *et al.*, 2004, 2005; Davies *et al.*, 2004; Audoin *et al.*, 2006) and have the potential to influence the clinical course. The concurrent correlation between T₂ lesion volume and EDSS change was most apparent in the first quinquennium and was not present in the fourth and final follow-up interval (Years 14–20) (Table 5). This suggests that the mechanisms of disability progression may change over time. Disability may be more dependent on lesion volume changes earlier on and less dependent later on (Li *et al.*, 2006). The investigation of other MRI measures—atrophy, normal-appearing white and grey matter and the spinal cord abnormality—could explore the hypothesis that they may be more closely related to disability changes at a later stage.

Finally, when looking at the associations between lesion volume and disability it is important to take into account the limitations of EDSS scale—e.g. intraobserver variability, being heavily weighted towards physical disability with limited assessment of key clinical features such as cognitive and sphincter dysfunction. In addition, interpreting the association between a succession of changes and a later outcome can be difficult for a number of reasons. Subjects with large changes during one period often have smaller changes over the next period, due to a phenomenon similar to regression to the mean. There also may be ‘ceiling effects’, where subjects with large early changes have less room for later changes. The rate of EDSS change in multiple sclerosis is not constant over time, with typically longer periods stationed at certain levels (e.g. 3 and 6) than others. Furthermore, there were some differences in the patient cohorts studied at the various study time-points—it is possible that this has influenced the results.

Is the MRI lesion volume increase linear or non-linear?

Our analysis suggests a relatively linear—or constant— increase in lesion volume in multiple sclerosis over the 20 years of follow-up, whether patients retain a relapsing remitting course or develop secondary progression. Further analysis investigating for non-linear changes revealed a non-significant trend in secondary progressive patients—who had an overall 3-fold greater increase in volumes than those who were still relapsing remitting—for the rate of lesion volume increase to slow over time. However, unlike the findings in a recent cross-sectional study (Li *et al.*, 2006), we did not detect a definite or complete plateauing of lesion volume with the higher levels of disability associated with secondary progression, at least within the 20-year time frame of the study. Because of their disability, proportionately more of the secondary progressive multiple sclerosis patients were not able to undergo MRI scans at later time-points and the imaging data at these times reflect a group of slightly less disabled patients—whether this contributes to the slight non-linearity is uncertain. Future longitudinal studies of larger cohorts may provide clarification.

In summary, this long-term follow-up study demonstrates that T₂ brain lesions have a moderate correlation with disability and their predictive value appears early on the disease. Lesion load continues to increase for at least 20 years in relapse-onset multiple sclerosis patients and the rate of lesion growth in those who develop secondary progressive multiple sclerosis is higher than those who retain a relapsing remitting course.

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