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Monitoring multiple sclerosis by multimodal evoked potentials: Numerically versus ordinally scaled scoring systems

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HIGHLIGHTS

- Combined evoked potentials are a robust monitoring tool in multiple sclerosis independently from the scaling level of the chosen scoring system.
- Quantitative evaluation of latencies is most sensitive in detecting clinically relevant short-term changes, as individual changes within the "normal" range are not lost for evaluation.
- The results of this study might be relevant for clinical trial design.

ABSTRACT

Objective: To compare the ability of different evoked potential scores (EPS) to monitor and predict the disease course in multiple sclerosis (MS).
Methods: Seventy-two patients with MS or clinically isolated syndrome were investigated by visual, motor, and somatosensory EP and expanded disability status scale (EDSS) at baseline (T0) and months 6, 12, 24, 36 (T4). EP results were rated according to ordinal (o), semi-quantitative (sq), and quantitative (q) EPS. Spearman rank correlation and multivariable linear regression were used to investigate the associations between EPS and clinical disability.
Results: All EPS correlated with EDSS cross-sectionally ($0.72 \leqslant \text{rho} \leqslant 0.87$, all $p < 0.001$) and longitudinally ($0.39 \leqslant \text{rho} \leqslant 0.47$, all $p \leqslant 0.004$). EPS_{T0} and $EDSS_{T0}$ together explained 85–86% of $EDSS_{T4}$ variance. A posteriori power calculation showed that the sample sizes needed to detect significant changes over 6 months in q-EPS, sq-EPS and o-EPS with 90% certainty would be 50, 129 and 222, respectively. q-EPS $change_{T1-T0}$ correlated with EDSS $change_{T4-T0}$ (rho = 0.56, $p < 0.001$), while sq-EPS and o-EPS $changes_{T1-T0}$ did not.
Conclusion: All three EPS allow disease course monitoring in MS. However, the quantitative EPS detects clinically relevant short-term changes with a smaller sample size than semi-quantitative or ordinal EPS.
Significance: These results underscore the potential of EPS to characterize MS disease evolution.

1. Introduction

Multimodal evoked potentials (EP) allow monitoring and prediction of MS disability in small groups of patients as was shown by our group and several others (Fuhr et al., 2001; Leocani et al., 2006; Kallmann et al., 2006; Jung et al., 2008; Invernizzi et al., 2011; Margaritella et al., 2012a; Schlaeger et al., 2012a,b, 2014a,b).

To summarize multimodal EP by a one-dimensional statistical measure, different scoring systems have been applied. Some groups used *ordinal* scores based on qualitative assessments of EP latencies, and amplitudes (O'Connor et al., 1998; Kallmann et al., 2006) or absence of principal EP components (Leocani et al., 2006; Invernizzi et al., 2011). Others applied more complex *semi-quantitative* scores with a step-wise rating of the extent of latency prolongation in relation to the upper limit of normal

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(Jung et al., 2008; Margaritella et al., 2012a) or *quantitative* scores based on z-transformed latencies (Fuhr et al., 2001; Schlaeger et al., 2012a, 2014a). However, there is currently no consensus on how to best score EP.

The goal of this study is to compare different EP scores (EPS) and their ability to monitor and predict the disease course in a cohort of patients with MS. For this purpose, we applied an ordinal and a semi-quantitative EPS on our previously quantitatively analyzed cohorts of relapsing-remitting and primary progressive MS patients (Schlaeger et al., 2012a, 2014a).

2. Methods

2.1. Patients

The current analysis is based on the data sets of two previously reported MS cohorts that were described in Schlaeger et al. (2012a, 2014a). Inclusion criteria comprised either a diagnosis of MS according to the McDonald criteria (McDonald et al., 2001) or a diagnosis of a clinically isolated syndrome (CIS). Patients with primary progressive MS additionally fulfilled the Thompson criteria (Thompson et al., 2000). Exclusion criteria were contraindications for magnetic evoked potentials, acute relapses or glucocorticosteroid treatment within 6 weeks prior to baseline examination, additional neurological diseases potentially interfering with MS symptoms, or severe additional other diseases.

Investigations consisted of a standardized neurological examination including assessment of the EDSS/Neurostatus (Kurtzke, 1983; Kappos et al., 2007), and multimodal EP. For the current analysis the examinations at entry (T0), months 6 (T1), 12 (T2), 24 (T3), and 36 (T4) were selected. If a patient had a relapse at the assigned study visit, the clinical and EP examinations were postponed to at least 6 weeks after the first relapse symptoms. Patients who decided to discontinue the study before T4 were again invited to our center for a neurological examination or underwent a structured standardized telephone interview for determination of the EDSS by phone (Lechner-Scott et al., 2003) at T3 and T4.

The local ethic committee of the University of Basel approved the study. Written informed consent was obtained from all participants.

All seventy-two participants of the two cohorts were included into this study: 50% women, mean age: 42 years (SD = 11.4), mean disease duration: 6.6 years (SD = 4.75), median EDSS at baseline: 2.5 (IQR: 1.5–3.5), median EDSS at year 3: 3.0 (IQR: 2.0–4.0). Forty-seven patients had relapsing (RR) MS, three a CIS and twenty-two primary progressive (PP) MS. At baseline, 44% of patients were treated with immunomodulatory drugs (glatiramer-acetate, interferon-b), 1.3% received immunosuppressive treatments (mitoxantrone).

A selective dropout of patients with a more severe disease course reduced the dispersion of the EP data at later time-points with an apparent ceiling effect of EPS. We were able to obtain the EDSS or EDSS by phone at T4 of fourteen out of nineteen dropouts, so that the clinical data of 93% of all participants was available for the predictive analysis. Patients with complete clinical and electrophysiological data sets at T4 had a median $EDSS_{T4}$ of 3.0 (IQR 2–4)), while patients who dropped out of the electrophysiological part of the study had a median $EDSS_{T4}$ of 4.5 (IQR 2.125–6.375).

3. Evoked potentials

Recording of visual evoked potentials (VEP), motor evoked potentials (MEP) to upper and lower extremities (UE/LE) and median and tibial nerve somatosensory evoked potentials (SEP) followed closely the recommendations of the International Federation of Clinical Neurophysiology (Mauguière et al., 1999; Celesia and Brigell, 1999; Rothwell et al., 1999) as described previously (Schlaeger et al., 2012a).

Briefly, full-field VEP were recorded from an active electrode placed 3 cm above Oz and a reference electrode at Fz. Pattern reversal stimulation was presented to each eye separately at a frequency of 0.5 Hz. The distance from the eye to the screen was 225 cm, each checkerboard field was 30 min of arc. VEP's were averaged twice, 256 times.

MEP were recorded from the abductor digiti minimi (ADM) and the tibial anterior (TA) muscles bilaterally. The muscles were pre-innervated by the participants. The examiner controlled the extent of contraction both manually and acoustically. Magnetic stimuli were delivered first to the hand and secondly to the leg areas of the motor cortex with a Magstim 200 device (The Magstim Company Ltd., Whitland, UK) via a round coil using maximal output of the stimulator (2.2 T). Four stimulations were done with the coil pointing in clock-wise current direction and four stimulations were done with the coil pointing in counter-clockwise current direction, for ADM and TA tests, respectively. The fastest conduction time out of these stimulations was used to calculate the central motor conduction time (CMCT). For spinal stimulation the rim of the coil was placed over the seventh cervical and fifth lumbar vertebra. Median and tibial nerve SEP were obtained by stimulating the median nerve at the wrist and the posterior tibial nerve at the ankle, respectively. The stimulus intensity exceeded visual motor threshold by about 3 mA. The stimulus frequency was 3 Hz. For the median nerve SEP active recording electrodes were placed subcutaneously between cervical vertebra 6 and 7 and 7 cm lateral and 2 cm posterior to Cz with the reference electrode placed at Fz. For the tibial nerve SEP active recording electrodes were placed between the 12th thoracic and first lumbar vertebra and 3 cm posterior to Cz with the reference electrodes placed subcutaneously near the anterior superior iliac spine and Fz, respectively.

Normal values were taken from our own laboratory for VEP and tibial nerve SEP (height adjusted) and from Stoehr (1996) for median nerve SEP and MEP (height adjusted). The P100 latency of the VEP, the latency difference N13 – N20 of the median nerve SEP, the P40 latency of the tibial SEP and the CMCT to upper and lower extremities were analyzed and regarded as pathological when exceeding the upper limit of normal (mean + 2.5 SD).

A VEP amplitude was regarded as pathologically reduced if either the P100-N145 amplitude was <5 μV or if the inter-side difference exceeded >50% corresponding to an amplitude ratio >2. In case of a W-shaped morphology VEP amplitudes were regarded as pathological if the difference between the two positive peaks exceeded 10 ms (Kallmann et al., 2006).

MEP amplitudes were regarded as pathologically reduced if the amplitude ratio between the MEP and the corresponding compound motor action potential (to stimulation of the peripheral nerve) was <17% in upper extremities and <10% in lower extremities (according to Stoehr (1996)) or in case of an inter-side difference >50% according to available definitions (Kallmann et al., 2006; Jung et al., 2008).

SEP amplitudes were considered reduced if the amplitude N20-P25 was <0.9 μV in median SEP (according to Stoehr (1996)) or if the amplitude N35-P40 was <0.3 μV in tibial SEP (according to Kallmann et al., 2006 who used the same SEP methodology as applied in our lab).

As judgments of amplitude morphology imply a subjective element, two experienced clinical neurophysiologists (RS, MH) independently rated the ordinal EPS (o-EPS) that includes amplitude morphology as a criterion in addition to latency. In case of discordant results a consensus reading was performed. The EP