Baseline MRI predicts future attacks and disability in clinically isolated syndromes

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Abstract—*Objective:* To determine the relation between baseline MRI and both conversion to multiple sclerosis (MS) and development of disability in a cohort of patients with clinically isolated syndromes (CIS). *Methods:* From 1995 to 1998, 175 consecutive patients with CIS underwent brain MRI within 3 months of their first attack and again 12 months and 5 years later. We studied the number and location of lesions at baseline and development of new T2 lesions. We also analyzed conversion to MS and development of disability (Expanded Disability Status Scale [EDSS] $\geq$ 3.0). *Results:* We included 156 patients with CIS followed for a median of 7 years. Compared to the reference group with 0 Barkhof criteria at baseline MRI, patients with one or two Barkhof criteria showed an adjusted hazard ratio (HR) of 6.1 (2.2 to 16.6) and patients with three to four Barkhof criteria of 17.0 (6.7 to 43) for conversion to MS and differentiated patients with low, medium, and high conversion risk. EDSS at year 5 correlated with baseline number of Barkhof criteria ($r = 0.46$, $p < 0.0001$). When categorizing by number of baseline lesions, similar results were seen. Patients with a baseline MRI with three to four Barkhof criteria had an adjusted HR of 3.9 (1.1 to 13.6) for reaching EDSS $\geq$ 3.0. Only 10% of the latter had disability at year 5, but 40% reached this at 8 years. *Conclusions:* Baseline MRI determines the risk for converting to clinically definite multiple sclerosis and correlates with disability at 5 years. The proportion of patients developing disability is low during the first 5 years but rapidly increases shortly after.

NEUROLOGY 2006;67:968–972

Multiple sclerosis (MS) is characterized by recurrent attacks of neurologic dysfunction in over 80% of patients. These patients present initially with a clinically isolated syndrome (CIS), typically optic neuritis, internuclear ophthalmoplegia, or partial myelitis. Once a first CIS has occurred, it is important to estimate the future risk of developing MS and disability. A number of clinical features, laboratory investigations, and MRI abnormalities have been associated with an increased risk of progression to MS. MRI, however, has been shown to be the most informative surrogate marker.[1-6] The group from London National Hospital reported the initial findings from 109 CIS patients, 89 of whom were reassessed at 5 years.[3] Sixty-four percent had an abnormal baseline MRI and 65% of these developed clinically definite MS (CDMS) at follow-up compared with only 3% in the group of patients without MRI abnormalities. The presence of MRI lesions was also associated with higher disability levels at 5 years. These data were further confirmed at 10 and 14 years of follow-up.[4-5] Several other prospective studies performed mainly in patients with optic neuritis with a follow-up of at least 5 years have confirmed that the presence of even few lesions in the baseline MRI is associated with an increased risk of developing MS.[6,7] Nevertheless the relationship between baseline MRI and disability at follow-up remains controversial. Recently the 10th year follow-up of the Optic Neuritis Treatment Trial (ONTT) has failed to find correlations between baseline MRI and disability at follow-up.[7] The aim of our study was to determine the relation between baseline MRI and both conversion to MS and development of disability in a cohort of patients with first attacks.

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Methods. The present study is based on longitudinal clinical, CSF, and MRI data prospectively acquired from a cohort of patients with CIS recruited in our center between 1995 and 1998. Patients presenting for the first time with monophasic neurologic symptoms of the type seen in MS were recruited at the Vall d'Hebron University Hospital in Barcelona. Inclusion criteria were as follows: 1) a CIS suggestive of CNS demyelination involving the optic nerve, brainstem, spinal cord, or other topography, not attributable to other diseases; 2) age < 50 years; 3) onset of symptoms within 3 months of both clinical and MRI examinations; and 4) follow-up of more than 5 years.

Clinical, CSF, and MRI assessments have been previously detailed elsewhere.[1,8]

Briefly, patients were initially asked about any previous history of neurologic disturbances and seen every 3 to 6 months. IgG

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Disclosure: Our unit has received research grants from drug companies named in the present study. J.R., M.T., and X.M. have received scientific honoraria and travel expenses from all companies mentioned in this study. No financial support has been received for the present study.

Received January 18, 2006. Accepted in final form May 18, 2006.

OB were examined by agarose isolectric focusing combined with immunoblotting and avidin-biotin amplified double-antibody peroxidase staining.[9] Brain MRI was performed after the first demyelinating event and repeated after 12 months and 5 years of follow-up. MRI was performed on a 1.0-T or 1.5-T machine with a standard head coil. MRI included the following pulses: transverse proton-density and T2-weighted conventional spin echo, and in some patients contrast-enhanced T1-weighted spin-echo. The MRI scans were assessed by two radiologists who were blinded to clinical follow-up. We applied the four Barkhof criteria.[10] For patients in whom a contrast-enhanced T1-weighted sequence was obtained, the presence of at least one enhancing area related to a lesion seen on T2-weighted images was scored. Number of baseline lesions and presence of new lesions at follow-up was also scored.

Patients with one or two Barkhof criteria on one hand and patients with three or four Barkhof criteria on the other hand were grouped because of their very similar behavior, thus three different categories for MRI Barkhof criteria were specified. Four different categories for number of lesions were also considered: 0 lesions; 1 to 3 lesions; 4 to 9 lesions; 10 or more lesions.

In patients with brainstem syndromes, patients with a single symptomatic lesion were considered to have a normal MRI.

According to the MRI component of the new McDonald criteria, evidence of dissemination in space (DIS) was provided in one of two ways[11-12]: (DIS1) presence of three out of four MRI Barkhof criteria; (DIS2) presence of at least two T2 lesions plus OB. Dissemination in time (DIT) was fulfilled when at least one new T2 lesion had appeared in the follow-up scan.[11] The MRI criteria were met when patients fulfilled the MRI definitions for dissemination in time and space. In addition, patients with a second clinical attack also fulfilled the new criteria. A diagnosis of conversion to CDMS was made when new symptoms occurred after an interval of at least 1 month and only when other diagnoses had been excluded. CDMS was diagnosed when there was a second attack with a new neurologic abnormality that was confirmed by examination.[13]

Time of follow-up was calculated on the difference between the date of the last visit and the date of the event.

Disability was evaluated according to the Expanded Disability Status Scale (EDSS) score in each visit and only EDSS performed during stability periods were considered. The cutoff for defining the presence of disability at year 5 was established when EDSS was superior or equal to 3.0.[14] Time to reach EDSS 3.0 considering the full follow-up was also considered.

Statistical analysis. Parametric and nonparametric descriptive statistics were performed. Spearman rank correlation coefficients were used to approximate association between continuous variables. Kaplan-Meier analysis was used to estimate cumulate survival probabilities and to build survival plots. In order to assess the association between baseline MRI (number of Barkhof criteria and number of lesions) and both the time to conversion to CDMS and the time to development of disability, multivariate analysis using Cox proportional hazard regression was performed. Age at disease onset, sex, topography of first attack, and treatment were considered as potentially relevant covariates. Age was categorized according to 25th–50th–75th percentiles.

Results. Of 175 patients, 120 were women and 55 were men with a mean age at onset of 29 years. Sixty-five patients (37%) presented with optic neuritis, 48 (27%) with brainstem symptoms, 49 (28%) with spinal cord syndrome, and 13 (7%) patients had a different presentation (hemispheric, polyregional, or undetermined topography presentation). The median clinical follow-up time was 84.4 months (7 years) (IQR: 74 to 93 months).

One patient was excluded because a diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy was finally made. Twenty-seven patients were initially considered to be lost to follow-up, whom we attempted to contact by phone to find out their current status (occurrence of a second attack and EDSS[15]). The 9 of the 27 patients lost to follow-up who were reached were included in the final analysis. Demographic and clinical characteristics of these patients (10% of the total cohort) lost to follow-up were similar to those of the whole group of patients (data not shown). A total of 156 patients (89%) were finally included in the analysis.

CDMS was diagnosed in 66 patients (42%). Fifty-five (35%) converted during the first 5 years and 11 converted after this period. The median conversion time for the whole cohort is 104 months and the mean 75.5 (SE: 3.6) months.

Baseline MRI. Fifty-three patients (34%) had a normal brain MRI. Of these, 4 patients (8%) developed a second relapse during follow-up and 5 (9%) developed MS according to McDonald criteria. A total of 103 patients (66%) had an abnormal baseline MRI. Of these 62 (60%) developed CDMS and 74 (72%) developed MS according to McDonald. The percentages of patients converting to CDMS during the study period according to the number of Barkhof criteria fulfilled and number of baseline lesions are shown in table 1. Conversion to CDMS ranges from 9% for 0 Barkhof criteria to 61% for three to four Barkhof criteria. Considering number of lesions, percentages go from 8% for normal brain MRI to 73% for patients with 10 or more lesions. Hazard ratio (HR) and 95% CI (adjusted by age, sex, and topography of first attack) for Barkhof criteria, taking 0 Barkhof criteria as the reference group, are shown in table 1. HRs range from 6.1 to 17.0 for developing CDMS. Table 1 also shows adjusted HR and 95% CI for each category taking 0 lesions as a reference category. HRs range from 4.3 to 19.3 for developing CDMS. Survival curves for cumulative probability of developing CDMS during follow-up according to baseline MRI features are shown in figure 1 and figure E-1 on the*Neurology* Web site at www.neurology.org. Figure 1 shows three different types of patient groups who were classified as having low, medium, and high risk for early development to CDMS. Figure E-1 shows the same approach dividing patients by number of baseline lesions. Mean time to CDMS according to each category is also shown in table 1. Note that time to CDMS is shorter in each category with respect to the previous.

First year and 5-year MRI. A total of 145 patients (93%) had at least one MRI scan performed during follow-up. No differences were found between patients with and without at least one follow-up scan in terms of conversion or baseline MRI features. New lesions at follow-up were seen in 76 patients (52%).

Poser vs McDonald criteria. Sixty-six patients (42%) presented a second attack (CDMS) during follow-up. Considering the MRI definitions proposed by McDonald, a diagnosis of MS could be made in 79 patients (51%). The number of patients fulfilling both definitions (CDMS by Poser and MS by McDonald) according to the Barkhof criteria or number of lesions at baseline MRI are presented in table 1.

Development of disability. EDSS at year 5. EDSS at year 5 was missing in three patients. Ten patients (7%) had an EDSS of 3.0 or higher at year 5. Of these, 7 patients had 10 or more lesions on the MRI at baseline. The correlation between EDSS at year 5 and the number of baseline Barkhof criteria (Spearman rho coefficient) was 0.46 ($p < 0.001$). Correlations between EDSS at year 5 and MRI measures were as follows: number of baseline lesions 0.43 ($p < 0.001$), presence of new T2 lesions at 12 months 0.39 ($p < 0.001$), and presence of new lesions at year 5, 0.51 ($p < 0.01$).

Table 1 *Patients converting to CDMS or MS according to number of Barkhof criteria or number of lesions in baseline MRI*

	CDMS					MS (McDonald)	
	N1/N2	%	HR	95% CI	Mean survival time (SE)	N1/N2	%
No. Barkhof criteria							
0	5/59	9	1*		103.3 (3.5)	6/59	10.2
1–2	16/34	44	6.1	2.2–16.6	77.7 (6.9)	20/36	55.6
3–4	45/61	61	17.0	6.7–43.5	46.8 (5.3)	53/61	86.9
No. lesions							
0	4/52	7.7	1*		104.8 (3.2)	5/52	9.6
1–3	7/23	30.4	4.3	1.3–14.8	83.6 (9.1)	8/23	34.8
4–9	9/18	50	7.4	2.3–24.5	71.3 (9.6)	14/18	77.8
10 or more	46/63	73	19.3	6.8–54.6	47.7 (5.3)	52/63	82.5

* 1: Reference category.

CDMS = clinically definite multiple sclerosis; N1/N2 = ratio between patients fulfilling CDMS or MS and total number of patients fulfilling the baseline MRI criteria; HR = hazard ratio (adjusted by age, sex, and topography of first attack); 95% CI = confidence interval. Mean survival time to CDMS is expressed in months.

that the great majority of patients have not reached EDSS 3.0 within the first 5 years. Table 2 shows that the mean time for reaching a disability level of 3.0 is greater than 98 months (8 years) in all groups of patients. Adjusted HR for reaching EDSS 3.0 was 3.9 (1.1 to 13.6) for patients with 3 or 4 Barkhof criteria and 3.6 (1.1 to 12.7) for patients with 10 or more lesions at baseline. After 8 years, around 40% of patients with CDMS had reached an EDSS of 3.0 and the same was true for patients with a baseline MRI with 3 or 4 Barkhof criteria or 10 or more lesions at baseline MRI (figure 2, A and B, and figure E-2).

In summary, only 10% of patients with a baseline MRI with high risk had an EDSS of 3.0 or more at year 5, but 40% reached this outcome at 8 years according to Kaplan Meier curves.

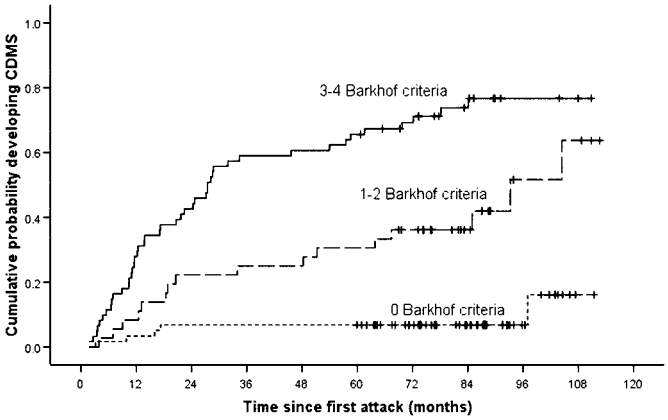

Figure 1. Development of clinically definite multiple sclerosis according to baseline MRI. Number of Barkhof criteria: no Barkhof criteria (low risk) dotted line, one or two Barkhof criteria (intermediate risk) dashed line, and three or four Barkhof criteria (high risk) solid line. Note that curves for Barkhof criteria 1 and 2 have been unified into one single category because of their very similar behavior and the same approach has been used for Barkhof criteria

Disease-modifying drugs. At year 5, 29% of the patients were on disease- modifying drugs, mainly one of the three available beta- interferons, all of whom had started treatment after their second attack. When patients had at least two relapses within 3 years, disease-modifying drugs were proposed and discussed with the patients. The mean time from CIS onset to drug prescription was 37 months (SD 24). The mean time on treatment was 47 months (SD 23). Mean EDSS at 5 years for patients on treatment was 2.2 (SD 1.3) compared to 0.9 (SD 0.9) ($p < 0.001$) in patients not receiving disease-modifying drugs.

Multivariate analysis for time to reach EDSS of 3.0 controlling for covariates such as sex, age, topography of first attack, and disease-modifying drug treatment showed that disease-modifying drugs was an important predictor of disability. Nevertheless, we consider that this is not a cause but a consequence. Patients were put on treatment because their disease was active. All patients on disease-modifying drugs had an abnormal baseline MRI compared to 55% of the non-treated patients. Seventy-nine percent of the treated patients vs 26% of the non-treated patients fulfilled three to four Barkhof criteria at baseline ($p < 0.0001$). In the same sense, 97% of the treated patients had new lesions on the follow-up scans vs 38.5% in the non-treated group ($p < 0.0001$).

Discussion. Of 156 patients followed for at least 5 years, 60% of patients with a CIS and an abnormal baseline MRI have developed CDMS. When adding MRI McDonald definitions, the percentage increases to beyond 70%. Patients with a normal baseline MRI developed CDMS in less than 8%, which could increase to 10% considering McDonald criteria. These results are in agreement with other published data.[3,6,16,17] As shown by the Kaplan-Meier curves, the number of lesions at baseline is related to the time to reach CDMS, therefore patients with fewer lesions at baseline require a longer follow-up to reach conver-

Table 2 *Patients reaching EDSS 3.0 according to baseline MRI or clinical status*

	EDSS ≥ 3.0				
	N1/N2	%	HR	95% CI	Mean survival time (SE)
No. Barkhof criteria					
0	3/59	5.1	1*		114.2 (3.0)
1–2	5/36	13.4	1.9	0.4–8.1	100.5 (3.5)
3–4	15/61	24.6	3.9	1.1–13.6	98.2 (3.9)
No. lesions					
0	3/52	5.8	1*		105.9 (3.1)
1–3	2/23	8.7	1.3	0.2–8.0	113.8 (3.9)
4–9	2/18	11.1	1.4	0.2–8.7	98.6 (4.3)
10 or more	16/63	25.4	3.6	1.0–12.7	97.8 (3.9)
Clinical status					
CIS	5/90	5.6	1*		106.7 (2.1)
CDMS	18/66	27.3	4.3	1.6–11.7	100.1 (3.9)

* 1: Reference category.

EDSS = Expanded Disability Status Scale; N1/N2 = ratio between patients reaching an EDSS of 3.0 and total number of patients in each category according to baseline MRI or clinical status; HR = hazard ratio (adjusted by age, sex, topography of first attack, and disease-modifying drugs); 95% CI = confidence interval. Mean survival time to CDMS is expressed in months; CIS = clinically isolated syndromes;
CDMS = clinically definite multiple sclerosis.

of baseline lesions. Kaplan-Meier curves very clearly differentiate three groups of patients with low, intermediate, and high risk of developing CDMS at short term (figures 1 and E-1). Patients with 0 Barkhof criteria have a low risk of developing CDMS, patients with 1 and 2 Barkhof criteria an intermediate risk and patients with three or four Barkhof criteria will develop CDMS in a very short lapse of time. These figures allow us to identify those patients that are at high risk to present a second attack shortly after the first one. In this sense, the cutoff established for the Barkhof criteria (three or more) looks very useful.[10] Nevertheless it is also true that patients fulfilling one or two Barkhof criteria will probably develop CDMS after a longer follow-up. Therefore this group of patients without DIS criteria according to McDonald criteria should be also carefully followed as with longer follow-up, they will probably develop the disease. In this sense, the McDonald criteria have been claimed to be more prognostic than diagnostic.[18] Moreover, the conversion rate applying Poser or McDonald criteria is similar after a certain time of follow-up. Our group showed that after 12 months of follow-up, the McDonald criteria more than tripled the number of patients diagnosed with MS vs the Poser criteria.[8] The present study shows that after 5 years of follow-up, we could only identify 10% more patients using the McDonald vs Poser criteria. This percentage may obviously increase depending on the number of MRI scans performed during the follow-up period.

As for development of disability, our study confirms that the disability development defined as

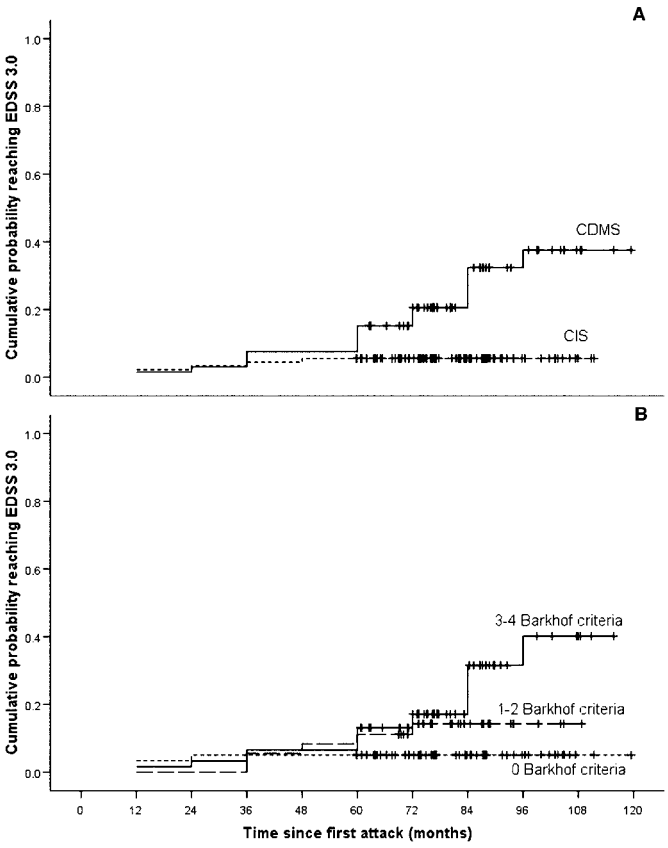

Figure 2. Time to reach an Expanded Disability Status Scale score of 3.0 according to baseline MRI. (A) Patients with (solid line) and without (dotted line) clinically definite multiple sclerosis. (B) Number of Barkhof criteria: 0 Barkhof criteria (low risk) (dotted line), one or two Barkhof criteria (intermedium risk) (dashed line), and three or

MRI at baseline and that the number of baseline lesions and the number of Barkhof criteria have similar Spearman rho coefficients 0.43 and 0.46. Others also found a significant correlation of 0.45 between the number of MRI lesions at presentation and disability at follow-up.[3] In the ONTT study group, the disability level after 10 years appeared to be unrelated to the number of baseline lesions.[7] Unfortunately, the ONTT study was not designed to assess long-term disability in MS. Surprisingly, moderate or severe disability was present in 29% of the patients with no lesions on the baseline MRI. In our study, the presence of new lesions at follow-up was also correlated with disability at year 5 with a correlation index of 0.41 ($p < 0.001$). The occurrence of disability in our cohort, at 5 years of follow-up, defined as an EDSS of 3.0 or higher, was seen in 10 patients (7%), all of whom developed MS. This percentage is considerably lower than the 20% reported by the London National Hospital group.[3] Although we cannot exclude that patients lost to follow-up (10%) may be partially responsible for this difference, the patients lost to follow-up were similar to the whole populations as to baseline characteristics and severe cases are usually less prone to giving up on clinical control. Another explanation can be found in recent updates of natural history cohorts where the degree of disability achieved by these populations is clearly lower than previously reported.[19] The ONTT Study Group also pointed to a milder disease course after 10 years of follow-up.[7] Genetic background may also contribute to these differences. In Northern European countries, MS is two- to fourfold more prevalent than in Mediterranean countries.[20-22] This difference in susceptibility to develop MS may also have a translation into clinical characteristics, such as disability. Disease-modifying drugs were specifically prescribed to patients with a more aggressive disease course, which probably explains the observation that this population was then more disabled than non-treated patients. Although disease-modifying drugs have consistently demonstrated a reduction in relapses in treated patients, their contribution to delay disability remains unproven.[23-25] Genetic or environmental factors may be responsible for the milder character in terms of disability seen in our cohort at 5 years. After this time point, disability clearly worsens.

Acknowledgment

The authors thank Xavier Vidal for statistical advisement and Joseph Graells for language editing. The authors also thank FEM (Fundació Esclerosi Multiple), María José Vicente and Rosalía Hornos (nurses of the MS Unit), and Red CIEN and Institut Català de Investigació en Neurociències (ICIN) for supporting in part the MS Unit at their center.

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