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High risk of early conversion to multiple sclerosis in clinically isolated syndromes with dissemination in space at baseline

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ABSTRACT

Introduction: Multiple sclerosis (MS) usually presents at onset with a clinically isolated syndrome (CIS). According to 2010 McDonald criteria, a diagnosis of MS can be made if CIS patients satisfy clinical/MRI criteria of both dissemination in time (DIT) and space (DIS).
Objective: The aim of this study was to analyze the follow-up data and possible prognostic factors of CIS patients satisfying DIS MRI criteria.
Patients and methods: We performed a retrospective, multicenter study across 2 Italian centers. Clinical, MRI, and laboratory assessments were performed according to real-life clinical workup.
Results: Out of the 137 enrolled patients, during a median follow-up time of 3.1 years, 116 (84.7%) converted to MS with the large majority (78.4%) of the converters developing MS within 1 year. In multivariate analysis, baseline predictors of an earlier conversion were a cerebellar/brainstem CIS (HR 2.00, 95% CI: 1.3–3.0, $p = 0.001$) and the presence of all the Barkhof-Tintore MRI criteria (HR 1.67, 95% CI: 1.1–2.6, $p = 0.028$).
Conclusions: Patients with CIS and DIS are at very high risk of an early conversion to MS. The onset with cerebellar/brainstem symptoms and the evidence of a higher MRI lesion load at baseline are the strongest independent predictors of an early conversion to MS.

1. Introduction and aim

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) [1]. In 85% of cases, MS presents at onset with an isolated episode of focal neurological deficit, the clinically isolated syndrome (CIS) [2]. CIS is defined as a focal neurological dysfunction sustained by an inflammatory and demyelinating process in the CNS, lasting at least 24 h in the absence of fever, infection or encephalopathy [3]. Recently, CIS has been added to the spectrum of clinical phenotypes of MS [4]. Indeed, CIS is strongly related to MS with 2/3 of patients converting during their life to MS [5]. In the clinical practice, it is important to define whether and when a CIS patient will convert to MS and several studies on CIS have investigated clinical and paraclinical baseline variables that could predict conversion to MS [6–13]. Specifically, 3 recent large studies performed on >1000 patients each have found that a higher number of magnetic resonance imaging (MRI) T2 lesions, as well as cerebrospinal fluid (CSF) IgG oligoclonal bands (OCB), a lower age at CIS onset and lower serum levels of 25-hydroxyvitamin D3 may be reliable predictors of conversion from CIS to MS [7,8,13]. Most of these demographical, clinical, MRI and CSF features have been used to build a nomogram able to predict the conversion to MS [13].

According to the 2010 revision of the McDonald criteria, a diagnosis of MS can be made if CIS patients satisfy clinical and/or MRI criteria of dissemination in time (DIT) and space (DIS). The presence of DIS without DIT or *vice versa* configures a diagnosis of possible MS [14]. In MS clinics, neurologists are often confronted with CIS patients satisfying MRI criteria for DIS without DIT. Although several studies have identified the possible risk factors for conversion from CIS to MS, the risk of conversion and the prognostic factors associated with an early conversion to MS in the specific population of patients with CIS and DIS have not been thoroughly investigated.

The aim of the present study was to identify the clinical, biological and MRI characteristics associated with a shorter time to development of MS in patients with CIS and DIS defined according to the 2010 revision of the McDonald criteria [14]. The identification, in these patients, of

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baseline characteristics associated with a higher risk of early development of MS could help clinicians in defining the individual benefit-risk ratio of an early disease-modifying treatment.

2. Patients and methods

We performed a retrospective, multicenter study across 2 Italian MS centers (Section of Neurology, University of Perugia and S. Andrea Hospital, Rome). Patients were included in the study if they met all of the following inclusion criteria: (i) a diagnosis of CIS with evidence of DIS at the baseline MRI according to the current diagnostic criteria (Supplementary Table 1) [14]; (ii) demographic, clinical, laboratory and MRI data available; (iii) a baseline complete work-up able to rule out possible differential diagnoses; (iv) a follow-up period lasting until conversion to MS or at least 1 year. All the patients were clinically assessed within 1 month from symptoms onset. The study was approved by the regional Ethics Committee (3015/2017).

2.1. CSF analysis

The patients underwent CSF analysis as part of the routine workup. The presence of OCB in the CSF was assessed with agarose gel isoelectrofocusing followed by immunoblotting or immunofixation, as recommended [15]. Patients were considered OCB positive if having >1 CSF OCB and OCB negative if having 0–1 CSF OCB [15].

2.2. MRI

All the patients underwent brain and spinal cord MRI at the baseline and during the follow-up as part of the usual workup (3, 6 and 12 months after the onset, then yearly if asymptomatic). All images were acquired with a 1.5 Tesla magnet according to published guidelines [16]. Reproducible slice positioning was maintained throughout the follow-up using the same anatomical landmarks for each patient. FLAIR, T1-, T2-weighted and axial T1-weighted post-gadolinium-DTPA (Gd) administration sequences were acquired with 3 mm thick slices. Patients were categorized according to the number of Barkhof-Tintore MRI criteria (Bc) as a measure of lesion load (Supplementary Table 1) [17,18]. Patients have also been categorized according to 2010 McDonald criteria for DIS (Supplementary Table 1) [14]. Patients with Gd enhancing (Gd +) lesions at the baseline MRI were included in the study only if contrast-enhancing lesions were symptomatic, in order not to have evidence of DIT as stated in the current diagnostic criteria (Supplementary Table 1) [14].

2.3. Follow-up data and outcomes

All the follow-up examinations and assessment visits were performed at least every 3 months as part of the usual workup. A relapse was defined as the appearance of new symptoms or the worsening of an existing symptom lasting for at least 24 h in the absence of fever [14]. At follow-up, conversion to MS and time to conversion to MS were evaluated. Conversion to MS was defined both clinically and radiologically [14].

2.4. Statistical analysis

Statistical analysis was performed using R software version 3.1 [19]. Continuous variables were described by means and standard deviations, while categorical ones were reported as count and percentages. Predictors of time to conversion to MS were assessed using univariate and multivariate Cox proportional hazards regression models. In the absence of a conversion event, data were censored at the most recent clinic visit. HR and 95% confidence intervals are reported. A backward stepwise approach was used for the multivariate Cox analysis, with a p-value equals to 0.10 as the critical value for entering and excluding demographic and clinical covariates in the model. Hazard proportionality was assessed through analysis of scaled Schoenfeld residuals. A p-value lower than 0.05 was considered for statistical significance.

3. Results

3.1. Characteristics of the patients

A total of 137 consecutive patients (102 F, 35 M, F/M: 2.9) diagnosed between 2003 and 2015 were selected from the databases of the centers. The details of the main demographic, clinic and MRI characteristics of the patients at the baseline are reported in Table 1. After the onset of CIS, 18 patients (13.1%) were treated with disease-modifying drugs (DMD) before the conversion to MS. All of them were treated with first-line injective drugs. Specifically, 7 patients (38.9%) were treated with interferon beta-1a 30 μg weekly, 5 (27.8%) with glatiramer acetate 20 mg daily, 4 (22.2%) with interferon beta-1b 250 μg every other day and 2 patients (11.1%) with interferon beta-1a 44 μg 3 times a week. Patients were longitudinally followed-up for a mean time of 45.6 ± 34.8 months. During the follow-up, 116 patients (84.7%) converted to MS. Mean time to conversion was 10.8 months (median 6, range 0.8–166.8). Specifically, 91 patients out of the 116 converters (78.4%), converted within 1 year (Fig. 1). Conversion to MS occurred clinically in 57/116 patients (49.1%) and radiologically in 59/116 patients (50.9%).

3.2. Predictors of conversion to MS

Baseline clinical and paraclinical variables were tested as predictor of an early conversion to MS in a Cox univariate analysis (Table 2).

Among baseline clinical features, an older age at diagnosis resulted to be slightly protective for the development of MS (HR 0.98, 95% CI 0.96–1.00, p = 0.021), whereas a clinical onset with brainstem/cerebellar CIS was associated with a higher risk of early conversion to MS (HR

Table 1
Demographics, clinical and MRI features at baseline.

Demographics	
N	137
Sex (female)	102 (74%)
Age at onset (mean ± SD)	31.4 ± 10.5
CIS type (n of patients; %)	
Multifocal	7 (5.1%)
Partial myelitis	49 (35.8%)
Brainstem/cerebellar syndrome	34 (24.8%)
Optic neuritis	33 (24.1%)
Hemispheric syndrome	14 (10.2%)
CSF features	
IgG index (mean ± SD)	0.56 ± 0.33
OCB positive (n of patients;%)	105 (79%)
EDSS at onset (mean ± SD)	1.62 ± 0.93
MRI Barkhof Tintore criteria for DIS (n of patients; %)	
≥1 Gd + lesions or ≥9 T2 lesions	81 (59.1%)
≥1 infratentorial lesion	55 (40.2%)
≥1 juxtacortical lesion	92 (67.2%)
≥3 periventricular lesions	121 (88.3%)
Number of satisfied MRI Barkhof Tintore criteria (n of patients; %)	
1	18 (13.1%)
2	49 (35.8%)
3	43 (31.4%)
4	27 (19.7%)
MRI 2010 revised McDonald criteria for DIS (n of patients; %)	
Periventricular lesions	93 (67.9%)
Juxtacortical lesions	123 (89.8%)
Infratentorial lesions	57 (41.6%)
Spinal cord lesions	73 (53.3%)
Treatment with DMD (n of patients; %)*	18 (13.1%)

Legend. CIS: clinically isolated syndrome. CSF: cerebrospinal fluid. OCB: IgG oligoclonal bands. EDSS: expanded disability status scale. Gd +: gadolinium enhancing lesion. DMD: disease modifying drugs.

* Treatment started before the conversion to MS.