

Usage of Multimodal Evoked Potentials in Diagnosis of Central Nervous System Changes in Multiple Sclerosis

Multipl Sklerozlu Hastalarda Santral Sinir Sistemi Değişikliklerinin Tanısında Multimodal Uyandırılmış Potansiyellerin Kullanımı

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ÖZET

Amaç: Uyandırılmış potansiyeller duysal ve motor yolların fonksiyonel değerlendirilmesi için kullanılır. Demiyelinizan hastalıklarda uyandırılmış potansiyellerin yeri hakkında farklı çalışmalarda birbiriyle çelişen bilgiler sunulmuştur. Multipl sklerozlu hastaların %80'den fazlası relapsing-remitting formda prezente olurlar. Bu çalışmada, her bir uyandırılmış potansiyelin relapsing-remitting hasta popülasyonundan oluşan homojen bir grupta demiyelinizan lezyon varlığını ortaya koyabilmekteki değeri araştırılmıştır. Ayrıca, uyandırılmış potansiyel anormalliği ile klinik durum arasındaki ilişki değerlendirilmiştir.

Hastalar ve Yöntem: Çalışmaya relapsing-remitting multipl skleroz tanılı 20 hasta ve 10 sağlıklı gönüllü dahil edilmiştir. Görsel (VEP), somatosensör (SEP) ve motor (MEP) uyandırılmış potansiyeller kayıtlanıp tüm hastaların EDSS skorları hesaplanmıştır.

Bulgular: Yirmi hastanın, 15 (%75)'inde VEP anormalliği, 14 (%70)'ünde MEP anormalliği ve 12 (%60)'sinde SEP anormalliği saptanmıştır. Hastaların tümünde en az bir uyandırılmış potansiyel patolojisi saptanmıştır. Uyandırılmış potansiyel anormalliği yükselen EDSS skorları ile korelasyon göstermiştir.

Yorum: Bu çalışmada, uyandırılmış potansiyellerin özellikle birlikte kullanılmasının santral sinir sistemi demiyelinizasyonunu göstermede hala güvenilir olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Multipl skleroz, relapsing-remitting, uyandırılmış potansiyeller.

ABSTRACT

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Objective: Evoked potentials are used in the functional assessment of sensory and motor pathways. Conflicting results have been reported in different studies about the value of evoked potentials in demyelinating diseases. Over 80% of patients with multiple sclerosis present with a relapsing-remitting form of the disease. In this study, we aimed to examine the value of each evoked potential

in demonstrating the demyelinating lesions in a homogeneous group of patients with relapsing-remitting multiple sclerosis. We also aimed to examine the correlation between clinical status and evoked potential abnormalities.

Patients and Methods: Twenty patients with relapsing-remitting multiple sclerosis, and 10 healthy volunteers were included in the study to evaluate the value of evoked potentials in a homogeneous group. Visual, somatosensory and motor evoked potentials (VEP, SEP, MEP) were measured and the Expanded Disability Status Scale (EDSS) scores of the patients were calculated.

Results: Of 20 patients, 15 (75%) had VEP abnormality, 14 (70%) had MEP abnormality and 12 (60%) had tibial SEP abnormality. All patients had at least one abnormal evoked potential measurement. Abnormality of evoked potentials was also correlated with high EDSS scores.

Conclusion: We concluded that evoked potentials, especially used in combination, are good markers to show nerve damage damage in patients with multiple sclerosis.

Key Words: Multiple sclerosis, relapsing-remitting, evoked potentials.

INTRODUCTION

Multiple sclerosis (MS) is defined as a disease with functional deficits due to multiple demyelinated central nervous system (CNS) lesions, seen in different ages (1). In most patients, it begins as a relapsing-remitting disease and later becomes secondary progressive, but in some patients it has a primary progressive course. Early diagnosis and assessment of the course of MS are difficult because of its relapsing-remitting natural course and involvement of multiple functional systems (2). Conventional magnetic resonance imaging (MRI) is the most sensitive test to diagnose MS, and it provides information about the disease activity, but it is not specific and does not show demyelination directly (1,2). In addition to MRI and cerebrospinal fluid testing, evoked potentials (EPs) can contribute valuable information in the diagnosis of MS (3-5). EPs allow functional assessment of nervous conduction along clinically eloquent pathways. They are diagnostically sensitive when multiple functional systems are affected at the same time. Comi et al. reported that EPs can demonstrate multifocal involvement of the CNS in the early phases of the disease and can provide information about the white matter lesion load in the follow-up (5).

Visual evoked potential (VEP) measurement is useful to diagnose MS in patients with a primary progressive course of the disease or clinical isolated syndrome (6). Strong correlations have been reported between VEP and visual acuity in patients with MS (2). Somatosensory evoked potential (SEP) measurement can detect clinical and subclinical abnormalities, and mainly explores the lemniscal pathways in MS (7). However, transcranial magnetic stimulation (TMS) is a relatively new and non-invasive technique to evaluate the conduction properties of the corticospinal tract and excitability of the motor cortex (8). TMS studies in patients with MS have shown variable sensitivities to clinical signs and symptoms (9,10). It is reported that central motor conduction time (CMCT) is frequently prolonged in MS patients (11,12).

Although it is reported that the combination of EP abnormalities correlates well with the disease status, conflict-

ing results have been reported on the correlation between clinical features and the changes in EPs (2,13,14). We performed a study to evaluate the diagnostic value of motor evoked potentials (MEPs) and to compare with the values of VEP and tibial SEP (tSEP) in a homogeneous group of patients with relapsing-remitting MS (RRMS).

PATIENTS and METHODS

We examined prospectively 20 patients (16 women, 4 men) with clinically definite RRMS according to the "McDonald criteria" (6). The study was performed between January 2007 and September 2008. The control group consisted of 10 age- and sex-matched controls (8 women, 2 men). All patients had at least two relapses and incomplete remission in the last two years and all of them were under interferon treatment. Patients with chronic steroid or immunosuppressive drug treatment during the last six months were excluded. A complete neurological examination was performed and rated according to the Expanded Disability Status Scale (EDSS) (15). All the patients had MRI scan of the brain consistent with the Barkhof criteria for MS (6). VEPs, SEPs and MEPs of all patients and control subjects were measured. The P100 latency of VEP, P40 latency of tSEP, MEP latency, MEP amplitude, and CMCT were compared between the patients and control subjects. When no response for any EP was identifiable, we took the longest latency (of VEP, tSEP or MEP) obtained in patients as the result, by this way the patients with no identifiable EP response were considered to be at least as pathological as the patients who had the longest EP latency. This procedure allowed us to include the data of the patients with the most pathological results in the statistical investigations. The study protocol was approved by the Ethics Committee of the University of Trakya, School of Medicine, and written informed consent was obtained from all the patients.

VEP Recording

The VEPs were recorded from an active Ag/AgCl cup electrode placed 3 cm above Oz and a reference electrode at Fz with a Medelec-Synergy EMG machine (Old Wo-

king, UK). Low and high filters were set at 0.5 and 100 Hz, respectively. Pattern reversal stimulation was presented to each eye separately at a frequency of 1 Hz. Analysis time was 200 ms, and at least 200 single recordings were averaged twice. The peak latency of P100 was used for further analysis. A P100 latency exceeding the mean value obtained from the healthy volunteers by > 2 standard deviations (SD) was accepted as abnormal (> 109.4 ms).

SEP Recording

The SEPs for the bilateral lower limbs were recorded from an active Ag/AgCl cup electrode placed 2 cm posterior of the vertex and a reference electrode at Fz with a Medelec-Synergy EMG machine (Old Woking, UK). For SEP recordings, the electrical stimulation of the tibial nerves was performed at the ankle. Low and high filters were set at 20 Hz and 2 kHz, respectively. The stimulus duration was 0.2 ms and the frequency was 5 Hz. The intensity of stimulation was slightly higher than the motor threshold. Latencies of the spinal and cortical components were measured. The analysis time was 100 ms, and at least 500 single recordings were averaged twice. The peak latency of P40 was used for further analysis. A P40 latency exceeding the mean value obtained from the healthy volunteers by > 2 SD was accepted as abnormal (> 43.6 ms).

MEP Recording

MEPs were recorded from the abductor pollicis brevis muscle with Ag/AgCl cup-shaped surface electrodes bilaterally with a Medelec Synergy EMG machine (Old Woking, UK). Low and high filters were set at 10 Hz and 2 kHz, respectively. Magnetic stimuli were performed with a Magstim 200 device (The Magstim Company Ltd, Whitland, UK) via a round coil with an inner diameter of 9 cm. The coil was centered at the vertex and stimulated using the maximal output of the stimulator. The shortest onset latency of MEPs was used for calculating the CMCT, and the CMCT was used for further analysis. The CMCT was calculated with the formulation of "MEP latency - (F latency + M latency - 1 ms)/2". F latency and M latency values were obtained from the abductor pollicis brevis muscle by stimulating the median nerve at the wrist. A CMCT value exceeding the mean value obtained from the healthy volunteers by > 2 SD was accepted as abnormal (> 10.2 ms).

Evaluation of Magnetic Resonance Imaging

We assessed the fulfillment of at least three out of four Barkhof criteria: (1) at least nine lesions on the T2-weighted images; (2) the presence of at least three periventricular lesions; (3) the presence of at least one juxtacortical lesion; and (4) the presence of at least one infratentorial lesion (6).

Statistical Analysis

Statistical analysis was performed using Kruskal-Wallis and Mann-Whitney U tests for ordinary variables and Fisher's exact test for categorical variables. Correlations were tested using Spearman's rank correlation coefficient. A p value of 0.05 was used as the cut-off value. SPSS version 7.0 was used for statistical analysis.

RESULTS

Twenty patients (16 women, 4 men) with RRMS and 10 control subjects (8 women, 2 men) were included in the study. The mean age of the patients was 36.9 ± 9.4 and the mean age of control subjects was 34.1 ± 5.2 , and there was no significant difference in age between patients and controls ($p > 0.05$). The mean duration of the disease was 7.2 years (range: 1 year to 27 years), and the mean EDSS score of the patients was 2.4 ± 1.4 .

All of the patients met the diagnostic MRI criteria for MS described by Barkhof et al. (6). Initial symptoms of the patients were motor in 6 (30%), sensory in 7 (35%), visual in 5 (25%) and brainstem/cerebellar in 2 (10%) patients. The cumulative neurological signs of the patients were pyramidal in 14 (70%), sensory in 10 (50%), optic nerve involvement in 15 (75%), cerebellar/brainstem in 8 (40%), and cognitive impairment in only 1 (5%) patient.

The mean P100 latency of VEP in control subjects was 102.3 ± 3.5 ms, and the upper limit for P100 latency was calculated by adding 2 SD to the mean P100 value (109.4 ms). The mean P40 latency of tSEP in control subjects was 40.2 ± 1.7 ms. The upper limit of P40 latency was calculated by adding 2 SD to the mean P40 latency (43.6 ms). The mean CMCT of control subjects was 7.2 ± 1.5 ms, and the upper limit was calculated with the formulation described above (10.2 ms).

The mean P100 VEP latency of patients (121.8 ± 18.3 ms) was found significantly prolonged when compared with healthy controls ($p = 0.001$). A comparison of the patients and the control subjects regarding VEP values is shown in Table 1.

The mean P40 tSEP latency of patients (43.5 ± 5.6 ms) was found significantly prolonged when compared with healthy controls ($p = 0.03$). A comparison of the patients and control subjects regarding tSEP values is shown in Table 2.

The mean CMCT of the patients (11.3 ± 4.2 ms) was significantly prolonged when compared with healthy controls ($p = 0.005$). The mean MEP amplitude of the patients (2.05 ± 1.23 mV) was significantly lower than the mean MEP amplitudes of healthy subjects (3.48 ± 1.49 mV) ($p = 0.013$). A comparison of the patients and control subjects regarding CMCT, MEP latency and MEP amplitude is shown in Table 3.

Table 1. Comparison of VEP latencies between patients with RRMS and control subjects

	Patients (n= 20)	Control subjects (n= 10)	p
N75 latency (R)	86.7 ± 15.4 ms	76.2 ± 5.6 ms	0.04
N75 latency (L)	88.5 ± 17.1 ms	73.7 ± 3.9 ms	0.01
P100 latency (R)	121.7 ± 17.5 ms	101 ± 3.3 ms	0.001
P100 latency (L)	122.0 ± 19.1 ms	103.0 ± 3.8 ms	0.005
N145 latency (R)	154.6 ± 14.7 ms	135.8 ± 6.7 ms	0.006
N145 latency (L)	156.4 ± 20.8 ms	143.2 ± 5.0 ms	0.05

R: Right eye, L: Left eye, VEP: Visual evoked potential, RRMS: Relapsing-remitting multiple sclerosis.

Table 2. Comparison of tSEP cortical latencies between patients with RRMS and control subjects

	Patients (n= 20)	Control subjects (n= 10)	p
N35 latency (R)	37.4 ± 4.8 ms	34.5 ± 1.5 ms	0.07
N35 latency (L)	36.9 ± 5.2 ms	34.2 ± 2.2 ms	0.09
P40 latency (R)	44.0 ± 5.2 ms	40.2 ± 1.6 ms	0.03
P40 latency (L)	42.9 ± 6.0 ms	40.2 ± 1.9 ms	0.04

R: Right, L: Left, tSEP: tibial somatosensory evoked potential, RRMS: Relapsing-remitting multiple sclerosis.

Table 3. Comparison of central motor conduction time, MEP latency and MEP amplitude between patients with RRMS and control subjects

	Patients (n= 20)	Control subjects (n= 10)	p
CMCT (R)	10.4 ± 3.4 ms	6.8 ± 1.5 ms	0.005
CMCT (L)	12.3 ± 5.0 ms	7.5 ± 1.6 ms	0.008
MEP latency (R + L)	25.33 ± 4.69 ms	21.53 ± 1.49 ms	0.001
MEP amplitude (R + L)	2.05 ± 1.23 mV	3.48 ± 1.49 mV	0.013

MEP: Motor evoked potential, RRMS: Relapsing-remitting multiple sclerosis, CMCT: Central motor conduction time, R: Right, L: Left.

All three tests (VEP, tSEP and MEP) were found abnormal in 7 of 20 patients with RRMS. Three patients had only abnormal VEP, 2 patients had only abnormal tSEP and 1 patient had only abnormal MEP. Eight patients had abnormal VEP and tSEP, 11 patients had abnormal VEP and MEP, and 9 patients had abnormal tSEP and MEP. The distribution of abnormal tests and clinical findings in 20 patients with RRMS are shown in Table 4.

The clinical findings of the patients were found in accordance with EP abnormalities. One of the five patients who had no visual impairment had unilateral VEP abnormality. Two of the 10 patients who had no sensory signs had SEP abnormality. From six patients who had no pyramidal signs, none had MEP abnormality.

The mean EDSS score of the seven patients who had abnormality in all three tests was 3.3 and the mean EDSS

score of six patients who had abnormality in only one of three tests (3 VEP, 2 tSEP, 1 MEP) was 1.5. The mean EDSS score of the remaining seven patients who had abnormality in two of three tests (VEP + tSEP or VEP + MEP or tSEP + MEP) was 2.07.

DISCUSSION

MS is a disease of the CNS with functional deficits due to multiple demyelinated lesions, seen in different ages (16). MS is characterized by areas of perivascular inflammation in the CNS. Although the primary pathology of the disease is demyelination, secondary axonal damage may also occur (17). The assessment of the course of MS is difficult because of its relapsing-remitting nature and the involvement of multiple functional systems. Although MRI is sensitive for diagnosis and provides information about the disease activity, it does not show demyelinati-

Table 4. The distribution of abnormal EP tests and clinical signs in 20 patients with RRMS

Patients	VEP		tSEP		MEP		Clinical signs
	Right	Left	Right	Left	Right	Left	
1		X	X	X		X	Visual, sensory, pyramidal, brainstem
2			X	X	X		Sensory, pyramidal, brainstem
3	X	X	NR	NR	NR	NR	Visual, sensory, pyramidal, brainstem
4	X	X	X	X	NR	NR	Visual, sensory, pyramidal, brainstem, cognitive
5	X					NR	Visual, pyramidal
6	X				X	X	Visual, pyramidal, brainstem
7					X	X	Pyramidal
8		X	NR	X			Visual, sensory
9	X	X	X		X	X	Visual, pyramidal
10				X			Sensory
11			X	X		X	Sensory, pyramidal
12			X				
13	X	X	NR	X		X	Visual, sensory, pyramidal
14	X	X			X		Visual, pyramidal, brainstem
15	X	X					Visual
16	X	X					Visual
17	X					X	Pyramidal
18	X	X	X		X	X	Visual, sensory, pyramidal, brainstem
19	X	X					Visual
20	X	X	X	X	X		Visual, sensory, pyramidal, brainstem

EP: Evoked potential, RRMS: Relapsing-remitting multiple sclerosis, VEP: Visual evoked potential, tSEP: tibial somatosensory evoked potential, MEP: Motor evoked potential, X: Prolonged latency response, NR: No response.

on directly and correlates only with the clinical findings (1,2). It is also known that the lesions on MRI are not specific for MS (1). In patients who need differential diagnosis, multimodal EPs may be more valuable in the diagnosis of MS, and a clearly prolonged latency may be more specific for demyelination (5,8).

The visual pathway is the frequently involved sensory system in MS (18). Mizota et al. evaluated the pattern VEPs in Japanese patients with MS and without any history of visual pathway involvement (18). They found a prolonged VEP latency in 9 of 29 MS patients (31%) without any visual complaint. This ratio was reported as 54% by Pinckers et al. (19). Weinstock-Guttman et al. reported that VEP measuring in MS-related pathology could provide not only diagnostic but also prognostic information during the evaluation of MS patients (3). The most common EP abnormality found in our study was also VEP abnormality (75%).

In patients with MS, prolongation of MEP latency, diminution of MEP amplitude and prolongation of CMCT

have been reported (20). Fachetti et al. compared the measurement of MEP responses in patients with RRMS and secondary progressive MS and healthy controls (11). They found a significantly prolonged CMCT in secondary progressive MS patients compared with RRMS patients and controls. Tataroglu et al. studied the cortical silent period and MEPs in 58 patients (37 relapsing-remitting, 21 secondary progressive) with MS (21). They reported a correlation between CMCT and disability scores. They also concluded that the prolongation of CMCT might be due to the axonal damage of motor tracts occurring in parallel with increased disability. We compared the cortical MEP latency and CMCT obtained from the abductor pollicis brevis muscle between RRMS patients and healthy controls, and we found significant prolonged responses in 14 (70%) patients. We did not perform the MEP recordings from the lower extremities since it is known to be difficult especially without facilitation, and we did not perform facilitation in our study in order to prevent latency changes (22). In a recent study, Oya et al. investigated MEP responses in lower extremity muscles (soleus, medi-

al gastrocnemius) during voluntary contractions at varying strengths (0 to 100% of a maximal voluntary contraction) (22). In both soleus and medial gastrocnemius, the amplitudes showed an evident increment at high-force levels. The amplitudes of MEPs may be too small to investigate without facilitation in the lower extremities. This situation may cause confusion as to whether this absent response is due to MS or is physiological.

It is known that SEP may be a good marker for the severity of nerve damage due to MS and may have a predictive value in the evaluation of disability (1,4). Nociti et al. evaluated the relationship between SEPs and clinical measures of the upper limb impairment in patients with MS (7). They demonstrated a strict relationship between SEP and the upper limb performance in MS patients. Twelve (60%) of our patients also had abnormal tSEP responses.

Conflicting results have been reported about the value of EPs, one of the most sensitive modalities, in demonstrating demyelinating lesions (14). In a series of 90 patients with definite or possible MS tested by Friedli and Fuhr, VEP was found the most sensitive modality when compared with SEP, brainstem auditory EP (BAEP) and cutaneous long-latency reflexes, whereas in other series, SEP and MEP were determined to be more sensitive than VEP (23,24). Leocani et al. reported that VEP, lower limb SEP and MEP were the most frequently involved EPs in MS (4). Sahota et al. studied the role of MEP in the evaluation of disability in patients with MS, and they found prolonged latency of MEP in patients with clinically definite MS as compared to the control subjects (25). The diagnostic yield of TMS was found higher than that of VEP, BAEP and cerebrospinal fluid investigations. Some authors reported that CMCT was a more sensitive parameter than other EPs (26). In our study, VEP (15 patients, 75%), MEP (14 patients, 70%) and tSEP (12 patients, 60%), respectively, were the most frequently involved EPs in patients with RRMS.

The diagnostic value of EPs strongly depends on their power to detect subclinical demyelination, and it is reported that the diagnostic value of EPs increases considerably when different methods are used in combination (6). The combination of EPs (VEP, SEP and BAEP) may show clinically undetected lesions in 60% of patients with suspected MS, and this rate approaches 100% for patients with definite MS. Fuhr et al. examined prospectively 30 patients with relapsing-remitting or secondary progressive MS to validate the VEP and MEP as measures for the course of MS (2). They concluded that the combined testing of VEP and MEP may be of value for estimating the course and prognosis of the disease. Kallmann et al. reported that together with clinical findings and MRI, combined EPs (VEP, SEP, MEP) might help to identify patients at high risk of long-term clinical deterioration (27). All of our patients had

at least one abnormal EP. We concluded that if we had performed only VEP, only MEP, or only tSEP in our 20 patients with RRMS, the ratios of abnormality would have been 75%, 70% and 60%, respectively. However, when we performed all these EPs together, the ratio approached 100%. The progressive forms of the disease were not included in the study to evaluate the values of EPs in a homogeneous group of RRMS. We also selected our normal range to be the mean \pm 2SD of our control subjects as described by Mizota et al (18). This value of normal range was also the value accepted in our EMG laboratory.

In conclusion, the EPs (VEP, MEP and SEP) remain valuable for demonstrating demyelinating lesions in patients with MS, and the diagnostic value of EPs increases considerably when different methods are used in combination.

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