Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis?

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ABSTRACT

Background: To evaluate whether oligoclonal bands (OB) add information to MRI in predicting both a second attack and development of disability in patients with clinically isolated syndromes (CIS).

Methods: From 1995 to 2006, 572 patients with CIS were included in a prospective study. Patients underwent brain MRI and determination of OB within 3 months of first attack. The number and location of lesions and presence of OB were studied. We analyzed time to second attack and to Expanded Disability Status Scale 3.0 according to number of Barkhof criteria (BC) and the presence or absence of OB.

Results: We studied 415 (73%) patients with CIS with both baseline MRI and determination of OB. Patients were followed for a mean of 50 months (SD 31). Compared to the reference group with 0 BC at baseline MRI, patients with one to two BC showed a hazard ratio (HR) for conversion to CDMS of 3.8 (2.0 to 7.2) and patients with three to four BC of 8.9 (4.8 to 16.4). Of the total cohort, OB were positive in 61% of the patients. However, broken down by MRI group, OB were positive in 31% of those with no BC; 69% of those with one to two BC; and 85% of those with three or four BC. The presence of OB increased the risk of a second relapse (HR 1.7; 1.1 to −2.7) independently of baseline MRI but did not modify the development of disability.

Conclusions: Presence of oligoclonal bands doubles the risk for having a second attack, independently of MRI, but does not seem to influence the development of disability.

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GLOSSARY

BC = Barkhof criteria; **CDMS** = clinically definite multiple sclerosis; **CIS** = clinically isolated syndromes; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **MS** = multiple sclerosis; **OB** = oligoclonal bands.

Patients with multiple sclerosis (MS) usually present with a first attack or clinically isolated syndrome (CIS) such as optic neuritis, brainstem syndromes, or partial myelitis. MRI is nowadays mandatory in such patients both to exclude other diseases and to establish the risk and time to a second attack as well as the probability to develop disability. In a recent article, we showed that baseline MRI was a useful tool to differentiate patients with CIS with low, medium, and high risk for developing clinically definite MS (CDMS).[1] The role of other surrogate markers in patients with first attacks is at present controversial. The presence of serum antibodies to MBP and MOG in patients with CIS was associated with rate and time to conversion to CDMS, although difficulties for several groups including ours to validate such results have limited the use of these antibodies in clinical practice.[2-4] To date, the presence of oligoclonal bands (OB) remains the best biologic marker to predict CDMS but its role in predicting development of disability remains controversial.[5-10] Due to the fact that this is an uncomfortable test for patients,

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and that in many countries, CSF studies are not performed in most patients with CIS, the aim of our study was to evaluate whether the presence of OB adds additional information to baseline MRI in predicting conversion of CIS to CDMS and development of disability.

METHODS Patients included in this prospective study were recruited at our hospital or referred to us by physicians, neurologists, and ophthalmologists of the neighboring area, presenting with first time monophasic neurologic symptoms of the type seen in MS. Inclusion criteria were 1) CIS suggestive of CNS demyelination involving mainly the optic nerve, brainstem, or spinal cord not attributable to other diseases; 2) age <50 years; and 3) syndrome onset within 3 months of clinical, CSF, and MR imaging examinations. Clinical, CSF, and MRI assessments have been previously described elsewhere.[1,11] Briefly, patients were initially asked about any previous history of neurologic disturbances and seen on a regular basis. Any neurologic symptom suggestive of MS lasting more than 24 hours, even not confirmed by a previous clinician, was considered as an exclusion criterion. IgG OB were examined by agarose isoelectric focusing combined with immunoblotting and avidin-biotin amplified double-antibody peroxidase staining.[12] 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 (BC).[13] Number of baseline lesions was also scored. Patients with one or two BC criteria on one hand and patients with three or four BC on the other hand were grouped because of their very similar behavior. Thus three different categories for MRI BC were specified. Another three different categories by number of lesions were also considered: 0 lesions; 1 to 9 lesions; 10 or more lesions.

Of patients with brainstem syndromes, patients with a single symptomatic lesion were considered to have a normal MRI. 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.[14]

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) on each visit though only EDSS scores recorded during stability periods were considered. Time to reach EDSS 3.0 taking the full follow-up was studied. EDSS 3.0 corresponds to a patient who is fully ambulatory, but has moderate disability in at least one system function or mild disability in three or four functional systems. EDSS scale evaluates seven different functional systems (visual, brainstem pyramidal, cerebellar, sensory, bladder/bowel, and mental).

Statistical analysis. Parametric or nonparametric comparative statistics were performed according to the normality of the distributions of the continuous variables. χ^2 test was performed to compare categorical variables. Kaplan-Meier analysis was used to estimate cumulative survival probabilities and to build survival plots. In order to assess the association between presence of OB and both time to CDMS and time to development of disability, multivariate analysis using Cox proportional hazard regression was performed. MRI parameters such as number of BC and number of lesions were considered as potentially relevant covariates. Time on treatment was included in the models as a time-dependent covariate.

Table 1 Demographic, clinical, and MRI characteristics of patients with and without determination of OB

	OB done, n = 415	OB not done, n = 157	*p* Value
Age, y, mean (SD)	29.5 (8.2)	31.0 (8.7)	0.057
Ratio women/men	2.9	1.9	0.035
Follow-up, mean (SD)	49.9 (31.3)	46.6 (43.8)	0.021
% Optic neuritis	34	50	0.0005
% Normal MRI	27	41	0.002

OB = oligoclonal bands.

RESULTS Of the 572 patients in this study, 412 (72%) were women and 160 (28%) were men. Mean age at onset was 30 (SD 8.4) years. A total of 218 (38%) presented with optic neuritis, 150 (26%) with brainstem symptoms, 141 (25%) with spinal cord syndrome, and the remaining 63 (11%) patients had a different presentation (hemispheric, polyregional, or undetermined topography presentation).

Nine patients initially included in the study (n = 581) have not been counted in the total number of patients (n = 572). For those, an alternative diagnosis appeared during follow-up: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (1); Leber disease (1); lacunar stroke (2); alcohol optic neuropathy (1); brain tumor (1); missed previous attack (3).

OB. OB were determined in 415 (73%) patients of the total cohort. Patients were followed for a mean of 50 months (SD 31). Demographic, clinical, and MRI characteristics of the 157 patients (27% of the total cohort) in whom a lumbar puncture was not performed are shown in table 1. Men with optic neuritis and a normal baseline MRI were more prone to turning down a CSF examination.

In the group of patients in whom OB were determined, these were positive in 254 (61%). However, broken down by MRI group, OB were positive in 31% of those with no BC; 69% of those with one to two BC; and 85% of those with

Table 2 Hazard ratio associated with conversion to CDMS according to number of Barkhof criteria, number of lesions in baseline MRI, and presence of OB

	CDMS			
	N1/N2	%	HR	95% CI
No. Barkhof criteria				
0	14/146	10	1[a]	
1–2	40/97	41	3.8	2.0–7.2
3–4	90/149	60	8.9	4.8–16.4
OB				
Negative	26/161	16	1[a]	
Positive	127/254	50	1.709	1.077–2.711
No lesions				
0	10/113	9	1[a]	
1–9	39/118	33	3.4	1.7–6.9
10 or more	92/155	59	9.2	4.6–18.7
OB				
Negative	26/161	16	1[a]	
Positive	127/254	50	1.681	1.1058–2.673

1[a] = Reference category.
CDMS = clinically definite multiple sclerosis; OB = oligoclonal bands; N1 = number of patients developing CDMS; N2 = number of patients fulfilling the baseline criteria; HR = hazard ratio (adjusted by age, gender, time on treatment, and presence of OB).

three or four BC ($p < 0.0001$). When considering number of baseline lesions, OB were positive in 27% of patients with 0 lesions, 64% of patients with 1 to 9 lesions, and 83% of patients with 10 or more lesions ($p < 0.0001$). The presence of OB was significantly associated with the development of CDMS. The percentages of patients converting to CDMS during the study period according to presence or absence of OB are shown in table 2. Patients with negative OB were more likely to present with optic neuritis, to have a normal MRI, to have a lower risk for conversion to CDMS, and to have a shorter follow-up (table 3).

Baseline MRI. We were able to analyze 95% of baseline MRI scans. Twenty-nine percent of patients had a normal brain MRI; of these, 9% developed a second relapse during follow-up. Seventy-one percent had an abnormal baseline MRI; of these, 49% developed CDMS. The percentages of patients converting to CDMS during the study period according to the number of BC fulfilled and number of baseline lesions are shown in table 2. Hazard ratio (HR) and 95% CI (adjusted by age, gender, time on treatment, and presence of OB) for BC, taking 0 Barkhof criteria as the reference group, are also shown in table 2. HR ranged from 3.8 to 8.9 for developing CDMS. Table 2 also shows adjusted HR and 95% CI for each lesion number category taking 0 lesions as the reference group.

Table 3 Demographic, clinical, and MRI characteristics of patients with positive and negative OB

	OB Neg, n = 161	OB Pos, n = 254	*p* Value
Age, y, mean (SD)	29.9	29.4	NS
Female, %	76	73	NS
Follow-up, mean (SD)	45 (32)	53 (30)	0.009
Optic neuritis, %	50	23	0.0001
Normal MRI, %	55	13	0.0001
CDMS, %	16	50	0.0001

OB = oligoclonal bands; CDMS = clinically definite multiple sclerosis.

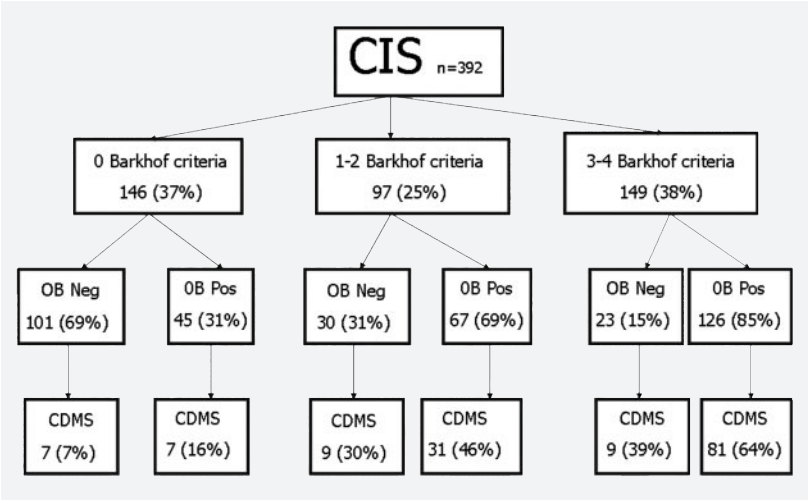
Baseline MRI and OB. HR of patients having positive OB is 1.7 (1.1 to 2.7) for developing CDMS, adjusted by age, sex, time on treatment, and number of BC (table 2). The same HR and 95% CI is seen for having positive OB when adjusting for lesion number category.

Figures 1 and 2 contain flow diagrams detailing percentage of patients according to number of BC and number of baseline lesions with respect to the presence of OB and conversion to CDMS.

When adjusting by baseline MRI, age, gender, and time on treatment, the presence or absence of OB was not associated with differences in time or percentages of patients reaching an EDSS equal or higher than 3.0 (data not shown).

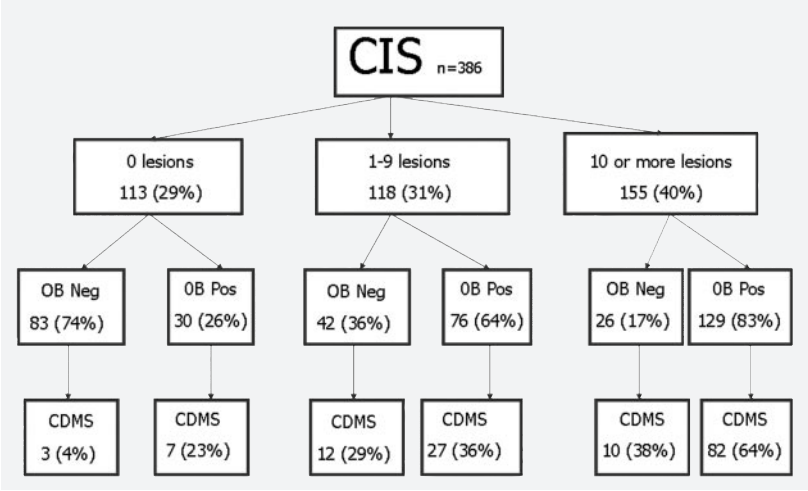
DISCUSSION Our study shows that the presence of OB increases the risk of having a second attack, independently of MRI, but they seem not to influence the development of disability. OB were positive in 61% of the total cohort. This percentage is highly variable in other publications, ranging from 46% to 75%.[6,15-18] The presence of OB is clearly different when stratifying patients with CIS according to MRI results. Patients with a low risk MRI (0 lesions or 0 BC) have positive OB in 27% to 31% compared to 64% to 69% in patients with a medium risk and 83% to 85% in patients with a high risk MRI defined as 10 or more lesions or 3 to 4 BC. What appears from our study is that the presence of OB is an independent risk factor and that it increases almost by twofold the risk of having a second attack in all patients. We need to keep in mind, however, that this increase in risk is mainly clinically relevant in those patients with a normal baseline MRI or with an

Figure 1 Flow diagram detailing percentage of patients with conversion to clinically definite multiple sclerosis according to number of Barkhof criteria and presence of oligoclonal bands



MRI not fulfilling criteria for dissemination in space. Patients with a normal baseline MRI have a low risk of developing a second attack; however, it is in this context where the presence or absence of OB may be clinically more relevant. In our study 4% of patients with normal MRI and negative OB developed CDMS compared to 23% in the subgroup with normal MRI but positive OB. As recommended by the McDonald diagnostic criteria, OB are also useful when baseline MRI is equivocal or does not demonstrate 3 to 4 BC.[13] Although the patients in our study with negative OB had a slightly shorter follow-up than patients with positive OB (45 vs 53 months), differences in conversion rate were so obvious between groups (16% vs 50%) that the 8-month difference in time of follow-up would probably play a minor role.

Figure 2 Flow diagram detailing percentage of patients with conversion to clinically definite multiple sclerosis according to number of lesions and presence of oligoclonal bands



Although a CSF study seems to add useful information, MRI remains the main prognostic factor. The Cox regression analysis analyzing both the information derived from MRI and by the CSF study shows that the HR associated with number of BC or number of lesions multiply the risk of having a second attack by a range of 3.8 (2.0 to 7.2) to 8.9 (4.8 to 16.4) and the information derived from the presence of OB gives a HR of 1.7 (1.1 to 2.7) using a multiregression analysis. Using a similar approach but in a group of 82 patients with optic neuritis, other authors have found that the presence of three or more MRI lesions was associated with a HR of 4.68 (2.21 to 1.56) and the presence of OB was associated to a HR of 5.39 (1.56 to 18.61) for developing CDMS at 3 years. The highest individual probability 0.66 (95% CI 0.48 to 0.80) of CDMS development, at 3 years, after optic neuritis was obtained for an individual presenting with three or more brain MRI lesions and presence of OB. The lowest individual probability 0.09 (95% CI 0.02 to 0.32) was found for those not presenting these traits.[19]

Few studies have analyzed the relation between the presence of OB and development of disability in patients with MS. Thirty-four patients with negative OB and a diagnosis of MS were matched for age, sex, duration of disease, and disease course with patients with MS with positive OB. Median EDSS was 6.0 in OB positive patients compared to 3.5 in OB negative patients.[9] The prognosis of OB-negative patients with MS was also reported to be more benign in another study with 105 patients performed more than 25 years ago; patients with negative OB (n = 17) were more likely to have a benign course compared to patients with positive OB (n = 88).[20] Nevertheless, a very recent study performed in 1,505 patients with MS could not show any difference in terms of prognosis and development of disability according to OB status.[10] Our study performed on a different population as we have studied patients with CIS could not find a relation between the OB status and development of disability. However, we cannot rule out that with a higher number of patients and longer follow-up, differences could appear. In fact, the presence of IgM OB has been associated in patients with CIS with a shorter time to developing CDMS and to higher disability development.[21]

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