Evoked potentials (EP) have a role in making the diagnosis of multiple sclerosis (MS) but their implication for predicting the future disease course in MS is under debate. EP data of 94 MS patients examined at first presentation, and after five and ten years were retrospectively analysed. Patients were divided into two groups in relation to the prior duration of disease at the time point of first examination: group 1 patients (n = 44) were first examined within two years after disease onset, and group 2 patients (n = 50) at later time points. As primary measures sum scores were calculated for abnormalities of single and combined EP (visual (VEP), somatosensory (SEP), magnetic motor evoked potentials (MEP)). In patients examined early after disease onset (group 1), a significant predictive value for abnormal EP was found with MEP and SEP sum scores at first presentation correlating significantly with Expanded Disability Status Scale (EDSS) values after five years, while the VEP sum score was not. The cumulative number of abnormal MEP, SEP and VEP results also indicated higher degrees of disability (EDSS ≥ 3.5) after five years. Combined pathological SEP and MEP findings at first presentation best predicted clinical disability (EDSS ≥ 3.5) after five years (odds ratio 11.0). EP data and EDSS at first presentation were not significantly linked suggesting that EP abnormalities at least in part represented clinically silent lesions not mirrored by EDSS. For patients in later disease phases (group 2), no significant associations between EP data at first presentation and EDSS at five and ten years were detected. Together with clinical findings and MR imaging, combined EP data may help to identify patients at high risk of long-term clinical deterioration and guide decisions as to immunomodulatory treatment. *Multiple Sclerosis* 2006; 12: 58–65. www.multiplesclerosisjournal.com

**Key words:** evoked potentials; multiple sclerosis; predictors of disability

**Introduction**

The individual course of multiple sclerosis (MS) is still unpredictable. Secondary progression with major disability may evolve in half the patients after 10 years of disease [1]. Several options now exist for disease-modifying treatments in MS but better guidance in the assessment of high-risk versus low-risk patients is still needed. Magnetic resonance imaging (MRI) is an established sensitive tool in diagnosing MS in patients with a clinically isolated syndrome (CIS) [2] and is currently used to select patients for MS treatment trials [3]. While the correlation between MRI findings and actual clinical disability is modest [4,5], some abnormalities on MRI, eg, increase of lesion volume, were shown to be predictive for the degree of long-term disability [6,7].

The diagnostic value of evoked potentials (EP) in establishing the diagnosis of MS has been addressed by several studies, and practice parameters were developed by a subcommittee of the American Academy of Neurology [8]. Visual evoked potentials (VEP) were regarded as ‘probably useful’ and somatosensory evoked potentials (SEP) as ‘possibly useful’ in identifying patients with CIS at increased risk for later clinically definite MS. Patients with suspected MS and EP abnormalities had a 71% higher risk of clinical deterioration during a two-year follow-up compared to individuals with...
normal EP [9]. Moreover, VEP were the most sensitive diagnostic tool in suspected MS [9,10] and were therefore included in the new diagnostic criteria for MS [2].

However, the predictive value of EP for future disability in MS is still under debate [11,12]. In line with natural MS history studies showing a predictive value of early clinical course, we here investigated whether EP alterations during early MS correlate with clinical disability at later stages of the disease [13]. In a sample of 94 patients followed at our MS centre over five to ten years we show that early MEP and SEP data recorded within two years after disease onset may indeed help to predict disease progression in subsequent years.

**Materials and methods**

**Patients**

All MS patients were seen at the MS centre of the University Department of Neurology of Würzburg during the period 1989–2002. Ninety-four patients with clinically definite MS according to the older criteria of Poser [14] were consecutively recruited and accepted for this study if they fulfilled the following inclusion criteria: All had been followed for at least 10 years using a standardized examination protocol including the Expanded Disability Status Scale (EDSS) [15] and multimodal EP, ie, VEP, MEP and/or SEP of the lower extremities, performed at first presentation and at least during two further visits within a 10-year interval. The majority of patients were seen in a clinically stable phase of the disease. However, because of the retrospective design of this study, we cannot exclude that some patients were examined in a more active phase.

According to natural history data showing that early alterations in the disease course of MS may better predict later clinical disability [13], patients were arbitrarily divided into two groups (Table 1): group 1 consisted of 44 patients who were seen within a two-year interval after disease onset (mean disease duration 1.2 years), and group 2 consisted of 50 patients who were first examined later in their disease (mean disease duration 9.6 years at first presentation). For this study, time of disease onset was determined either by reported clinical signs suggestive of MS or by establishing the diagnosis through appropriate history and examination.

**Evoked potentials**

All electrophysiological examinations were performed on a commercial PC-based neurophysiological recording system (Multiliner, Toennies Division of Viasys Healthcare, Höchberg, Germany). Standard temperature was maintained (≥32°C for skin temperature measured at the mid-calf level) for SEP and MEP recordings. Filters and other technical settings for all stimulations and recordings were chosen according to established guidelines [16].

**Somatosensory evoked potentials (SEP)**

The tibial nerve was stimulated at the ankle with surface electrodes at 1.5 times motor threshold; stimulation rate was set at 3/s with a pulse duration of 100–200 μs. According to the standard montage in the 10/20-system, a steel needle recording electrode was positioned at Cz (between Cz and Pz), the reference electrode at Fz, and 200 responses were averaged followed by a second run under identical conditions. Latencies were read from the beginning of the stimulus artefact to the P40 peaks. Upper normal limits for the P40 latency were determined from data established in our laboratory at 43.9 ms (mean ±2.5 standard deviations) for individuals with a body height of 175 ± 5 cm. For patients with a body length below 170 cm or above 180 cm, the upper limit for the P40 latency was corrected by 0.17 ms/cm deviation from 175 cm. In the age range of our patients the influence of age on SEP latencies accounts for less than 0.1 ms/year and the mean age at first examination was similar in both groups, therefore we abstained from additional corrections for age [17]. The upper limit of latency side differences was 2.1 ms (mean ± 2.5 standard deviations) with no further correction.
for body height. The lower normal limit of the P40 amplitude was 0.3 μV and less than 50% reduction from the highest P40 amplitude on either side.

Magnetic motor evoked motor potentials (MEP)

Magnetic motor cortex stimulation was performed in accordance with standard methodology and protocols [18]. A circular high-performance coil attached to a Magstim 200 stimulator (Micromed, Freiburg, Germany) was optimally positioned over the vertex for stimulating the leg representation of the motor cortex. MEP responses were recorded using surface EMG electrodes from both anterior tibial muscles. For preactivation, patients were asked to perform a weak voluntary contraction of the foot dorsiflexors. Stimulus intensity was adjusted to 1.5 times the motor threshold or to the maximal output if the threshold exceeded 66% of the stimulator output. L5 lumbar roots were stimulated by placing the coil over the upper lumbar region using 80–100% of the maximal stimulator output. For both cortex and root stimulation, three successive stimuli were delivered for each side. The shortest latencies between the trigger signal and the MEP response were accepted. Central motor conduction time (CMCT) was calculated as the latency difference between cortical and radicular stimulation.

Upper limits of normal CMCT were taken as 17.8 ms (for total body length ≤ 175 cm) and 19.3 ms (for total body length > 175 cm), 2.0 ms for side differences in latency and less than 50% difference between the MEP amplitudes on either side. In addition to amplitude and latency criteria, dispersed MEP with ≥ 4 baseline crossings on cortical stimulation were also rated abnormal.

Visual evoked potential (VEP)

Monocular visual stimulation was performed using a pattern-reversal checkerboard screen with 14 × 10 checks of 1° each reversing at a frequency of 2/s. The minimal luminance was 0.1 cd/m², the maximal 40 cd/m², resulting in a mean luminance of 20 cd/m² with a contrast of 99.5%. Background luminance was adjusted to match the mean monitor luminance. A steel needle recording electrode was placed at Oz (5 cm above the inion) and the reference electrode at Fz. Two to three trials with 200 pattern reversals each were averaged. According to laboratory normal values, the upper latency limit for the P100 (N2) latency was 120 ms, and the lower limit for the P100 (P1–N2) amplitude was 5 μV. A W-shaped P100 deformity was rated abnormal if the difference between the two positive peaks exceeded 10 ms. Normal limits were 60% for side differences in amplitude (calculated from the highest amplitude) and 7.0 ms for differences in latency.

Scoring and analysis of EP data

The analysis of EP data was performed along two lines:

As primary goal of this study we defined an ordinal EP score as predictor for clinical disability, in which each abnormal result scored one point, determined as outlined above, eg, abnormal latency and/or amplitude on either side. Hence, EP sum scores for each EP modality adopted values between ‘0 (zero)’ (a normal EP result) and ‘4 (four)’ (eg, abnormal amplitudes and/or latencies on both sides). In addition, EP data from different modalities were joined into combined scores according to O’Connor et al. [11] Thus, combined two (MEP + SEP) and three modality (VEP + MEP + SEP) sum scores of EP data at first presentation were computed. Single and composite scores were then correlated with EDSS data.

In a second approach, we correlated single EP parameters and the number of abnormal EPs in the early disease course with the EDSS at later time points to test whether they may serve as predictors for clinical disability as previously proposed by Fuhr and colleagues [12]. Furthermore, odds ratios for single and combined EPs were calculated based on these data.

Statistics

At first presentation, 10 patients in group 1 and 11 in group 2 had two of the EP modalities examined, while in 28 patients of group 1 and 20 in group 2 all three EP modalities were performed. Therefore, computations for the modalities had different denominators.

Nonparametrical tests were employed for all statistical comparisons using the Professional Edition Version 5 of JMP Statistical Discovery Software (SAS Institute, Cary, NC, USA). Associations between EP data and the EDSS were examined by the χ²-test and presented in two-by-two tables.

To investigate the relationship between the disease course and EP abnormalities, changes in EDSS scores were calculated between the values at first presentation (T0) and at five (T1) and ten (T2) years. EP scores were correlated with the EDSS values at five and ten years as well as with changes of EDSS within five (AEDSS-T1) or ten years (AEDSS-T2) by calculating Spearman rank
correlation coefficients. The Kruskal–Wallis test was used to assess the correlation between the degree of clinical disability after five years and the cumulative number of abnormal EP results at first presentation. Odds ratios for EP data at first presentation were computed based on a nominal logistic fit model included in the JMP Statistical Discovery Software. Using hypotheses derived from previous studies [11,12,19], we restricted the number of comparisons to single tests, thereby avoiding the need for adjustments for multiple comparisons [20]. Individual $P$-values are indicated for each comparison in the results section. Significance was assumed for $P < 0.05$ in all tests.

Results

Clinical characteristics of MS patients

Patients were divided into two groups according to disease duration at first electrophysiological examination (Table 1). As expected from this method of stratification, patients with the relapsing–remitting type of MS (RRMS) were more frequent in group 1. In group 2, a higher prevalence of patients with secondary progressive MS (SPMS) was found, reflecting the natural disease course of definite MS, with most patients progressing from the RR to the SP phase during the first two decades [1]. While age at disease onset differed significantly between both groups ($P < 0.01$) (as an effect of consecutive recruitment), age at first examination did not (Table 1). Therefore, all further comparisons of EP results obtained at first examination with clinical data at different time points were performed with age-matched groups.

Correlations of EP sum scores with EDSS

In group 1 patients, the MEP as well as the SEP sum scores at first examination correlated significantly with clinical disability (EDSS) after five years (correlation coefficients $r = 0.55$ and 0.5, respectively, $P < 0.003$). After 10 years, a close correlation was found only for the MEP sum score ($r = 0.65$, $P < 0.003$) (Figure 1). No correlation was found for EP sum scores of any modality with EDSS at first presentation. Furthermore, VEP sum scores did not correlate with EDSS at any time point (Figure 1).

Longitudinal changes in EDSS over five ($\Delta$EDSS-T1) and ten years ($\Delta$EDSS-T2) correlated with MEP sum score ($r = 0.75$ for $\Delta$EDSS-T1, $r = 0.8$ for $\Delta$EDSS-T2; both comparisons, $P < 0.001$). No significant correlation was detected between EDSS-T1 or -T2 and SEP sum score ($r = 0.43$ for $\Delta$EDSS-T1, $r = 0.45$ for $\Delta$EDSS-T2) or VEP sum score ($r = 0.13$ for $\Delta$EDSS-T1, $r = 0.38$ for $\Delta$EDSS-T2).

However, when EP modalities were combined, we found a significant correlation: in group 1 patients, the compound MEP + SEP sum score as well as the VEP + MEP + SEP sum score both correlated significantly with EDSS after 5 and 10 years (Spearman rank correlation coefficients ranging from 0.5 to 0.6; $P < 0.05$) (Figure 2) as well as with $\Delta$EDSS-T1 and $\Delta$EDSS-T2 (Spearman rank correlation coefficients ranging from 0.6 to 0.88; $P < 0.01$).

![Figure 1](https://www.multiplesclerosisjournal.com)

Figure 1 Correlations between individual EP abnormalities of MEP, SEP or VEP sum scores at first presentation with EDSS at first presentation as well as after five and ten years in patients with recent onset of MS (group 1). Numbers under columns indicate absolute values of correlation coefficients.
For patients of group 2, no significant correlation between EP sum scores and EDSS at different time points was found. The correlation coefficient ranged from 0.13 to 0.40 not reaching the level of significance; this was also true for ΔEDSS-T1 and ΔEDSS-T2 (data not shown). In regard to compound EP data, only for the VEP + MEP + SEP sum score significant correlations with EDSS at first presentation ($r = 0.59, P < 0.05$) and after five years ($r = 0.51, P < 0.05$) were found (Figure 2).

### Correlation of single EP parameters with EDSS

Comparing single pathological alterations of EP parameters (latency, amplitude, side differences) with clinical disability, a correlation of delayed latencies of SEP (Figure 3A) and of MEP (Figure 3B) with EDSS ≥ 3.5 at five years (SEP, MEP; $\chi^2$-test, $P < 0.05$) was found for group 1 patients. Furthermore, pathological side differences despite normal absolute VEP latencies at first presentation were correlated with higher degrees of clinical disability.

![Figure 2](image_url)

**Figure 2** Correlations between combined MEP + SEP sum score or three modality VEP + MEP + SEP sum score at first presentation with EDSS at first presentation, after five and ten years in group 1 and group 2 patients. Numbers under columns indicate absolute values of correlation coefficients.

<table>
<thead>
<tr>
<th>SEP latency (tibial nerve)</th>
<th>EDSS after 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDSS&lt;3.5</td>
</tr>
<tr>
<td>normal</td>
<td>12 * (37.5%)</td>
</tr>
<tr>
<td>pathol.</td>
<td>6 (18.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MEP latency (tibial muscle)</th>
<th>EDSS after 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDSS&lt;3.5</td>
</tr>
<tr>
<td>normal</td>
<td>10 * (27.8%)</td>
</tr>
<tr>
<td>pathol.</td>
<td>9 (25%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VEP latency (interocular differences)</th>
<th>EDSS after 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDSS&lt;3.5</td>
</tr>
<tr>
<td>normal</td>
<td>10 * (31.2%)</td>
</tr>
<tr>
<td>pathol.</td>
<td>3 (9.4%)</td>
</tr>
</tbody>
</table>

* $P < 0.05$

![Figure 3](image_url)

**Figure 3** Contingency tables for correlations of normal and abnormal (A) SEP and (B) MEP latency and (C) VEP interocular latency differences at first presentation versus later clinical disability (EDSS at five (A, B) and ten (C) years) in patient group 1.

* BA Kallmann et al. Multiple Sclerosis 2006; 12:58–65*
(EDSS $\geq 3.5$) after ten years ($\chi^2$-test, $P < 0.05$, Figure 3C).

In contrast, no significant correlation for single EP parameters at first presentation with EDSS after five or ten years was detected in group 2 patients (data not shown).

**EP as a potential predictive marker of future clinical disability**

For group 1, the number of abnormal EPs at first presentation out of the three EP modalities correlated with the degree of clinical disability after five years (Figure 4): a single pathological EP finding indicated a mean EDSS of 2.4, two an EDSS of 3.5 and three an EDSS of 4.8.

Abnormal results of combined SEP and MEP data at first presentation in group 1 were found highly predictive for an EDSS $\geq 3.5$ after five years (odds ratio 11, $P < 0.01$). The single abnormality of SEP alone was a weaker predictor (odds ratio 7.5, $P < 0.01$). In contrast, neither a single abnormal MEP nor an abnormal VEP had a significant predictive value.

For group 2 patients abnormal EP at first presentation did not predict clinical disability at five years (odds ratios <5, $P > 0.05$, Figure 5).

For the 10-year period, no predictive value of EP alone or in combination was found for either patient group (data not shown).

**Discussion**

Our study indicates that standard EPs recorded within two years after disease onset of MS (group 1) correlate with EDSS scores after five and ten years, while at later disease stages (group 2) no such projections are possible. These findings confirm and extend results of previous studies [11,12,19]. All three longitudinal studies showed a correlation of EP data with EDSS at various time points despite different methodological approaches. O’Connor and colleagues found a correlation between an EP abnormality score based on the sum of abnormal results of eight EP modalities with the EDSS score at the same time point, but these measures failed to predict EDSS progression over a period of two years [11]. Only the study by Fuhr et al. found a slight correlation of VEP and MEP at baseline with changes of EDSS over two years [12].

The failure of the former studies to establish a prognostic implication of EP testing may be explained by the fact that our study for the first time specifically has taken into account the timing of electrophysiological examinations in relation to patients’ individual disease course.

EP alterations in patients examined early (ie, within two years after disease onset, group 1) were only predictive for clinical disability after five but not after 10 years, and EPs failed to predict clinical disability in those with advanced disease at the time of first examination (group 2) at any time interval. This observation fits well with a recent MRI study demonstrating that MRI changes in lesion volume during the first five years correlated better with the EDSS score at 14 years than did MRI changes appearing later [6]. The authors concluded that lesion development during early years as evidenced by MRI imaging has an important impact on the long-term disability in MS. From our data, a similar statement can be made for EP.

Our finding that the cumulative number of pathological EPs in the early disease phase indicates
a higher probability for later clinical disability is in accordance with results by the previous study of Fuhr and colleagues showing an association of EP abnormalities with changes in the EDSS over a two-year period in a cohort of 30 patients [12]. In our study, the combined information derived from abnormal MEP and SEP at first presentation had the highest predictive value for an EDSS ≥ 3.5 after five years with an odds ratio of 11.0 in group 1, while the single abnormality of SEP alone was a much weaker predictor (odds ratio of 7.5). Patients of both groups were age-matched in relation to the time point of first neurological and electrophysiological examination as indicated in Table 1, thereby excluding a potential age effect on EP findings. Due to the retrospective character of this study, our patients were not selected for disease activity. We do not consider this a critical factor as differential effects of disease activity on the relationship between the clinical status as reflected by EDSS and electrophysiological data (eg, MEP) have not been established [19].

VEP abnormalities found early after definite diagnosis of MS do not show a significant correlation with EDSS at any time point in our study. We therefore conclude that VEP, while being a sensitive tool for establishing the early diagnosis of MS [2,9], fail to provide prognostic clues for future disability. The increase of correlation coefficients of MEP sum scores with EDSS over time in contrast to SEP sum scores as shown in Figure 1 may be due to the nature of EDSS overestimating motor function at higher degrees of disability.

It is widely accepted that EP abnormalities may uncover clinically silent lesions [9], and the proportion of clinically silent lesions disclosed by multimodal EP has been estimated at around 50% [21], as well as 42% for VEP and 51% for SEP [22]. In our study, EP data of group 1 at first examination did not correlate with EDSS at the same time point. Thus, EP at this early stage do not reflect the existing degree of clinical disability as mirrored by EDSS. EP rather provide evidence of myelin and axonal pathology anywhere along the visual and long sensory or motor tracts. In long nerve fibres, cumulative small lesions may add up to abnormal EP findings. This information may differ from evidence provided by focal MRI lesions that may not be linked to brain areas relevant for the generation of EP [4,5,11]. The ability of EP to disclose clinically silent lesions at early disease stages that also do not show on MRI is a strong argument for employing EP techniques in addition to MRI early in MS.

Our study supports the notion that combined testing of EP modalities may help to predict the severity of future clinical disability in MS patients examined at early disease stages. We suggest that EP may assist in early decisions and help in introducing immunomodulatory treatments. The results of this study encourage further prospective studies aiming to investigate the predictive power of EP in comparison to MRI and whether or not additional information can be gained by performance of EP.

References


