

Visual and motor evoked potentials in the course of multiple sclerosis

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Summary

While evoked potentials are sensitive tools for diagnosing multiple sclerosis, little is known about their prognostic value and their role in determining the course of the disease. To validate the visual and motor evoked potentials (VEP and MEP) as measures for the course of multiple sclerosis, we examined prospectively 30 patients with relapsing–remitting or secondary progressive multiple sclerosis. The Expanded Disability Status Scale (EDSS), VEP and MEP were measured at entry and after 6, 12 and 24 months. The Spearman rank correlation was used for statistical analysis. Applying multiple regression in 15 randomized patients allowed derivation of a formula for predicting changes in EDSS score based on changes in MEP and VEP. Validation was done by comparing the predicted with the real changes in EDSS in the other 15 patients. The number of pathological VEP and MEP

results correlated at all four measurement points with the EDSS ($\rho \geq 0.6$, $P \leq 0.01$). When the latencies of VEP and MEP were combined using the sum of their Z scores, correlation with the EDSS was even more significant ($\rho \geq 0.6$, $P < 0.001$). Changes over time of electrophysiological data and EDSS were also correlated ($\rho = 0.43$, $P < 0.05$). Moreover, VEP and MEP at baseline correlated with the EDSS after 2 years ($\rho = 0.43$, $P = 0.03$). Reliable prediction of the course of multiple sclerosis for individual patients is not possible from VEP and MEP data. However, we conclude that, for groups of patients with secondary progressive or relapsing–remitting multiple sclerosis the combined testing of VEP and MEP yields numerical data that allow objective estimation of the course and prognosis of the disease.

Keywords: multiple sclerosis; visual evoked potentials; motor evoked potentials; electrophysiology; magnetic resonance imaging

Abbreviations: CMCT = central motor conduction time; EDSS = Expanded Disability Status Scale; MEP = motor evoked potentials; VEP = visual evoked potentials

Introduction

The assessment of the course of multiple sclerosis is difficult because of its relapsing–remitting natural course and the multiplicity of functional systems that are involved. While conventional MRI is diagnostically sensitive and provides information on some aspects of the activity of the disease at a given point in time, it does not depict the demyelination directly and correlates only weakly with the clinical findings. Moreover, there is currently no valid measurement of the mechanisms that cause the lesions and consequently the dysfunctions of the CNS, and there are no useful predictors of the course of the disease.

Evoked potentials have long been used as a diagnostic tool in multiple sclerosis. They are diagnostically sensitive when multiple functional systems are tested. In contrast to MRI, each pathological finding represents an alteration of

function due to at least one lesion. It is plausible, therefore, that an alteration in evoked potentials correlates with an alteration in the load of functionally relevant lesions. The aim of the present study was to determine whether evoked potentials may be useful in the assessment of the actual course of multiple sclerosis and whether they may serve as a predictor of the future course of the disease.

Methods

Patients and clinical examination

We examined prospectively 30 patients (24 women and six men, mean age 37.5 years, range 26–50 years) with clinically definite multiple sclerosis according to the criteria of Poser

and colleagues (Poser *et al.*, 1983). The inclusion criteria were a relapsing–remitting course (with at least two relapses and incomplete remission in the last 2 years; 25 patients) or a secondary progressive course (five patients), a score of minimally 2 and maximally 6.5 points on the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983), an MRI scan of the brain during the last 12 months consistent with the diagnosis of multiple sclerosis (at least three lesions at least 2 mm in diameter, or two lesions, one of which had to be located in the periventricular area and the other had to have a diameter of at least 5 mm), at least one gadolinium-enhancing lesion on a brain MRI obtained during the 2 weeks before entry, and written informed consent. Patients with chronic steroid or immunosuppressive drug treatment during the last 6 months or patients who had received acute steroid treatment for a relapse during the last 4 weeks were excluded. Mean disease duration at study entry was 9.2 years (range 1.5–22 years).

The duration of the study was 2 years. A complete neurological examination was performed and motor and visual evoked potentials (VEPs) were measured at entry (T_0) and after 6 (T_1), 12 (T_2) and 24 (T_3) months. The study was approved by the Ethics Committee of the University Hospital, Basel.

The clinical examination was rated according to the EDSS scale. The median EDSS score was 4.65 (range 2–6.5) at study entry and 5.1 (range 2–9) at the end of the study (after 2 years). Eleven patients had no change in EDSS score between entry and the end of the study or a change in either direction of only 0.5 points, four had a decrease (improvement) and nine had an increase (deterioration) of at least one point; six patients had a relapse at one of the intermediate measuring points but recovered by the end the study, when their score was the same as at entry to the study or differed from their entry score by only 0.5 points.

Motor evoked potentials

The motor evoked potentials (MEP) were recorded from the pre-innervated abductor digiti minimi and tibialis anterior muscles bilaterally with a Counterpoint EMG machine (Dantec, Skovlunde, Denmark). Low and high filters were set at 50 Hz and 2 kHz, respectively. Magnetic stimuli were delivered from a Magstim 200 device (The Magstim Company Ltd, Whitland, UK) via a round coil (inner diameter 9 cm). The cortex was stimulated using the maximal output of the stimulator (2.2 T), with the coil centred at the vertex for stimulation of the hand. For the leg area, the coil was placed with the stimulating surface over the vertex (the centre of the coil was 5 cm anteriorly), and from this point the coil was moved in steps of 1 cm in anteroposterior and lateral directions in search of the location producing the largest MEP in the tibialis anterior muscle. For both upper and lower extremities, four stimulations were done with clockwise and four with anticlockwise current flow. Spinal stimulation was done by placing the rim of the same coil over the seventh

cervical and fifth lumbar vertebra, with two stimulations for each current direction. When MEPs were identifiable, the shortest onset latency of MEPs was determined and used for calculating the central motor conduction time (CMCT), which was the only parameter of MEPs used for further analysis. The sum of the CMCT to both upper extremities and the sum of the CMCTs to both lower extremities were used to calculate the deviation from the (doubled) normal mean values and to create the regression model. The CMCT was assessed according to the normal values for the same stimulation method quoted in Stöhr and colleagues (Stöhr *et al.*, 1996). When no MEP was identifiable, we took the longest CMCT found in our study for the upper or lower extremities, as the result was then considered to be at least as pathological as that with the longest CMCT ('censored' latencies). This procedure allowed us to include the data of the patients with the most pathological results.

Visual evoked potentials

The VEPs were recorded from an active electrode placed 3 cm above Oz and a reference electrode at Fz with a Neuropack (Nihon-Kohden, Tokyo, Japan) or a MS-92 machine (Medelec, Old Woking, UK). Low and high filters were set at 0.5 and 100 Hz, respectively. Analysis time was 200 ms, and at least 256 single recordings were averaged twice. Pattern reversal stimulation was presented to each eye separately at a frequency of 0.5 Hz. The screen measured 18° and individual squares 42 minutes of arc. The luminance of the white and black chequers was 85 and 2 cd/m², respectively. When VEPs were identifiable, the peak latency of P₂ (P₁₀₀) was determined. It was the only parameter of VEPs used for further analysis. The sum of the latencies of the component P₂ after stimulation of the right and left eyes was used to calculate the deviation from the (doubled) normal mean values and to create the regression model. The latency of P₂ was assessed according to normal values determined in our laboratory with the same equipment; values exceeding the mean normal value by >2.5 SD were regarded as abnormal (normal latency of P₂ is ≤109.5 ms). When no VEP was identifiable, the longest latency of P₂ found in our study was taken, as the result was considered to be at least as pathological as that with the longest identifiable P₂.

Statistical analysis

Cross-sectional comparisons and prognostic value

The association between visual acuity and the latency of P₂ was assessed by simple regression analysis and the Spearman rank correlation coefficients between the EDSS and evoked potential data. Data for all evoked potentials were summarized in two ways: (i) as the number of pathological results outside the normal range (normal mean + 2.5 SD), counting VEP on each side and MEP at each limb separately; (ii) as

the sum of Z scores of latencies calculated according to the formula:

$$\Sigma Z = Z(\text{sum of CMCT}_{\text{UE}}) + Z(\text{sum of CMCT}_{\text{LE}}) + Z(\text{sum of } P_2)$$

where the Z score $Z_{i,t}$ associated with a given summed latency value $x_{i,t}$ of patient i at time t was computed according to the transformation formula

$$Z_{i,t} = (x_{i,t} - \text{sample mean of } x \text{ at baseline}) / \text{standard deviation of } x \text{ at baseline.}$$

Longitudinal comparisons

The relationship between the course of EDSS and changes in evoked potentials was described using a linear mixed model with a random subject effect that accounted for the correlation of residuals within subjects. For this purpose, individual changes in EDSS scores and in evoked potentials from their baseline values were computed for each measuring time-point according to the formulae

$$\begin{aligned} \Delta \text{EDSS}(T_x) &= \text{EDSS}(T_x) - \text{EDSS}(T_0) \\ \Delta \text{CMCT}_{\text{UE}}(T_x) &= \text{CMCT}_{\text{UE}}(T_x) - \text{CMCT}_{\text{UE}}(T_0) \\ \Delta \text{CMCT}_{\text{LE}}(T_x) &= \text{CMCT}_{\text{LE}}(T_x) - \text{CMCT}_{\text{LE}}(T_0) \\ \Delta P_2(T_x) &= P_2(T_x) - P_2(T_0) \end{aligned}$$

where $\text{EDSS}(T_x)$ is the EDSS score at time T_x , $\text{CMCT}_{\text{UE}}(T_x)$ is the sum of the CMCTs to the upper extremities at time T_x , $\text{CMCT}_{\text{LE}}(T_x)$ is the sum of the CMCTs to the lower extremities at time T_x and $P_2(T_x)$ is the sum of the latencies of the VEP component P_2 after stimulation of the right and left eyes at time T_x . In a preliminary step, the changes in the EDSS scores were regressed against the concurrent changes in latencies using the model

$$\begin{aligned} \Delta \text{EDSS}(T_x) &= \alpha + \beta_1 * \Delta \text{CMCT}_{\text{UE}}(T_x) + \beta_2 * \\ &\Delta \text{CMCT}_{\text{LE}}(T_x) + \beta_3 * \Delta P_2(T_x). \end{aligned}$$

Where α = intercept term; β = slope between $\Delta \text{EDSS}(T_x)$ and $\Delta \text{CMCT}_{\text{UE}}$; β_2 = slope between $\Delta \text{EDSS}(T_x)$ and $\Delta \text{CMCT}_{\text{LE}}(T_x)$; and β_3 = slope between $\Delta \text{EDSS}(T_x)$ and $\Delta P_2(T_x)$.

This analysis included the complete set of data for all 30 subjects. The result suggested that the variable $\Delta \text{CMCT}_{\text{LE}}(T_x)$ could be omitted from the model. In the next step, the simplified model

$$\Delta \text{EDSS}(T_x) = \alpha + \beta_1 * \Delta \text{CMCT}_{\text{UE}}(T_x) + \beta_3 * \Delta P_2(T_x)$$

was fitted to the data of 15 randomly selected subjects. For the purpose of validation, the resulting regression equation was then applied to the evoked potential data for the other 15 patients and predicted values of ΔEDSS were calculated. Observed and predicted values of ΔEDSS were compared by means of the Spearman rank correlation coefficient ρ_s . The statistical significance of this association was estimated with a random permutation test (i.e. by generating 5000 random permutations of the individual triples $[\Delta \text{EDSS}(T_1), \Delta \text{EDSS}(T_2), \Delta \text{EDSS}(T_3)]$ across subjects and determining the percentage of simulated values of ρ_s exceeding the observed value in absolute size). This was to account for the fact that

repeated observations from the same subject are likely to be correlated (Fisher and van Belle, 1993). The number of observations included in our analyses varied because some patients had incomplete series of measurements. Statistical analyses were done with the programs StatView 4.5 and SAS 6.12 (both SAS Institute Inc., Cary, NC, USA).

Results

Cross-sectional correlations between evoked potentials and clinical data

The sum of the P_2 latencies correlated at all times with the sum of the visual acuities of the two eyes, and the sum of the CMCTs to all four extremities with the EDSS score (Table 1). In our group of patients, the latter correlation was based primarily on the CMCTs to the upper extremities.

The number of pathological results in the combined testing of MEP and VEP correlated with the EDSS score at all measuring points. When the sum of the Z scores of the latencies of MEP and VEP were compared with the concurrent EDSS score, the correlation was even closer (Table 1 and Fig. 1).

Longitudinal correlations between evoked potentials and clinical data

The regression estimates for the data of 15 randomized patients (group A) were as follows: $\alpha = 0.1049$; $\beta_1 = 0.0231$ ($P = 0.052$); $\beta_3 = 0.0073$ ($P = 0.133$). We used these coefficients to compute predicted values of $\Delta \text{EDSS}(T_x)$ among the remaining patients (group B). Observed and predicted EDSS scores within this group were compared by means of the Spearman rank correlation coefficient, giving the following results: $n = 38$, $\rho = 0.431$ ($P = 0.043$, estimated using a random permutation test). This correlation coefficient was only slightly smaller than that obtained within group A (i.e. $\rho = 0.442$).

Prognostic value of evoked potentials data

The number of pathological results in the combined testing of MEP and VEP as well as their Z -transformed latencies at baseline correlated with the alteration in the EDSS score over the time-span of the study. Moreover, the change in evoked potential data during the first year is a predictor of the change in the clinical score during the second year. Contrarily, no correlation was detected between the EDSS score at study entry and change in the EDSS score over the time-span of the study (Table 1 and Fig. 2).

Discussion

The development of new treatments for multiple sclerosis requires a reliable and objective measurement of the course of the disease with emphasis on the early stages, as the goal

Table 1 Correlations between evoked potentials, clinical data and clinical outcome

Variable	Correlation coefficient	P
CMCT _{all} versus EDSS at T ₀	0.52	0.006
CMCT _{all} versus EDSS at T ₁	0.62	<0.001
CMCT _{all} versus EDSS at T ₂	0.67	<0.001
CMCT _{all} versus EDSS at T ₃	0.75	<0.001
P ₂ versus visual acuity at T ₀	-0.58	<0.001
P ₂ versus visual acuity at T ₁	-0.61	<0.001
P ₂ versus visual acuity at T ₂	-0.53	0.003
P ₂ versus visual acuity at T ₃	-0.66	<0.001
No. path. EP versus EDSS at T ₀	0.66*	<0.001
No. path. EP versus EDSS at T ₁	0.63*	0.002
No. path. EP versus EDSS at T ₂	0.52*	0.01
No. path. EP versus EDSS at T ₃	0.52*	0.02
Σ Z versus EDSS at T ₀	0.67	<0.001
Σ Z versus EDSS at T ₁	0.62	<0.001
Σ Z versus EDSS at T ₂	0.69	<0.001
Σ Z versus EDSS at T ₃	0.72	<0.001
#path. EP(T ₀) versus ΔEDSS(T ₃)	0.60	0.003
Σ z(T ₀) versus ΔEDSS(T ₃)	0.43	0.03
EDSS(T ₀) versus ΔEDSS(T ₃)	0.13	0.51
EDSS(T ₃) - EDSS(T ₂) observed versus	0.43	0.03
EDSS(T ₃) - EDSS(T ₂) as predicted from ΔEP(T ₂)		

*Corrected for ties. CMCT_{all} = sum of CMCT to all four extremities; ΔEDSS(T₃) = change in EDSS over time-span of study; P₂ = sum of latencies of component P₂ after stimulation of each eye; No. path. EP = number of pathological results of evoked potential measurement; Σ Z = sum of Z scores of CMCTs to upper and lower extremities and of P₂; EDSS(T₃) - EDSS(T₂) was predicted from ΔEP(T₂) according to the regression model EDSS(T₃) - EDSS(T₂) = α + β₁ × ΔCMCT_{UE}(T₂) + β₂ × ΔCMCT_{LE}(T₂) + β₃ × ΔP₂(T₂).

is to stop further progression of the disease after the diagnosis has been made. Moreover, reliable prediction of rapid progression is necessary in order to identify patients at high risk, whether for the recruitment of suitable patients in clinical trials in order to achieve fast progress in therapeutic research or for the tailoring of therapy to individuals.

Conventional MRI (T₂-weighted and gadolinium-enhanced T₁-weighted images) is currently the single most sensitive test for multiple sclerosis (Filippini *et al.*, 1994; Beer *et al.*, 1995; Comi *et al.*, 1998; Miller *et al.*, 1998) and it also allows the exclusion of a number of possible differential diagnoses. While evoked potentials can test the function of only a very limited number of central tracts, MRI examines the whole cerebrum at once (Comi *et al.*, 1998). However, as white matter lesions identified by conventional MRI are not identical with zones of malfunction, their number and extent correlate only weakly with the clinical status (IFNB Multiple Sclerosis Study Group, 1995; O'Connor *et al.*, 1998; Simon *et al.*, 1998). A more robust correlation was established between the extent of T₁ lesions ('black holes') and the EDSS score, but only in patients with a secondary progressive course (Truyen *et al.*, 1996). In longitudinal comparisons, correlations between clinical outcome and conventional MRI were insignificant (O'Connor *et al.*, 1998; Simon *et al.*, 1998), weak (IFNB Multiple Sclerosis Study Group, 1995; O'Riordan, 1998) or limited to patients with secondary

progressive multiple sclerosis (Truyen *et al.*, 1996). While abnormalities in T₂-weighted MRI in patients with isolated syndromes reliably predict the risk of developing clinically definite multiple sclerosis, its course and the EDSS score after 10 years (Miller *et al.*, 1998; O'Riordan, 1998), the correlations between T₂-lesion load and disability become modest at best once the diagnosis of multiple sclerosis has been established (Losseff *et al.*, 1996; Miller *et al.*, 1998; O'Connor *et al.*, 1998). Moreover, a meta-analysis including a total of 307 patients showed that the number of gadolinium-enhancing lesions at baseline and even the mean number of gadolinium-enhancing lesions in monthly repeated brain scans during the first 6 months correlate only weakly with the number of relapses and not at all with the change in EDSS score in the subsequent 12 or 24 months (Kappos *et al.*, 1999).

Measurements of evoked potentials are also sensitive tests for multiple sclerosis, as they can detect subclinical malfunction of the tested systems (Chiappa and Ropper, 1982; Hess *et al.*, 1986, 1987). Their diagnostic sensitivity increases considerably when different methods are used in combination and approaches 100% for patients with definite multiple sclerosis (Khoshbin and Hallett, 1981). In a series of 90 patients with definite or possible multiple sclerosis tested in our laboratory, VEPs were the most sensitive modality when compared with somatosensory evoked potentials from the upper and lower extremities, brainstem

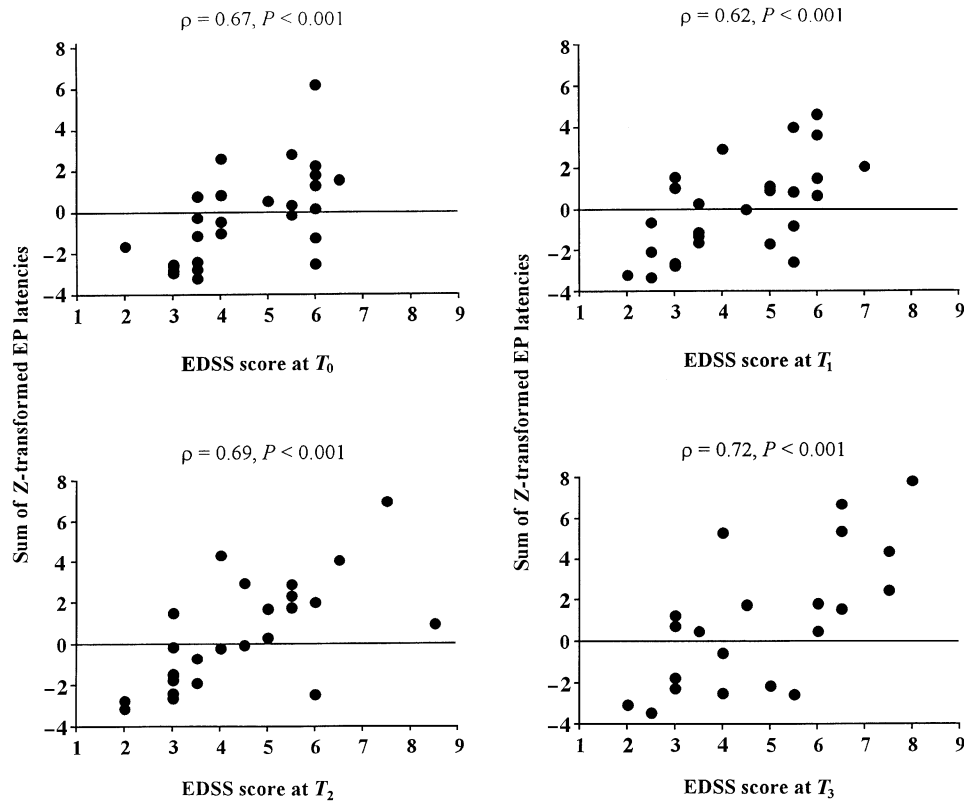


Fig. 1 Correlations of combined VEP and MEP results with EDSS scores at all measurement points. To combine the different latencies on a single scale, the sum of their Z scores was computed. Statistical assessment of the associations was based on the Spearman rank correlation coefficient. EP = evoked potential.

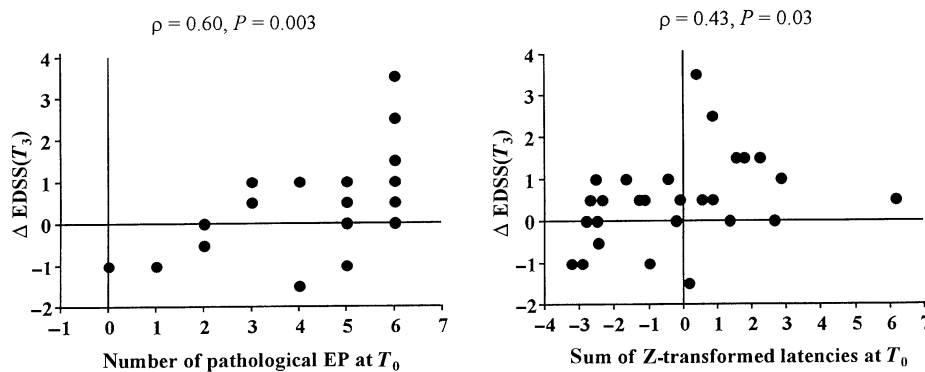


Fig. 2 Correlation of combined VEP and MEP results at baseline with the change in clinical scores over 2 years. Data on evoked potentials are represented by the number of pathological results (*left*) and by the sum of Z scores of their latencies (*right*). Statistical assessment of the associations was based on the Spearman rank correlation coefficient. EP = evoked potential.

auditory evoked potentials and the cutaneous long-latency reflex (Friedli and Fuhr, 1990), whereas in other series somatosensory evoked potentials and MEPs were more sensitive than VEPs, and MEPs were more sensitive than somatosensory evoked potentials (Beer *et al.*, 1995). Consequently, a combination of MEPs and VEPs constitutes a sensitive test battery in multiple sclerosis patients.

Evoked potentials are useful in the detection of subclinical lesions, but it is clear that they can deteriorate before the clinical examination does, and it was long considered doubtful whether they can also recover (Matthews and Small, 1979; Walsh *et al.*, 1982; Lowitzsch and Welkoborski, 1983). However, significant improvement of VEPs after an episode of optic neuritis (Brusa *et al.*, 2001) as well as improvement

of MEPs in patients with multiple sclerosis under treatment has been documented (Waxman, 1988; Kandler *et al.*, 1991; Salle *et al.*, 1992). If a shortening of the latency by at least 10 ms of component P₂ of the VEP (Becker and Richards, 1984) and a decrease of the CMCT by at least 10% (Salle *et al.*, 1992) are regarded as significant, our data show improvement in 17 of 60 eyes, in 37 of 60 upper extremities and in 24 of 54 lower extremities tested. This demonstrates that the improvement of pathological evoked potentials is possible. Therefore, they fulfil the requirement of variability in both directions in order to serve as parameters of the course of multiple sclerosis. Since this is also true of subclinical lesions, evoked potentials are suitable for monitoring the early stages of the disease. Given the normal test–retest variability of the different parameters of evoked potentials, however, it is important to restrict the analysis to ‘solid’ components, such as the latencies of clearly defined components (Comi *et al.*, 1999).

Evoked potentials yielded disappointing correlations with individual courses (Aminoff *et al.*, 1984; Anderson *et al.*, 1987). Comparisons of group data also produced negative results in some earlier studies. Methodological factors, such as the lack of standardization of laboratory procedures and the transformation of continuous electrophysiological data to coarse ordinal scores and consequently a loss of statistical power, have been implicated (Emerson, 1998).

Cross-sectional analysis of our data shows that VEP results correlate with visual acuity and MEP results and the combined VEP and MEP results correlate with the EDSS score at all points in time. The correlations are closer than those reported between MRI findings and EDSS score and corroborate earlier studies by others (Nuwer *et al.*, 1987; Rossini *et al.*, 1989; Kandler *et al.*, 1991; Salle *et al.*, 1992; Brigell *et al.*, 1994; Andersson *et al.*, 1995; Facchetti *et al.*, 1997; Davies *et al.*, 1998; O’Connor *et al.*, 1998). The most parsimonious explanation for this is that, unlike MRI abnormalities, each pathological evoked potential measurement represents at least one zone of malfunction, even if it is subclinical and of microscopical dimensions.

Longitudinal analysis of the data shows that the change in combined MEP and VEP data correlates with the change in EDSS score over 2 years. The correlations are closer than those reported between the change of conventional MRI findings and EDSS score, if they reach significance at all (IFNB Multiple Sclerosis Study Group, 1995; O’Connor *et al.*, 1998; O’Riordan 1998; Simon *et al.*, 1998).

The predictive value of evoked potentials is documented by the correlation between the result of combined testing of MEP and VEP at baseline with the change of the EDSS score over the next 2 years. No correlation exists between the EDSS score at baseline and its change over 2 years. These results are in agreement with those of O’Connor and colleagues using visual, brainstem auditory and somatosensory evoked potentials (O’Connor *et al.*, 1998). The difference in predictive value between the EDSS score and evoked potential data may be explained by the power of evoked potentials to detect subclinical lesions that may become manifest later.

Nevertheless, reliable prediction of the individual course from VEP and MEP data is not possible. While in our small cohort no patient with two or fewer abnormalities in evoked potentials deteriorated clinically, some patients with four to six abnormal tests remained on the baseline EDSS score or improved. However, for individual patients meeting the clinical criteria used in this study we can infer that the *probability* of an unfavourable clinical course over 2 years increases with the number of VEP and MEP abnormalities found at baseline.

Several explanations are possible for differences between multimodality evoked potentials and conventional MRI assessments in their validity for monitoring and predicting the course of patients with relapsing–remitting and secondary progressive multiple sclerosis. An early ceiling effect preventing the assessment of the course of patient groups by MRI may play a role. An alternative explanation with interesting implications for the biology of multiple sclerosis is the apparent dissociation between inflammatory and destructive activity of the disease. Opening of the blood–brain barrier (as visualized by gadolinium-enhanced T₁-weighted MRI) and accumulation of water in the surrounding brain (as visualized by T₂-weighted MRI) are early and possibly reversible steps in the pathogenesis of multiple sclerosis, whereas evoked potentials test for the final result in the cascade of pathomechanisms.

Conclusion

Repeated testing of VEPs and MEPs in patients with multiple sclerosis yields objective numerical data. This helps to identify patients at higher risk of rapid progression, represents the burden of dysfunctional lesions and documents the course of the disease even in patients at an early stage, for whom future therapeutic studies are needed most. The combination of VEP and MEP data is powerful enough to yield significant results in a small study population, but it is likely that its sensitivity can be enhanced by including somatosensory evoked potentials.

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