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Original Article / Özgün Araştırma

The Role of Visual Evoked Potentials in the Differential Diagnosis of Demyelinating Diseases

Görsel Uyandırılmış Potansiyellerin Demiyelinizan Hastalıkların Ayırıcı Tanısındaki Yeri

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Abstract

Objective: Demyelinating diseases are included in the differential diagnosis of non-specific white matter lesions (NSWMLs), which are incidentally detected by magnetic resonance imaging (MRI) of the brain. This study aimed to investigate the role of visual evoked potentials (VEPs) in the diagnosis of patients with demyelinating diseases.

Material and Methods: In this retrospective study, the VEPs performed in our electrophysiology laboratory between 2017 and 2018 were evaluated. One hundred and thirty-two patients with complete medical records were included in the study. After 2 years of follow-up, three groups were formed: 1st group: Demyelinating spectrum (multiple sclerosis, clinically isolated syndrome, radiologically isolated syndrome, and possible demyelinating disease); 2nd group: NSWMLs; and 3rd group (control): Subjects with normal neurological examination and neuroimaging after presenting with symptoms.

Results: The VEP findings demonstrated a significant latency prolongation and an amplitude reduction in the demyelinating disease group compared to the NSWMLs and control groups. The VEP parameters of the NSWMLs group did not differ from those of the control group.

Conclusions: Abnormalities in VEP suggest a demyelinating spectrum, whereas a normal VEP may suggest the absence of a demyelinating process. In cases where non-specific MRI findings cannot be supported by clinical data, a normal VEP diagnosis may help exclude demyelinating diseases.

Keywords: Visual evoked potentials, non-specific white matter lesions, demyelinating disease, multiple sclerosis

Öz

Amaç: Beyin manyetik rezonans görüntülemede (MRG) tesadüfen saptanan non-spesifik beyaz cevher lezyonları (*non-specific white matter lesions*, NSWML) demiyelinizan hastalıkların ayırıcı tanısında da yer almaktadır. Bu çalışma, demiyelinizan hastalıkların tanısında görsel uyandırılmış potansiyellerin (*visual evoked potentials*, VEP) rolünü araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Çalışmada elektrofizyoloji laboratuvarımızdaki 2017 ile 2018 yılları arasında yapılmış olan VEP'ler retrospektif olarak değerlendirildi. Çalışmaya tıbbi kayıtları tam olan 132 hasta dahil edildi. İki yıllık takibin sonucuna göre demiyelinizan spektrum (multipl skleroz, klinik izole sendrom, radyolojik izole sendrom ve olası demiyelinizasyon) (1. grup), MRG'de NSWML saptanan hastalar (2. grup) ve çeşitli semptomlarla başvuru sonrası yapılan nörolojik muayene ve nörogörüntülemelerde herhangi bir anormallik saptanmayan kontrol grubu olarak değerlendirilen hastalar (3. grup) olmak üzere 3 grup oluşturuldu.

Bulgular: Demiyelinizan hastalık spektrum grubunun VEP parametrelerinde NSWML ve kontrol grubuna göre anlamlı latans uzaması ve amplitüd düşüklüğü gözlendi. NSWML grubunun VEP bulguları kontrol grubundan farklı değildi.

Sonuçlar: VEP'deki anormallikler tanıyı demiyelinizan spektruma yaklaştırırken, normal VEP parametreleri demiyelinizasyon sürecinin mevcut olmadığına işaret edebilir. Non-spesifik MRG bulgularının klinik verilerle desteklenemediği durumlarda, normal VEP tanıyı demiyelinizan hastalıktan uzaklaştırabilir.

Anahtar Kelimeler: Görsel uyandırılmış potansiyeller, non-spesifik beyaz cevher lezyonları, demiyelinizan spektrum bozuklukları, multipl skleroz

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Introduction

With the development of magnetic resonance imaging (MRI), incidental T2 hyperintensities, also known as non-specific white matter lesions (NSWMLs), are frequently detected. Although the etiology is not fully known, age, hypertension, cerebrovascular disease, Parkinson's disease, and Alzheimer's disease are pathological conditions that increase the incidence (1,2,3,4). NSWMLs are important in the differential diagnosis of various diseases. If the patient is a young adult, there is a possibility of multiple sclerosis (MS). These lesions differ from MS lesions in certain aspects, such as their small dimensions and their usual peripheral-subcortical location rather than periventricular location, and no change are observed on successive MRIs (5). However, NSWMLs are the most common cause of overdiagnosis (6). In such cases, additional diagnostic tests are needed.

Electrophysiological tests are diagnostic tools frequently used in the differential diagnosis of demyelinating diseases. They are widely accepted in neurological practice since they are easy to use, safe, and cost effective. They can also detect subclinical lesions in pathways that are not well studied on routine MRI examinations, such as the optic nerve and spinal cord (7). Thus, they make an important contribution to early diagnosis in asymptomatic patients. Today, visual evoked potentials (VEPs) are commonly used for this purpose, with latency, amplitude, and waveform being the parameters studied (8). VEP was included among the diagnostic criteria of Poser and McDonald and their revisions, which were used for MS at different stages with different significance (9,10,11,12,13).

To date, there is no study investigating VEPs in NSWMLs in the differential diagnosis of demyelinating diseases in literature. In this regard, this study aimed to investigate the role of VEP in the differential diagnosis of demyelinating diseases.

Materials and Methods

In this study, VEPs performed in our electrophysiology laboratory between 2017 and 2018 were retrospectively evaluated. The demographic data, clinical information, VEP results, and MRI findings of the patients were obtained from the medical records of our hospital. Patients with a follow-up of at least 24 months were included in this study. According to the final diagnosis, three groups were formed: 1st group: Demyelinating spectrum [MS, clinically isolated syndrome (CIS), radiologically isolated syndrome (RIS), and possible demyelinating disease]; 2nd group: NSWML; and 3rd group: Control (clinical examination or neuroimaging without abnormalities). The diagnosis of MS was done according to the revised 2017 McDonald criteria and brain MRI was interpreted according to MRI in the MS group (MAGNIMS).

VEPs were obtained in all patients by sequentially stimulating each eye with a 30 min checkerboard pattern at 1.5 Hz on a video monitor. Cortical responses were recorded at Oz relative to Fz. A total of 100 responses were averaged twice and the superimposed filter bandpass was 0.5-100 Hz. The P1 latency of the negative-positive-negative complex (N1-P1-N2) was measured and the peak-to-peak amplitude was calculated from N1 to P1. The analysis time was 500 ms. Latency prolongation, low amplitude, and waveform distortion were assessed as pathological. In addition, the relationship between the VEP results and the presence of optic neuritis (ON) was investigated. Patients with high myopia, astigmatism, lens or vitreous obscuration, dry eye syndrome, uveitis, diabetes mellitus, sinus vein thrombosis, ischemic optic neuropathy, and pseudotumor cerebri were excluded.

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Local Ethics Committee of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (date: 25/12/2020, no: 2020.12.2.02.202).

Statistical Analysis

Statistical analysis was done using IBM SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, frequency, and percentage in categorical regions. Normality test was performed by Kolmogorov-Smirnov Goodness from Fit test. Kruskal-Wallis test and comparisons between the two groups were performed using the Mann-Whitney U test (with Bonferroni correction if necessary). The chi-square test was used for categorical comparisons. For the MS patients, an appropriate cut-off value and area under the curve for VEP were required and the sensitive, specific, negative, and positive predictive values were determined using the receiver operator characteristic (ROC) curve analysis method. The statistical level of significance was set at $p<0.05$.

Results

A total of 350 VEP examinations were performed in our electrophysiology laboratory within one year, of which 132 patients with complete medical records were included in this study. All patients had a follow-up period of at least 24 months.

Of these patients, 56 patients were diagnosed with demyelinating processes (group 1). The disease distribution in group 1 was 58.9% (n=33) MS, 8.92% (n=5) CIS, and 3.5% (n=2) RIS. In 28.5% (n=16) of group 1 patients, clinical and MRI findings were not compatible with the definitive diagnosis of MS, CIS, or RIS; however, demyelinating processes were suspected. In 31 patients, brain MRI lesions did not meet the criteria for MAGNIMS and were classified as NSWML (group 2). The remaining 45 patients had no lesions on their cranial MRI and were classified as the control group. The final diagnoses of the control group were as follows: Depression in 16 patients (35.5%), migraine and other primary headaches in 15 patients (33.3%), vestibulopathy of various etiologies in 3 patients (6.6%), cerebrovascular disease (transient ischemic attack) in 2 patients (4.4%), neuromuscular disease (myasthenia and spinal atrophy) in 2 patients (4.4%), and no diagnosis in 7 patients (15.5%). There were no statistically significant differences between the groups in terms of age and gender ($p>0.05$, Table 1).

VEP parameters, including latency, amplitude, and waveform, showed abnormalities in group 1 compared to group 2 and group 3. P100 latency values in patients with MS, CIS, and possible demyelinating diseases (112.45±22.57, 115.70±13.39, and 106.83±11.30, respectively) were statistically significantly prolonged ($p<0.001$) compared to the values in NSWML and control groups (100.43±4.47 and 101.17±10.13, respectively). P100 amplitude values were significantly decreased ($p<0.05$) in only patients with MS compared to those of group 2 and group 3 (Table 1). Regarding waveforms, the distorted waveform was

found in 4 patients (7.1%) from group 1, while no waveform disturbance occurred in group 2 and group 3 (p>0.05).

When a total of 264 eyes were evaluated as having ON and not ON, P100 latencies were significantly delayed in the affected eyes compared to the unaffected eyes; however, there were no differences in the amplitude values (Table 2).

The calculated predictive values of the VEP parameters in the MS are shown in Table 3. After the ROC curve analysis, the cut-off values for P100 latency and N75-P100 amplitude were determined as 102.5 ms and 8.19 µV, respectively. Using these values, the sensitivity and specificity for P100 latency were 66.7% and 69.7%, respectively. For the N75-P100 amplitude, the sensitivity and specificity were 66.7% and 65.1%, respectively. In addition, the positive (PPV) and negative (NPV) predictive values for P100 latency were 41.3% and 58.7%, respectively. The PPV and NPV for the N75-P100 amplitude were 44.5% and 55.5%, respectively (Table 3, Figures 1, 2).

Discussion

This study revealed that VEP is commonly impaired in demyelinating diseases. In this study, it was observed that both latency and amplitude values were impaired in the MS group, whereas only latency was impaired in the group with possible demyelination and in the CIS group.

VEP examination is a frequently preferred method in the evaluation of visual pathways in terms of demyelinating diseases, with the advantages of low cost, easy applicability, and safety. In the cross-sectional evaluation of our electrophysiology laboratory, it was documented that a total of 350 VEP examinations were performed in a year.

Similar to our results, VEP findings in MS have been described in literature, with a prolongation in latency and reduction in amplitude (14,15,16). VEP abnormality is considered to be associated with pathophysiological processes. While latency prolongation indicates demyelination, low amplitude suggests axonal degeneration (17). In MS patients, the presence of amplitude abnormalities, in addition to latency prolongation, is consistent with the presence of axonal degeneration in the current concept of MS pathophysiology (18). In ON patients, the presence of latency prolongation in the VEP rather than an amplitude decrease may indicate the benign nature of ON in MS (19).

In this study, the sensitivity and specificity of P100 latency for the diagnosis of MS were 66.7% and 69.7%, respectively. Similar sensitivity and specificity values were also determined for N75-P100 amplitude. In literature, the sensitivity of VEP in

Table 1. The demographics and VEP parameters of the study groups

	Patients with possible demyelinating disease (n=16)	MS (n=33)	CIS (n=5)	RIS (n=2)	NSWML (n=31)	Control (n=45)	Total	p
Age (year) (mean ± SD)	37.69±10.33	35.55±9.91	31.80±15.53	42.50±14.84	39.81±9.30	35.24±13.61	36.67±11.50	0.492*
Gender (F/M) (n, %)	13 (81.2%)/ 3 (18.8%)	27 (81.8%)/ 6 (18.2%)	4 (80.0%)/ 1 (20.0%)	0 (0.0%)/ 2 (100.0%)	22 (71.0%)/ 9 (29.0%)	32 (71.1%)/ 13 (28.9%)	98 (74.2%)/ 34 (25.8%)	0.176**
P100 latency (ms) (mean ± SD)	106.83±11.30***	112.45±22.57***	115.70±13.39***	103.75±2.98	100.43±4.47***	101.17±10.13***	105.09±14.67	<0.001*
N75-P100 amplitude (µV) (mean ± SD)	8.96±3.75	7.54 ± 3.54***	10.04±5.60	11.62±2.11	10.42±4.22	11.65±10.30***	9.95±6.97	<0.001*
Distorted waveform	1 (6.3%)	2 (6.1%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	4 (3.0%)	0.112**

*Kruskal-Wallis test (p<0.05), **Chi-square (Fisher's Exact) test (p<0.05), *** Mann-Whitney U test (for Bonferroni correction, p<0.008)
MS: Multiple sclerosis, CIS: Clinically isolated syndrome, RIS: Radiologically isolated syndrome, NSWML: Non-specific white matter lesions, SD: Standard deviation

Table 2. Comparison of P100 latency and amplitude values of patients with and without a history of optic neuritis

	ON history		
	Yes (n=19)	No (n=245)	p
P100 latency (ms) (mean ± SD)	115.42±17.85	103.35±10.22	<0.001*
N75-P100 amplitude (µV) (mean ± SD)	8.32±3.96	10.22±7.33	0.054*

*Mann-Whitney U test, ON: Optic neuritis, SD: Standard deviation

Table 3. Cut-off, sensitivity, specificity, and positive and negative predictive values for the VEP parameters in the MS patients

	VEP	ROC curve						p
	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	95% CI	
P100 latency (ms)	≥102.5	66.7	69.70	41.3	58.7	0.74	0.660-0.812	<0.001*
N75-P100 amplitude, µV	≤8.19	66.7	65.1	44.5	55.5	0.70	0.627-0.782	<0.001*

**ROC: receiver operator characteristic, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval, VEP: Visual evoked potential

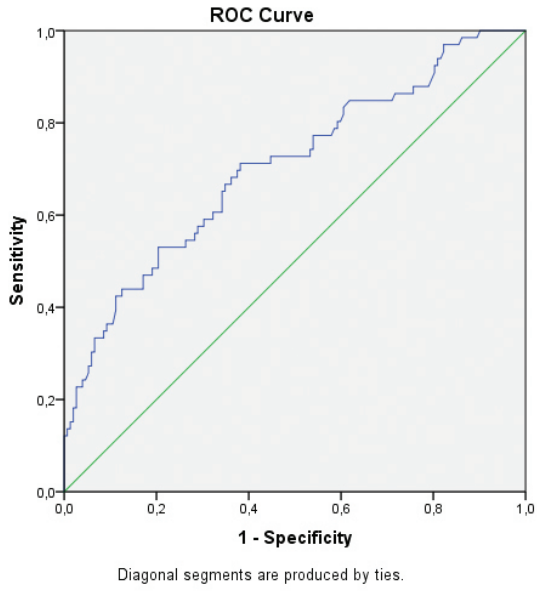

Figure 1. ROC curve for P100 latency in the MS patients
ROC: Receiver operator characteristic, MS: Multiple sclerosis

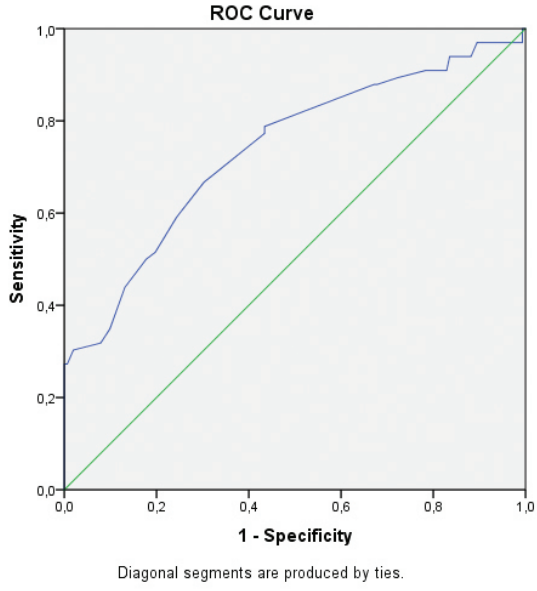

Figure 2. ROC curve for P100 amplitude value in the MS patients
ROC: Receiver operator characteristic, MS: Multiple sclerosis

the diagnosis of MS was reported to be within the range of 25-83%, while the specificity was reported in the range of 63-87% (20,21,22,23).

Among paraclinical investigations, MRI is the most important diagnostic tool for MS, given its high sensitivity of up to 95% (24). However, non-specific lesions can also be easily detected by MRI and these can sometimes lead to overdiagnosis of MS. Studies have shown that people with non-specific MRI lesions may be diagnosed with a psychiatric disorder, migraine, or fibromyalgia, especially in the third and fourth decades of life (25,26,27). In this study, although there was no significant difference, the mean age of the NSWML patients was slightly higher than that of the demyelinating group. In addition, depression and primary headache accounted for the majority of the final diagnoses of the NSWML patients, which is consistent with the findings in literature. To the best of our knowledge, this is the first study reporting VEP findings in NSWML. In this study, no VEP abnormality was found in any of the NSWML patients. In the context of this study, NSWMLs may not be associated with demyelinating diseases. However, VEP examination may be useful in such cases, which is expected to be within the normal range.

Conclusion

This study emphasizes the clinical utility of VEP in patients with suspected demyelinating disease. The large sample size is the strength of this study. However, the retrospective nature of this study may constitute a limitation. Therefore, prospective studies with a large sample size are needed.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Local Ethics Committee of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (date: 25/12/2020, no: 2020.12.2.02.202).

Informed Consent: Written informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.K.İ., Design: T.A., Data Collection or Processing: N.K.T., E.S., Analysis or Interpretation: N.K.T., Literature Search: S.Ö., E.S., Writing: N.K.T.

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