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Early disturbances in multimodal evoked potentials as a prognostic factor for long-term disability in relapsing-remitting multiple sclerosis patients

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HIGHLIGHTS

- There is an unmet need for markers predicting long-term disability in multiple sclerosis patients.
- Multimodal EP alterations at diagnosis predict future disability worsening in RRMS patients.
- Correlation with long-term disease burden was the highest for MEPs, BAEPs and upper limb SSEPs.

ABSTRACT

Objective: The aim of this study was to investigate whether early alterations in evoked potentials (EPs) have a prognostic value in relapsing-remitting multiple sclerosis (RRMS).
Methods: We retrospectively selected 108 early MS patients with a neurological follow-up ranging from 5 to 15 years, in whom multimodal EPs (visual, brainstem auditory, somatosensory and motor) were performed at diagnosis. A conventional ordinal score was used to quantify the observed abnormalities.
Results: The extent of change in the composite EP score was well correlated to the Expanded Disability Status Scale (EDSS) at ten years (Y_{10}) and up to 15 years (Y_{11-15}) after disease onset. Analysis of the predictive value of the EP score showed an increased risk of disability progression at Y_{10} and Y_{11-15} of 60% ($p < 0.0001$) and 73% ($p < 0.0001$) respectively in patients with an EP score >4. Conversely, the risk of disability progression at Y_{10} and Y_{11-15} associated with a lower EP score ($\leqslant 4$) was reduced to 16% and 20% respectively.
Conclusions: Our data support the good predictive value for long-term disability progression of multimodal EPs performed early after disease onset in RRMS patients.
Significance: This study, performed in a homogeneous RRMS cohort with long term follow-up, demonstrates the value of an early comprehensive neurophysiological assessment as a marker for future disability.

1. Introduction

Multiple sclerosis (MS) is a long-lasting neurologic disorder that affects mostly middle-aged subjects and can lead to significant disability (Weinshenker et al., 1989). Despite recent advances in the understanding and the treatment of this disease, early prognostic markers are still lacking. Although a clinical diagnosis of MS can be supported by detecting subclinical nervous conduction abnormalities of sensory, motor, visual and brainstem auditory pathways, with the progress made in magnetic resonance imaging, evoked potentials (EPs) are no longer required for establishing the diagnosis of MS (Polman et al., 2011). Despite previous reports demonstrating the prognostic value of EPs in predicting MS disability progression, the clinical usefulness of a multimodal neurophysiological assessment is still being debated (Fuhr et al., 2001; Kallmann et al., 2006; Leocani et al., 2006; Jung et al., 2008; Invernizzi et al., 2011; Schlaeger et al., 2012b; Hutchinson, 2013). In most of the previously published studies, many included patients had disease of long duration and some of them included primary and secondary progressive forms. As the clinical neurological examination was significantly impaired in these patient populations, the utility of predicting disease progression is questionable (Margaritella et al., 2012). The added value of a multimodal

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neurophysiological assessment would be to identify patients with a higher risk of unfavourable clinical course close to disease onset, before further accumulation of neurological burden.

2. Methods

2.1. Data collection

The data of patients followed in the Department of Neurology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium were retrospectively collected from our local clinical database (iMed® software).

The study inclusion criteria were: (1) occurrence between 01/01/2000 and 31/12/2005 of a clinically isolated syndrome (CIS) or clinically definite MS (CDMS) according to Poser's criteria, not attributable to another disease, (2) complete multimodal assessment (visual, brain stem auditory, upper and lower limbs somatosensory and motor EPs) performed less than 6 months from diagnosis, (3) availability of a complete neurological examination with disability rating using the Expanded Disability Status Scale (EDSS) and Kurtzke's functional system scores at diagnosis, (4) availability of further clinical examinations with disability rating at 5, 10 and up to 15 years (Y_5, Y_{10} and Y_{11-15} respectively) (Poser et al., 1983). As defined in clinical trials, disability progression was defined as a 6 month sustained increase of the EDSS score by 1.0 or more (in comparison to the baseline EDSS) if the initial EDSS was <5.5 and by 0.5 if it was >5.5 (Baumstarck et al., 2013). Of the 396 patients screened, 209 patients were excluded due to an incomplete EP assessment, 31 were excluded because of primary or secondary progressive MS at the time of EP assessment, and 48 were lost before reaching 5 years of follow-up. A flowchart describing the selection of patients is provided in Fig. 1. There were no inclusion criteria on EDSS at the time-point of EPs assessment as the whole sample had an EDSS $\leqslant$4.0 at baseline. If a relapse occurred during follow-up at a time-point close to key evaluations (Y_5, Y_{10} and Y_{11-15}), the EDSS score was not taken into account and replaced by the EDSS score reported 6 months later. Functional system and EDSS scores were calculated by Neurostatus certified raters.

2.2. Ethical statement

Any patient admitted in our hospital has ratified a chart issued from the local ethics committee, authorizing confidential data exploitation for retrospective studies.

2.3. Multimodal evoked potentials

Visual, auditory, upper and lower limb motor and somatosensory EPs were recorded bilaterally according to guidelines of the International Federation of Clinical neurophysiology published in 1999 (Celesia and Brigell, 1999; Mauguiere et al., 1999; Pratt et al., 1999; Rothwell et al., 1999). EPs were interpreted by experienced neurophysiologists (J.M.G. and M.d.T.).

2.4. Evoked potentials analysis

In order to quantify the abnormalities separately for each stimulus modality, we used a conventional 4-point graded ordinal score (0 = normal; 1 = increased latency; 2 = increased latency plus morphological abnormalities of a major central potential; 3 = absence of a major potential) as proposed by Leocani et al. and modified by Invernizzi et al. (Leocani et al., 2006; Invernizzi et al., 2011). The global EP (GEP) score was calculated retrospectively by F.L. as the sum of the bilateral brainstem auditory EP (BAEP) score (from 0 to 6), the visual EP (VEP) score (from 0 to 6), the bilateral upper and lower limb somatosensory EP (SSEP) score (from 0 to 12) and finally the motor EP (MEP) score (from 0 to 12) (Leocani et al., 2006). The GEP score thus ranges from 0 to 36, with a higher score indicating more severe alterations. The EP assessment was performed either during the study inclusion relapse or during the relapse-free interval (>6 weeks after the clinical episode).

2.5. Statistical analysis

The nonparametric Spearman's rank correlation coefficient was used (1) to determine whether there is a correlation between individual EP scores and GEP score severity at baseline and EDSS at Y_0, Y_5, Y_{10} and Y_{11-15}, (2) to assess whether the strength of the

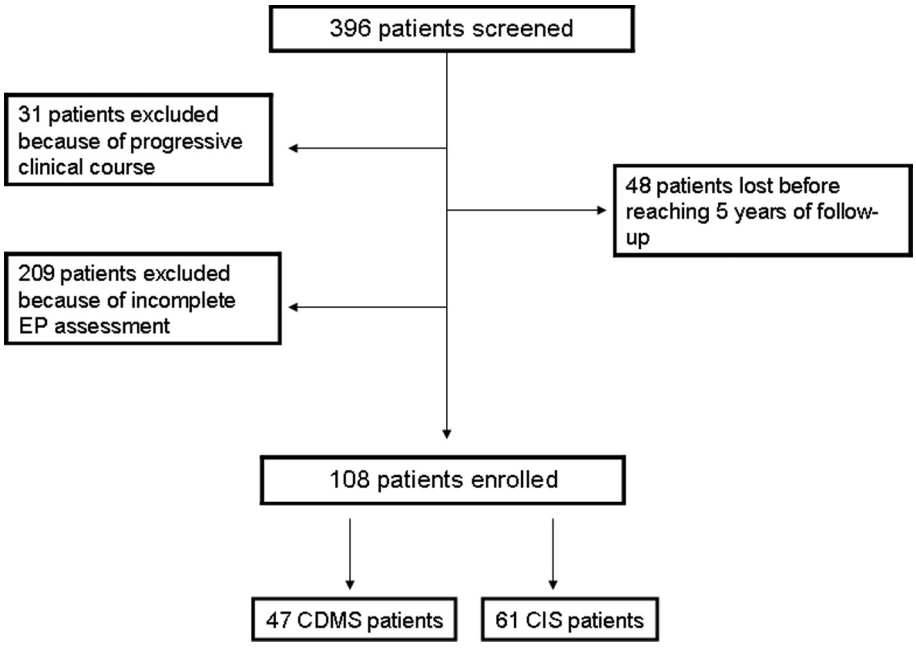

Fig. 1. Flowchart describing patient selection for this study.