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Does cerebrospinal fluid analysis add predictive value to magnetic resonance imaging for long term irreversible disability in patients with early multiple sclerosis?

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ABSTRACT

Background: The independent prognostic value of cerebrospinal fluid analysis in multiple sclerosis is not established.
Objective: To determine the prognostic value of intrathecal synthesis in a cohort of patients with relapsing-onset MS taking into consideration demographic and imaging parameters.
Methods: In this prospective cohort study conducted from 1993 to 2013, we analyzed the time to confirmed disability (persistent above 6 months) and irreversible disability (persistent for the entire disease course) of two disability milestones, Expanded Disability Status Scale score ≥4 or 6, and the time to secondary progressive onset in 579 patients with relapsing-onset multiple sclerosis. Demographic parameters (age at onset, gender) and imaging parameters (periventricular lesions) were included in the Cox models.
Results: 447 patients (77.2%) had intrathecal synthesis (oligoclonal bands and/or increased immunoglobulin G index value). No statistically significant relation was found between intrathecal synthesis and the time to reach each disability milestone or secondary progressive onset. An age older than 40 years and more than 3 periventricular lesions predicted a worse prognosis.
Conclusions: Cerebrospinal fluid analysis did not predict the time to disability milestones in relapsing-onset multiple sclerosis independently of age and imaging data.

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1. Introduction

Multiple sclerosis (MS) is the most common disabling neurological disease that occurs in young adults. The course of the disease and the risk for developing permanent disability are very different from one patient to another and predicting long term disability is not possible in a patient presenting with a new diagnosis of MS. Several long term clinical studies have been conducted to determine the clinical predictors of disability accumulation and some consistent results have been found. A review of natural history studies performed before 2009 concluded that negative prognostic factors include progressive disease type and disability at 2 and 5 years when considering all clinical phenotypes [1]. In the same study, the negative prognostic factors for relapsing–remitting MS (RRMS) and secondary progressive MS (SPMS) were identified as the onset of progression, a higher early relapse rate, greater disability in the first 5 years, shorter interval to the second relapse and the involvement of more functional systems [1]. None of these predictors are available when a patient is presenting with a first neurological episode that is suggestive of MS, in so-called clinically isolated syndromes (CIS). The significance of other potential predictors, such as an older age of onset or male gender, are equivocal but some studies have found that they are significantly associated with a worse outcome [2–7].

Among the parameters available at the CIS stage that have a potential prognostic value, brain magnetic resonance imaging (MRI) is of particular interest. MRI data collected at the onset of the disease have been shown in two longitudinal studies to be prognostic markers of interest [8–10]. The London CIS study, which followed a group of patients with CIS over 20 years, yielded important results in this regard [8,9]. T2 lesion volume at baseline and at several other time points during follow-up moderately predicted an increase in two disability scores: the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) [8,9]. Another cohort study consisting of patients presenting with CIS followed for a median of 7 years, identified the baseline number of Barkhof criteria and the baseline number of brain lesions as predictors of the EDSS score at year 5 [10]. A further potentially

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predictive parameter available to CIS stage patients is cerebrospinal fluid (CSF) analysis. The presence of intrathecal synthesis of immunoglobulin G (IgG) is frequent in MS patients and is a strong predictor of conversion from CIS to MS [11]. Intrathecal synthesis can be demonstrated by identification of oligoclonal bands (OB) detected in the CSF but not in the serum or an increased IgG index [12]. Data concerning the prognostic value of CSF analysis are more equivocal. A recent meta-analysis suggested that OB could predict disability outcomes [11]. However, the results did not take into account several negative studies. It is not currently known whether CSF data add any prognostic information to MRI parameters.

The aim of this study was to determine the prognostic value of the presence of intrathecal synthesis (OB or increased IgG index in the CSF) in a cohort of patients with relapsing-onset MS followed in one center since 1993, taking into account early MRI results and demographic data as covariates.

2. Patients and methods

2.1. Patients and data collection

Patients were included in this study after being identified through our local EDMUS (European Database for Multiple Sclerosis) database. This database software has been used since 1993 to follow individual patients affected by MS, regardless of the clinical course, starting from the first neurological examination in the MS clinic at Bordeaux University Hospital. The database is reported to the French Commission Nationale Informatique et Libertés, and patients are informed of the use of this database.

All data have been entered into the database prospectively from 1993 to 2013. However, some historical data, such as relapses that occurred prior to the first visit to the MS clinic, have been added retrospectively based on patients' interviews and referring physician information at the first visit. These data cannot be considered with the same level of confidence. Therefore, relapse dates and numbers were not included in the analyses. We not only considered all clinical, biological and imaging data obtained in our center but also considered those reported by other neurologists and local hospitals when available and clearly documented. Demographic and clinical variables, such as disease course, disability, biological parameters and MRI data have been analyzed retrospectively. At each medical consultation with a senior neurologist of the MS clinic, data entered in the database previously was checked.

To evaluate the representativeness of our cohort, the demographic characteristics and the proportion of patients with CSF results available were compared with the national French MS cohort (data provided by the Observatoire Français de la Sclérose en plaques, OFSEP).

Before the present analysis, all data used in the study were checked in the patients' medical files, which were considered source files.

The inclusion criteria for this study were as follow: relapsing–remitting (RR) or secondary progressive (SP) clinically definite multiple sclerosis (CDMS) according to the standard diagnostic criteria [13,14], that was diagnosed between 1993 and January 2013, available CSF analysis results, and a detailed results of a brain MRI performed within two years after their first episode available.

Subjects were excluded from the analysis if they were suffering from CIS, primary progressive MS (PPMS), an unconfirmed diagnosis or an alternative diagnosis.

2.2. Patients' assessment

The primary endpoint was the time to disability onset (confirmed and irreversible).

The disability assessment was performed during each visit by senior neurologists, according to a French-adapted version of the Kurtzke EDSS [15]. Two milestones, reflecting the main steps of disease evolution that are easy to determine by the clinician, were taken into account: confirmed EDSS 4 (limited walking ability, but without aid or rest for more than 500 m), and confirmed EDSS 6 (ability to walk with unilateral support for no more than 100 m without rest). All patients were treated according to current recommendations. No patient received disease modifying therapy before the lumbar puncture.

Confirmed disability scores were only taken into account if they persisted for at least a six month period and were checked by a neurologist. This information was not retained if the disability score was recorded during a relapse. A relapse was defined as the occurrence, recurrence or worsening of neurological dysfunction symptoms lasting more than 24 h and usually ending with a remission (partial or complete). Symptoms occurring within 1 month were considered part of the same relapse. However, if EDSS decreased after a six month delay, disability was considered confirmed for at least 6 months but was not considered as irreversible. Irreversible disability is a sustained and confirmed disability and was defined as a steady EDSS after at least a six month delay and for the duration of the follow-up period.

Secondary progression was defined as the initial RR disease course followed by progression for at least 6 months, with or without occasional relapses, minor remissions, and plateaus [14]. The date of SPMS onset was determined by senior neurologists during individual consultations with patients. In a limited number of cases, missing EDSS scores were calculated based on detailed neurological evaluations of medical files when available, according to a published algorithm [15].

2.3. Potential prognosis factors taken into account

To determine the role of CSF analysis and consequently the predictive value of intrathecal synthesis of immunoglobulin on multiple sclerosis-related disability, the presence of at least two IgG oligoclonal bands (OB) in the CSF but not in the serum, or an IgG index above 0.7 was considered pathological. The parameter taken into account was, then, the presence or not of an intrathecal synthesis. From 1993 to 2013, different techniques have been used to detect intrathecal synthesis. All of them met standards found in hospital laboratories and are concordant with actual literature [11]. Before 2000, high resolution agarose gel electrophoresis was used. In 2000 sensitized immunofixation electrophoresis with paired CSF and serum was introduced. Isoelectrofocusing on agarose gel performed on semi-automatic HYDRASYS system, followed by immunofixation with anti-IgG serum was generalized after 2004. In the latter analysis, serum and CSF IgG are detected and identified using HYDRAGEL 9 CSF ISOFOCUSING SEBIA kit. Since these techniques have different sensitivity, we analyzed separately these three periods and did not take into account the absolute number of supplementary OB as a prognostic factor.

To study CDMS prognosis, we also studied baseline parameters known or suggested to have a prognostic value in early MS such as age at disease onset, gender and periventricular MRI lesions (≥ 3 or <3) as covariates. MRI was performed according to technical standards. Neuroimaging study protocol included at least a whole-brain T1-weighted scan with intravenous injection of gadolinium-based contrast agent and a fast fluid-attenuated inversion-recovery (FLAIR) axial images or T2-weighted scan. Since the follow-up period lasted over twenty years, MRI acquisitions have changed over time, according to current recommendations. Image analysis was confirmed by senior neurologists.

2.4. Statistical analysis

The clinical characteristics of the Bordeaux EDMUS database and the national OFSEP database were compared using the chi square test, Fisher test and t test as required.

The predictive value of intrathecal synthesis and covariates on the time to occurrence of confirmed disability or irreversible disability was assessed using a Cox model for censored data. Disability milestones could be determined by clinical evaluation in 91% of cases. In the remaining patients the EDSS scores increased directly from one evaluation

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