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Can Electrophysiological Studies Predict Multiple Sclerosis Prognosis?

Elektrofizyolojik Çalışmalar Multipl Skleroz Prognozunu Öngörebilir mi?

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Abstract

Objectives: Multiple sclerosis (MS) is an autoimmune neurodegenerative disease with an unpredictable course. MS lesions can affect the evoked potentials (EP) of electrophysiological studies. In this study, we aimed to predict the prognosis of MS patients with electrophysiological parameters.

Materials and Methods: MS patients with visual EP (VEP) and somatosensorial EP (SEP) were included in the study during two-year period. Demographic characteristics, MS type, attack numbers, current expanded disability status scales (EDSS), electrophysiological EP, blood tests, first cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings of the patients were evaluated.

Results: Two hundred and fifty-nine MS patients were evaluated. There was a statistically significant difference between EDSS scores and the pathologies detected in both electrophysiological examinations ($p<0.001$). The number of MS attacks were only associated with SEP pathologies ($p=0.045$). IgG index of CSF had no significant effect on VEP ($p=0.065$) but had a statistically significant effect on posterior tibial SEP. Posterior tibial SEP was statistically significant in two-sided abnormalities in MS patients with an elevated IgG index ($p=0.039$). MS patients who met the International Restless Legs Syndrome Study Group consensus criteria had two-sided abnormalities that were statistically significant on both VEP and tibial SEP examinations ($p=0.003$ and 0.000, respectively). Patients who had pathology in electrophysiological examinations at the beginning had statistically significantly more frequent demyelinating lesions in spinal and infratentorial according to current MRI.

Conclusion: EP can predict clinical deterioration in MS patients. Neurophysiological abnormalities can be considered in MS disease as a prognostic factor.

Key Words: Multiple Sclerosis, Prognosis, Electrophysiology, Evoked Potentials

Öz

Amaç: Multipl skleroz (MS), prognozu öngörülemeyen otoimmün nörodejeneratif bir hastalıktır. MS lezyonları, elektrofizyolojik çalışmaların uyarılmış potansiyellerini (UP) etkileyebilir. Bu çalışmada elektrofizyolojik parametreleri kullanarak MS hastalarının prognozunu öngörmeyi amaçladık.

Gereç ve Yöntem: İki yıl boyunca, vizüel UP (VUP) ve somatosensoryal UP (SUP) tetkikleri yapılmış olan MS hastaları çalışmaya dahil edildi. Hastaların demografik özellikleri, MS tipi, atak sayıları, muayene esnasındaki genişletilmiş engellilik durum skalaları (EDSS), elektrofizyolojik UP, kan testleri, ilk beyin omurilik sıvısı (BOS) ve manyetik rezonans görüntüleme (MRG) bulguları değerlendirildi.

Bulgular: Toplam iki yüz elli dokuz MS hastası değerlendirildi. Her iki elektrofizyolojik inceleme için de, tespit edilen patolojik sonuçlar ile hastaların EDSS skorları arasında istatistiksel olarak anlamlı bir ilişki vardı ($p<0,001$). MS ataklarının sayısı, sadece SEP patolojileri ile ilişkili bulundu ($p=0,045$). BOS IgG indeksinin VEP üzerinde anlamlı bir etkisi yokken ($p=0,065$), posterior tibial SEP üzerinde istatistiksel olarak anlamlı bir etkisi vardı. IgG indeksi yüksek olan MS hastalarında, posterior tibial SEP incelemeleri istatistiksel olarak anlamlı derecede iki yanlı patolojikti ($p=0,039$). Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu tanı kriterlerini karşılayan MS hastalarında hem VEP hem de tibial SEP incelemelerinde istatistiksel olarak anlamlı olan iki taraflı bozukluk vardı (sırasıyla $p=0,003$ ve 0,000). Başlangıçta elektrofizyolojik incelemelerde patolojisi olan hastaların güncel MRG'lerinde spinal ve infratentoryalde istatistiksel olarak anlamlı derecede daha sık demiyelinizan lezyonlar vardı.

Sonuç: UP MS hastalarında klinik progresyonu öngörebilir. MS hastalığında nörofizyolojik anormallikler prognostik faktör olarak kullanılabilir.

Anahtar Kelimeler: Multipl Skleroz, Prognoz, Elektrofizyoloji, Uyarılmış Potansiyeller

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Introduction

Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system. Its etiology is still unclear, but it is thought to be triggered by genetic and environmental factors (1,2). The disease is characterized by immune-mediated myelin destruction. Although MS pathogenesis is complex and only partially understood, the main underlying factors are thought to be inflammation and neurodegeneration (3). MS is a chronic disease and predicting disease progression at an individual level is difficult.

Demyelination pathologies cause prolonged latency, while conduction blocks or axonal loss cause lower amplitude in electrophysiologically evoked potentials (EP) (4). In young adults, the onset of the disease is more likely to manifest as a clinically isolated syndrome (CIS) involving the optic nerve, brain stem, or spinal cord. In some patients, the disease is seen as an attack and is known as Relapsing-Remitting MS (RRMS), while in others, it manifests as a progressive disease known as Primary Progressive MS (PPMS), or Secondary Progressive MS (SPMS). MS clinical types are also classified in this manner according to the progression of the disease (5). There is no pathognomonic clinical or laboratory finding that will allow the MS diagnosis to be performed precisely, and therefore studies have been conducted to develop valid diagnostic criteria. The disease is now diagnosed using the 2017 revised McDonald diagnostic criteria (6). These criteria take into account the number of neurological attacks, the number of lesions causing objective clinical evidence, and any additional studies that may be required.

Visual EP (VEP) and somatosensorial EP (SEP), also known as EP, are no longer used as diagnostic criteria for MS disease. These electrophysiological studies are thought to have prognostic significance for the detection, progression, and disability of non-clinical lesions (7). Well-defined biomarkers are required to monitor the effects of neuro-axonal damage on disease today. As the disease affects the optic nerve, somatosensorial, and pyramidal systems, the use of VEP, SEP, and motor stimulated potentials (MEP), which are neurophysiological evaluation methods that reveal pathologies in these systems, is extremely beneficial (8). In light of this information, our study aims to assess the availability of electrophysiological parameters as a biomarker that can predict the prognosis of MS patients.

Materials and Methods

The first patients were recruited for our study in January 2020. Patient recruitment ended in December 2021. Patients were who had two-sided VEP and two-sided posterior tibial SEP investigations on the same EMG device (Synergy on Nicolet ® EDX) during their primary examination were followed and diagnosed at our MS clinic in Ankara City Hospital. After the work plan was developed, patients who applied to the MS polyclinic where they had routine check-in were evaluated to obtain the information required for the study after approval was obtained. All patients were examined by the same neurologist who specializes in the field. The following information was recorded for the study:

- Gender
- Age
- Body mass index (BMI)
- The age of the disease
- Time of illness
- Family history for demyelinating disease
- First attack (optic neuropathy)
- MS type (CIS, RRMS, PPMS, SPMS)
- Total number of times the patient has had an attack
- Current Expanded Disability Status scale (EDSS)
- First VEP and posterior tibial SEP exams were recorded in our patient's MS clinic using the same EMG device on both sides (for our study of electrophysiological examination results of all patients were divided into three groups: two-sided normal, one-sided abnormal, and two-sided abnormal)
- Current laboratory findings
- First cerebrospinal fluid (CSF) findings if a lumbar puncture was performed during the diagnostic phase [presence of an oligoclonal band (OCB) and elevated IgG index]. An IgG index above 0.66 was considered pathological.
- Restless leg syndrome questionnaire (9)
- Localization of demyelinating lesions in current brain and spinal magnetic resonance imaging (MRI) studies (as localization; periventricular, juxtacortical, spinal, optic, and infratentorial areas it was noted whether lesions were present)

Those patients excluded from our study:

- Under 18 years old
- Anyone who declined to participate
- Patients who were thought to be in the attack phase based on their history and neurological examination findings, or who had described an MS attack in the previous month
- Patients who had lesions that showed contrast enhancement in a recent brain or spinal MRI
- Patients with radiological isolation syndrome.

The standard values used in our laboratory were used to group VEP and tibial SEP results. In the two-side full-field pattern VEP, the P100 latency values were measured in milliseconds (ms). For

the VEP examination, if the P100 latency value was greater than 114 ms or the difference between the two eyes was greater than 8 ms, the examination was deemed pathological for that side. The cortical tibial SEP responses obtained with a submaximal electrical stimulation of two sides of the ankle were noted for the posterior tibial SEP study. P40 wave latency, amplitude, and morphology were analyzed to evaluate the posterior tibial SEP study. P40 latency was considered increased if it was greater than the standard values used in our electrophysiology laboratory, as determined by the patient's vertex-wrist distance, or if the difference between the two sides was greater than 1.5 ms. The results from the stimulated potentials are divided into three groups: two-sided normal, one-sided abnormal, or two-sided abnormal.

Statistical Analysis

Statistical analysis of the data was performed with the SPSS 20 (Statistical Package for Social Sciences) program. Descriptive statistics were expressed with mean ± standard deviation, minimum and maximum value, frequency, and percentage. Fisher's Exact test, Kruskal-Wallis test and Pearson chi-square methods were used for analysis, and the method used was shown in Tables. The local ethics committee approved the study protocol (Ankara City Hospital, E1-21-2252).

Results

The study included a total of 259 patients, 181 of whom were women and 78 of whom were men. Table 1 depicts the relationship between gender distribution and basal VEP and posterior tibial SEP studies. Patients enrolled in the study ranged in age from 19 to 72 years old (37.43+/-10.37 years). Patients who were taken to work at 30.38+/-9.22 had an average period of 7.23+/-6.10. The mean disease duration of the patients was found 7.23+/-6.10, while the disease onset age was 30.38+/-9.22. There was no statistically significant relationship between BMI and basal VEP or posterior tibial SEP studies in our study (p-values of 0.099 and 0.573 respectively). Neither did we see a statistically significant relationship between a family history of demyelinating disease and basal VEP or posterior tibial SEP (p-values of 0.604 and 0.394 respectively). The VEP and SEP results of 88 patients with early MS disease in the form of an optical neuritis (ON) attack were statistically significant. VEP examinations of these patients were statistically significant when they were unilaterally abnormal (p<0.001) and when SEP examinations were two-sided normal (p-values=0.008).

Table 2 shows the relationship between patients' baseline VEP, and posterior tibial SEP examinations and the MS type determined by the current evaluation result. Table 3 shows the total number of attacks that patients have passed and the relationship between the current EDSS scores. While the EDSS scores calculated for the study of patients and the pathologies detected in both electrophysiological examinations were statistically significant (p<0.001 for both examinations), the number of MS attacks was only associated with tibial SEP pathologies (p-value=0.045). Table 4 depicts the relationship between laboratory values and basal VEP and posterior tibial SEP after neurological evaluation of the patients.

In patients with CSF findings, the presence of an OCB has no statistically significant effect on VEP or tibial SEP (p-values of 0.200 and 0.248 respectively). An elevation in the IgG index had no significant effect on VEP (p-value=0.065) but had a statistically significant effect on posterior tibial SEP. In our study, we discovered that posterior tibial SEP was statistically significant in two-sided abnormalities in MS patients with an elevated IgG index (p-value=0.039).

In our study, MS patients who met the International Restless Legs Syndrome Study group consensus criteria (9) had two-sided

Table 1: Initial VEP and posterior tibial SEP results according to gender distribution of patients

		VEP					
		Two-sided normal		One-sided abnormal		Two-sided abnormal	
		Count	%	Count	%	Count	%
Gender	Male	30	26.8%	13	31.0%	35	33.3%
	Female	82	73.2%	29	69.0%	70	6.7%
		112		42		105	
		SEP					
		Two-sided normal		One-sided abnormal		Two-sided abnormal	
		Count	%	Count	%	Count	%
Gender	Male	39	26.2%	6	30.0%	33	36.7%
	Female	110	73.8%	14	70.0%	57	63.3%
		149		20		90	

P-value=0.571 for the VEP header.
P-value=0.231 for the SEP header. Pearson chi-square test for both of headers
VEP: Visual evoked potentials, SEP: Somatosensorial evoked potentials

abnormalities that were statistically significant on both VEP and tibial SEP examinations (p-values 0.003 and <0.001 respectively).

Based on the effects of basal VEP and SEP, examinations of patients' current brain and spinal MRI localizations, lesions in the MRI of patients with pathology initially detected in both electrophysiological examinations were statistically significantly more frequent in spinal (p-values 0.019 and <0.001 respectively), and infratentorial demyelinating lesions (p-values 0.046 and 0.036 respectively).

Discussion

For the last 30 years, MS disease diagnosis, disease activity monitoring, clinical and MRI findings have all been considered (10). As is well-known, EP that are easily applied in electrophysiology laboratories are useful for performing quantitative functional measurements of the well-defined central nervous system pathways. Although the role of EP in MS disease diagnosis and evaluation is limited, because the disease affects the optic nerve, somatosensorial, and pyramidal systems, the use of visual-somatosensorial and motor EP, which show pathologies in these systems, is particularly useful for detecting subclinical pathologies and clinical changes (11). VEP has a significant role in determining the degree of demyelination along the optic nerve, a functional region of the central nervous system (12), and SEP is important in detecting pathologies along the main lemniscal route (13). Various prospective and retrospective studies have found that quantitative stimulated potential scores derived from visual, somatosensorial, and motor-stimulated potential

Table 2: The relationship between initial VEP and posterior tibial SEP results and current MS types of patients determined by course

		VEP					
		Two-sided normal		One-sided abnormal		Two-sided normal	
		Count	%	Count	%	Count	%
Type of MS	CIS	13	11.6%	4	9.5%	6	5.7%
	RRMS	87	77.7%	34	81.0%	66	62.9%
	PPMS	8	7.1%	1	2.4%	12	11.4%
	SPMS	4	3.6%	3	7.2%	21	20%
		112		42			
		SEP					
		Two-sided normal		One-sided abnormal		Two-sided normal	
		Count	%	Count	%	Count	%
Type of MS	CIS	19	12.8%	0	0.0%	4	4.4%
	RRMS	117	78.5%	15	75.0%	55	61.1%
	PPMS	8	5.4%	2	10.0%	11	12.2%
	SPMS	5	3.4%	3	15.0%	20	22.2%
		149		20		90	

P-value=0.005 for the VEP header.
P-value <0.001 for the SEP header. Fisher's Exact test for both of headers
VEP: Visual evoked potentials, SEP: Somatosensorial evoked potentials, MS: Multiple sclerosis, CIS: Clinically isolated syndrome, PPMS: Primary Progressive multiple sclerosis, SPMS: Secondary Progressive multiple sclerosis, RRMS: Relapsing-Remitting multiple sclerosis

Table 3: The relationship between initial VEP and posterior tibial SEP results and the total number of previous MS attacks and EDS

	VEP								
	Two-sided normal			One-sided abnormal			Two-sided abnormal		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum	Minimum	Mean	Maximum
The total number of MS attacks*	0.0	2.6	15.0	0.0	3.0	12.0	0.0	3.2	12.0
EDSS**	0.0	1.1	6.0	0.0	1.2	6.0	0.0	2.4	8.0
	SEP								
	Two-sided normal			One-sided abnormal			Two-sided abnormal		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum	Minimum	Mean	Maximum
The total number of MS attacks*	0.0	2.6	15.0	1.0	2.6	7.0	0.0	3.6	12.0
EDSS**	0.0	1.0	6.5	0.0	1.5	4.5	0.0	2.7	8.0

*P-value: 0.164, **p-value: <0.001 for the VEP header.
*P-value: 0.045, **p-value: <0.001 for the SEP header. Kruskal-Wallis test for both of headers.
VEP: Visual evoked potentials, SEP: Somatosensorial evoked potentials, EDSS: Expanded disability status scales, MS: Multiple sclerosis

values are far more sensitive than clinical evaluation and can be used as a biomarker to monitor disease progression (8,14,15). EP can be used during presentation of the disease to verify missed and undetectable recurrence in patients with uncertain or transient symptoms (16). Previous studies have generally only correlated with EDSS values in terms of disease progression.

Women have a threefold higher prevalence ratio of MS disease than men (17). In our study, there is a female predominance among our patients, which is consistent with current literature.

Table 4: The relationship between current biochemical results and initial VEP and posterior tibial SEP results

	VEP								
	Two-sided normal			One-sided abnormal			Two-sided normal		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum	Minimum	Mean	Maximum
WBC (x10^9/L)	3.7	7.3	13.9	4.2	7.9	20.2	2.9	7.7	16.9
Neutrophil count (x10^9/L)	1.8	4.8	44.1	2.4	4.9	16.1	1.1	4.8	11.3
Lymphocyte count (x10^9/L)	0.8	2.2	4.1	0.7	2.3	4.0	0.5	2.1	5.9
Hemoglobin (g/dL)	9.0	13.5	17.0	8.9	13.5	17.0	10.0	13.6	17.6
Hematocrit (%)	30.0	41.1	51.8	29.0	41.0	51.2	31.4	41.7	87.3
MCV (fL)	8.0	84.5	103.0	70.0	84.6	96.0	32.0	84.9	95.3
MCH (pg/cell)	20.0	28.0	36.0	21.0	27.7	36.2	21.0	28.1	33.0
Platelet count (x10^9/L)	100.0	267.2	418.0	132.0	270.2	504.0	102.0	252.2	477.0
LDL (mg/dL)	27.0	105.1	269.0	36.0	98.8	171.0	24.0	107.3	214.0
HDL (mg/dL)	21.0	49.3	105.0	26.0	49.3	96.0	29.0	49.2	93.0
AST (U/L)	10.0	18.6	62.0	8.0	16.0	30.0	8.0	17.6	42.0
ALT (U/L)	5.0	19.5	93.0	8.0	16.0	32.0	5.0	19.5	71.0
Ferritin (µg/L)	3.40	55.38	338.00	5.00	62.86	813.00	2.00	65.01	773.00
Vitamin B12 (ng/L)	37.0	317.1	1084.0	26.0	300.5	1000.0	98.0	307.9	1306.0
Folate (ng/mL)	2.30	7.43	21.00	3.30	7.58	24.00	1.40	7.24	20.00
Vitamin D (nmol/L)	3.00	18.52	75.00	3.00	17.63	45.00	3.00	17.77	87.00
	SEP								
	Two-sided normal			One-sided abnormal			Two-sided normal		
	Minimum	Mean	Maximum	Minimum	Mean	Maximum	Minimum	Mean	Maximum
WBC (x10^9/L)	2.9	7.6	20.2	4.2	7.1	13.1	4.0	7.6	16.9
Neutrophil count (x10^9/L)	1.1	4.9	44.1	2.5	4.5	10.1	2.2	4.7	11.3
Lymphocyte count (x10^9/L)	0.7	2.2	4.6	0.8	2.0	3.5	0.5	2.1	5.9
Hemoglobin (g/dL)	9.0	13.4	17.4	12.6	14.1	17.0	8.9	13.7	17.6
Hematocrit (%)	30.0	40.8	51.8	38.0	42.3	50.0	29.0	41.9	87.3
MCV (fL)*	8.0	83.7	96.0	81.6	87.9	103.0	70.0	85.7	95.7
MCH (pg/cell)**	20.0	27.7	36.2	26.0	29.0	33.0	21.0	28.2	33.0
Platelet count (x10^9/L)	100.0	261.3	456.0	157.0	259.3	380.0	102.0	262.6	504.0
LDL (mg/dL)***	27.0	99.3	238.0	53.0	103.0	173.0	24.0	114.7	269.0
HDL (mg/dL)****	30.0	50.1	105.0	32.0	52.4	78.0	21.0	47.1	96.0
AST (U/L)	8.0	17.3	46.0	11.0	18.4	24.0	9.0	18.4	62.0
ALT (U/L)*****	5.0	17.8	69.0	9.0	17.5	32.0	5.0	21.2	93.0
Ferritin (µg/L)******	3.40	57.33	813.00	5.00	80.44	265.00	2.00	61.31	773.00
Vitamin B12 (ng/L)	26.0	305.2	1079.0	37.0	285.7	501.0	98.0	325.2	1306.0
Folate (ng/mL)	2.80	7.47	21.00	3.40	8.16	20.00	1.40	7.04	24.00
Vitamin D (nmol/L)	3.00	18.26	75.00	4.60	20.73	87.00	3.00	17.17	55.00

Kruskal-Wallis test
*P-value: 0.018
**P-value: 0.042
***P-value: 0.010
****P-value: 0.047
*****P-value: 0.041
******P-value: 0.044.
WBC: White blood cell, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, HDL: High density lipoprotein, LDL: Low density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Male MS patients were more likely than women to have two-sided abnormalities detected in VEP and posterior tibial SEP studies, but this relationship was not statistically significant (p-values 0.571 and 0.231 respectively). Previous studies have yielded conflicting results regarding the effect of gender on the prognosis of MS disease. Tremlett et al. (18) conducted a major geographically based study in a large MS population (2,837 patients) and found that men initially showed a statistically significant faster progression than women (p-values<0.0005), but when patients were 58-60 years old, this difference was eliminated, and it was later found that both sexes had similar sequencing. So, while being male was a significant risk factor for progression in the early period, they discovered that this was not associated with a poor prognosis in the long term (18). In our study (similar to Tremlett's), 26 out of 181 female patients and 23 out of 78 male patients progressed. We have also detected two-sided pathologies of EP at the beginning of the disease, in men more often than in women. In our study, the disease beginning at a young age was a good prognostic factor (19) and a late start was reported as a bad prognostic factor (20). There was no statistically significant relationship between the initial age of the disease and the initial VEP pathologies, but the age of the disease was statistically higher in patients with two-sided posterior tibial SEP pathologies than those found to be normal.

The VEP examination was recommended for MS patients to evaluate the degree of optic nerve demyelination, a functional central nervous system region, to predict the degree of improvement after an ON attack, and to assess the assuring results of events in clinical and subclinical demyelination on the afferent visual path (12). In our study, patients with an ON attack began with the VEP study, and while the VEP study was statistically significantly unilaterally defective, the tibial SEP examination was statistically significant and normal. As is known, the most common symptom of origin is isolated ON, and while it may remain a single isolated attack, new attacks may develop long after the initial attack.

In a previous study, 84 patients with clinically definite MS were assessed using the EDSS and functional system scoring at the beginning and end of the study. After 11.7 months of monitoring, all EP (VEP, lower extremity SEP, lower and upper extremity MEP; p-values 0.03, 0.002, and <0.001 respectively) were found to be statistically significant with patient's EDSS scores and the calculated global EP score (21). In our study, EP were grouped in a simple manner rather than the complex scores mentioned in other studies, and the current EDSS scores calculated for patients with two-sided pathology detected in VEP and posterior tibial SEP were statistically higher. Our patient follow-up time is longer than this study's.

Some previous studies that found a relationship between patient clinics and EP had conflicting or even negative results (22-25), but in other studies, a very strong relationship was found (26,27). The disparities in these studies' findings may be due to the use of quantitative different EP measurements, the inclusion of different types of MS patients, and differences in patient monitoring times in the studies. The scores used in practice and in the clinic to assess the EP in studies are difficult and time-consuming to achieve and use (21,28,29). Unlike previous studies, we used a classification (two-sided normal, one-sided abnormal, and two-sided abnormal) to assess the potential that was evoked in our study, which we believe can be used more easily and practically in the clinic.

In our study, we observed that the progression of MS patients with two-sided pathology was statistically significant in basal VEP and tibial SEPs. The course of MS patients with bilateral pathology in basal VEP and tibial SEP was statistically significantly progressive. VEP examination was observed PPMS 1.6 times and SPMS 2.3 times more often in patients with bilateral abnormalities than in two-sided normal patients, while posterior tibial SEP examination was detected PPMS 2.3 times and SPMS 6.5 times more often in patients with bilateral abnormalities than in two-sided normal patients. In progressive MS, lesions may be equally common in gray and white matter and both cortical and deep gray matter have a common neuroaxonal loss. New developments have shown that cortical demyelination is common, particularly in SPMS (30). As a result of our findings, it was hypothesized that SEP examination pathologies obtained through somatosensory cortical stimulation, especially at the beginning of the disease, may predict progression to SPMS, particularly in MS patients. It is known that the thalamus, which plays an important role in the transmission of motor and sensory signals to the cerebral cortex, is also critically important in MS. Some studies indicate that thalamic pathologies may reflect the net accumulation of damage associated with MS in the central nervous system (31).

We found that the first SEP examinations of MS patients with low-density lipoprotein cholesterol (LDL) values and high-density lipoprotein cholesterol (HDL) values were statistically significantly bilaterally pathological. A recent study has shown that a high level of circulating LDL and total cholesterol harms clinical and MRI results. In the study, they argued that cholesterol values in MS patients can be used as a biomarker to predict disease activity or treatment outcomes (32). The relationship between cholesterol levels and MS disease is still unclear. In MS patients, vascular complications caused by hypercholesterolemia may cause disease progression. More longitudinal studies are needed to explain the relationship between cholesterol levels and cholesterol-related biomarkers in MS patients and demyelination, remyelination, and axonal degeneration seen in MS patients. According to the results of our study, bilateral SEP pathologies are more common in MS patients with a high LDL

value and a low HDL value, and therefore they may have a poor prognosis in the following period.

In the first CSF examination, we found that MS patients with a high IgG index had a statistically significant double-sided abnormality of the tibial SEP values. One of the most well-known biological characteristics of MS disease is an increase in intrathecal immunoglobulin synthesis. According to immunopathological studies, this humoral immune response, which is important in disease pathogenesis, is thought to have caused irreversible central damage (32). This attitude is not only a major factor in disease activity but also in the progression of a CIS in MS (33). In a very new and important study of 18 centers, it was found that the intrathecal IgG synthesis had statistically worsened the EDSS intensity after four years (34). This study found that OCB positivity has no meaningful relationship with EDSS violence. In our study, it was thought that the presence of the OCB did not make a prognostic difference because most patients with CSF examination were positive for OCB (113 out of 148 patients were OCB positive). According to the above-mentioned multi-center study, the OCB positivity ratio among patients is high, and band positivity is not a meaningful parameter that can indicate disease progression. Another retrospective study of 40 patients with definitive MS found no statistically significant relationship between OCB positivity and VEP and SEP parameters (35).

The lesions of spinal and infratentorial demyelination were statistically significantly more frequent in our study when compared to the current brain and spinal MRI lesion localization of patients with normal initial VEP and SEP studies and patients with pathological EP. In other studies, the number of lesions, as well as the presence of spinal (36) and infratentorial lesions, were found to be an important prognostic factor in predicting the risk of transition from CIS to clinically definite MS (37). Restless legs syndrome (RLS) is a sleep-related sensory-motor disorder characterized by an irresistible urge to move the legs, accompanied by unpleasant sensations in the lower extremities. Many studies have found that RLS is more common in MS patients than in non-MS people of similar age. Previous research has found that EDSS values of MS patients with RLS are higher than those without RLS (38). The underlying mechanism of RLS is now thought to be complex cortico-spinal excitability. A high-frequency somatosensory EP examination revealed functional impairment in the thalamocortical projections and sensorial cortex, especially in severe cases of RLS, according to a recent study (39). In our study, SEP examinations of MS patients with RLS may therefore be found to be significantly pathological. In one study that conducted VEP examinations of patients with RLS, it was reported that RLS is part of the neuro-degenerative process and pathologies can be detected in VEP examinations due to the disease's incomplete demyelination (40). According to the results of our work, which may result in our patients' RLS MS basal EP of the above-mentioned possible reasons for the more pathological resides, and EDSS scores were in the later stages. It can be said that MS with RLS can predict poor prognosis compared to patients without RLS. Unfortunately, more research on the relationship between the presence of RLS and the prognosis of MS is required.

Study Limitations

Previous studies only evaluated the relationship between EP and EDSS, whereas our study looked at the relationship between these electrophysiological examinations and other parameters thought to be effective in disease prognosis. However, limitations of our study include the fact that it was conducted in a single center and that the patient's follow-up times varied. More long-term research is required to predict disease progression and to determine individual risk scores using neurophysiological data.

Conclusion

In our study, we discovered that EP measured during the diagnosis phase of MS patients can predict clinical deterioration. EP can detect early-term lesions on long sensory pathways but are not clinical and can therefore help predict prognosis by determining the sequence progression. Patients may contribute to early recognition of non-recyclable damage such as demyelination, axonal loss, or transmission block. We recommend that optic nerve involvement, neurophysiological and CSF abnormalities are considered in MS disease diagnostic criteria and as a prognostic. We believe that this will benefit patients who are unable to access the MRI due to cost or contraindication. Also, pathological studies have shown that cortical and deep grey matter involvement is extensive in MS, and imaging cortical lesions is difficult because lesions are not well visualized on conventional MRI scanners. In addition, the results of two-sided pathological EP detected during the diagnosis phase can be a motivator for aggressive treatment of these patients early on.

Ethics

Ethics Committee Approval: The local ethics committee approved the study protocol (Ankara City Hospital, E1-21-2252).

Informed Consent: Informed consent was not obtained.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.E.B., S.Ö.M., Concept: S.Ö.M., Design: S.Ö.M., Data Collection or Processing: Ö.E.B., S.Ö.M., Analysis or Interpretation: Ö.E.B., Literature Search: Ö.E.B., Writing: Ö.E.B.

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