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The risk of relapse after a clinically isolated syndrome is related to the pattern of oligoclonal bands

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ABSTRACT

We prospectively assessed the risk of second relapse in 192 patients with clinically isolated syndromes (CIS) divided into three groups: patients lacking oligoclonal IgG bands (OC-IgG, 25.7%), those showing OC-IgG (52.4%), and those with both OC-IgG and lipid-specific IgM bands (LS-OC-IgM, 22%). OC-IgG increased 9.3-fold the risk compared to lacking OC-IgG; OC-IgG + LS-OC-IgM increased the risk 39.6-fold compared to not having OC-IgG and 4.4-fold compared to having only OC-IgG. Median time to second relapse was 0.7 years for patients with OC-IgG + LS-OC-IgM and 3.3 years for those with only OC-IgG. Therefore, CSF analysis identifies CIS patients at risk of second relapse.

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1. Introduction

About 85% of patients with multiple sclerosis (MS) initially present with an acute demyelinating event suggestive of MS (clinically isolated syndrome, CIS). Over the past years, interest has been focused on the effect of immunomodulatory treatments after this first episode, as clinical trials have demonstrated that immunomodulators delay conversion to MS. (Comi et al., 2001; Comi et al., 2009; Jacobs et al., 2000; Kappos et al., 2006) On the other hand, not all CIS patients will have MS, and in those who do there is a high variability in the disease course, ranging from asymptomatic to aggressive cases. (Confavreux et al., 1980). This heterogeneity raises controversy about when to start treatment, and it is currently discussed if every patient with a single demyelinating event should receive immunomodulatory therapy. (Frohman et al., 2006; Pittock et al., 2006) Therefore, the determination of markers able to predict long-term outcome in CIS patients seems warranted. To date, type of first relapse, (Confavreux et al., 1980) time between the first and second relapse, (Confavreux et al., 1980; Confavreux et al., 2003) baseline MRI characteristics, (Brex et al., 2002; Fisniku et al., 2008; Rocca et al., 2008; Tintoré et al., 2006) and the change in the lesion volume over five years (Brex et al., 2002; Fisniku et al., 2008) provide partial prognostic information.

The intrathecal immunoglobulin synthesis (both the presence of oligoclonal bands of the IgG type -OC-IgG- and intrathecal IgG synthesis) has a long known significance in the diagnosis of MS, (Poser et al., 1983; Tourtellotte et al., 1984) and the presence of OC-IgG has demonstrated high sensitivity and specificity to predict conversion to clinically definitive MS after a CIS.(Masjuan et al., 2006). However, OC-IgG are present in more than 95% of patients with MS, (Andersson et al., 1994) and they do not provide information about the time to a second relapse. Previous studies demonstrated that intrathecal synthesis of IgM (OC-IgM) predict an aggressive course in MS in terms of new relapses in MS patients and cumulative disability. (Mandrioli et al., 2008; Perini et al., 2006; Villar et al., 2002b; Villar et al., 2003) In addition, lipid-specific OC-IgM (LS-OC-IgM) were shown to have a predictive value in relapsing-remitting MS (RRMS) (Villar et al., 2008; Villar et al., 2005) The prognostic significance of LS-OC-IgM in patients with CIS has not been tested yet.

The objective of this study was to assess the predictive value of OC-IgG and LS-OC-IgM for the occurrence of an earlier relapse in a cohort of patients presenting with a CIS.

2. Methods

2.1. Patients

This is a prospective collaborative multicentre study of 192 patients with an acute demyelinating event suggestive of MS (CIS) consecutively recruited at the MS Units of Hospital Universitari La Fe

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and Hospital Clinic Universitari in Valencia (HLF/HCU) and Hospital Ramón y Cajal in Madrid (HRC), Spain. Inclusion criteria were: (1) first episode of symptoms suggestive of acute demyelination of the CNS; (2) no previous history of possible demyelinating events; (3) onset of symptoms within 3 months of clinical, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examinations; and (4) symptoms not explained by other disease when a complete laboratory and MRI examination was performed. 206 patients initially fulfilled the inclusion criteria. 6 patients were excluded due to insufficient CSF sample for LS-OC-IgM determination; and 8 patients were excluded because immunomodulatory treatment was started after the first relapse. There were no demographical or clinical differences between the included and excluded patients.

A relapse was defined as a new episode of neurological symptoms, with clinical evidence of at least one new central nervous system (CNS) lesion. Symptoms had to last more than 24 h and had to be separated by at least one month from the initial episode.(Poser et al., 1983).

2.2. MR imaging

MRI imaging of the brain was performed within three months of the demyelinating event in three different 1.5 tesla scanners with standard head coil. Slice thickness of 3 mm (no gap, spacing 0) (HLF and HCU) and 5 mm (gap 0.5 mm) (HRC) and field of view of 24 cm, were acquired to obtain contiguous axial sections that covered the entire brain from the foramen magnum to the vertex. The following sequences were performed: T1 weighted imaging; axial FLAIR T2; axial T2 weighted imaging; axial proton density T2 weighted imaging; and T1 weighted imaging with gadolinium.

We prospectively evaluated the fulfilment of Barkhof MRI criteria (Barkhof et al., 1997) modified by Tintoré (Tintoré et al., 2000) (BC), consisting of the following: (1) presence of at least one gadolinium-enhancing lesion or nine lesions in the T2-weighted images, (2) presence of at least three periventricular lesions, (3) presence of at least one juxtacortical lesion and (4) presence of at least one infratentorial lesion. MRI was considered positive for BC when it fulfilled at least three out of four criteria.

2.3. Cerebrospinal fluid studies

Paired CSF and serum samples were obtained within 3 months of the initial symptoms. Two aliquots of serum and CSF of each patient were sent to Hospital Ramón y Cajal in Madrid, Spain, where oligoclonal band studies were performed by immunologists who were blinded to the clinical and MRI data. Oligoclonal IgG and lipid-specific IgM bands were studied as previously described.(Sádaba et al., 2004; Villar et al., 2005). Nitrocellulose membranes coated with 20 μg/ml solutions of purified phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, sphingomyelin, gangliosides, and sulphatides (SIgMa-Aldrich) were used for LS-OC-IgM determination.

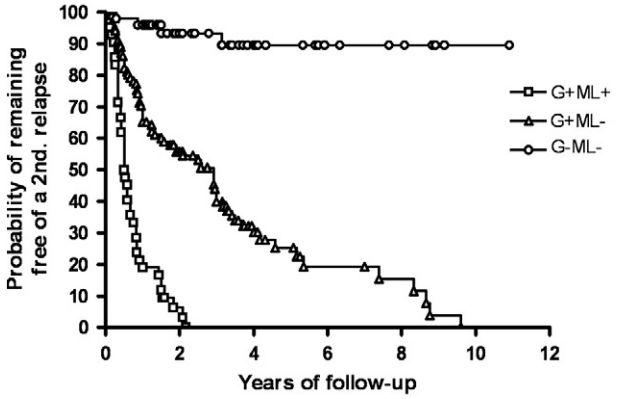

Fig. 1. Kaplan–Meier estimates of the time from first relapse to the second relapse, according to the presence of oligoclonal IgG bands and lipid-specific oligoclonal IgM bands. Legend: G+/ML+: oligoclonal IgG and lipid-specific IgM bands present ($n=42$); G+/ML−: oligoclonal IgG bands present and lipid-specific IgM bands absent ($n=101$); G−/ML−: oligoclonal IgG and lipid-specific IgM bands absent ($n=49$).

2.4. Statistical analysis

Results were analyzed with SPSS 13.0v and Prism 4.0 statistical packages. Patients were stratified according to: absence of both OC-IgG and LS-OC-IgM; presence of OC-IgG only; and presence of both OC-IgG and LS-OC-IgM. Comparisons between demographic, clinical and MRI data for patients with and without OC-IgG and LS-OC-IgM were performed with ANOVA and chi-square as appropriate. The cumulative probability of having a second relapse according to the presence of OC-IgG and LS-OC-IgM was calculated with Kaplan-Meier survival curves. Finally, hazard ratios for a second relapse for demographic variables, MRI data, OC-IgG and LS-OC-IgM were calculated using univariate and multivariate Cox regression analysis.

3. Results

One hundred and ninety two patients presenting with CIS, 71.9% females and mean age at onset 31.9 years, have been followed for a mean of 6.17 years (SD 3.3). Presenting syndromes were optic neuritis in 29.8% of cases, transverse myelitis in 21.3% of cases, brainstem in

Table 1
Comparison of demographical, clinical, CSF and MRI parameters of patients with or without a second relapse during follow-up.

Characteristics	Total	Oligoclonal bands			*p* value
		G+/M+	G+/M−	G−/M−	
No. patients (female %)	192 (71.9%)	42 (61.9%)	101 (75.2%)	49 (73.5%)	0.260 (χ^2)
Mean age years (SD)	31.9 (9.59)	31.34 (9.98)	31.80 (8.79)	32.60 (10.88)	0.155 (ANOVA)
Mean follow-up years (SD)	6.17 (3.3)	6.35 (3.3)	6.32 (3.4)	5.69 (3.4)	0.510 (ANOVA)
Clinical syndrome (%)					0.081 (χ^2)
Optic neuritis	29.8%	19.0%	26.8%	44.9%	
Spinal cord	21.3%	19.0%	22.7%	20.4%	
Brainstem	18.1%	16.7%	20.6%	14.3%	
Polyregional	30.9%	45.2%	29.9%	20.4%	
BTC+ (%)	43.5%	73.8%	48.0%	8.2%	<0.001 (χ^2)
CDMS (%)	60.4%	97.6%	70.3%	8.2%	<0.001 (χ^2)

SD: standard deviation; MRI: magnetic resonance imaging; BTC: Barkhof–Tintore MRI criteria; G+/M+: oligoclonal IgG and IgM bands present; G+/M−: oligoclonal IgG bands present and IgM bands absent; G−/M−: oligoclonal IgG and IgM bands absent; CDMS: clinically defined multiple sclerosis.

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