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The Comparison of VEP Parameters in Neuromyelitis Optica Spectrum Disorders and Multiple Sclerosis Patients with Acute Optic Neuritis

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ABSTRACT

Introduction: Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are idiopathic, autoimmune, and central nervous system inflammatory diseases. The similarity in the clinical course of both diseases creates difficulties in the differential diagnosis. Pattern reversal visual evoked potentials (VEP) are used at this stage. This study aimed to investigate VEP's role in the differential diagnosis of MS and NMOSD when the patients apply with acute optic neuritis.

Method: The data of 15 relapsing-remitting MS patients (RRMS) and 10 NMOSD patients (1 seropositive patient) presenting with blurred vision and who were diagnosed with acute optic neuritis were retrospectively analyzed. Demographic, disease, and VEP characteristics of the patients were recorded.

Results: According to retrospective data obtained from NMOSD patients, the mean P100 latency was 117.3 ± 12.3, and the mean amplitude was 6.1 ± 3.5. When the VEP characteristics obtained from 15 RRMS patients were evaluated, the P100 latency was 131.7 ± 17.3, and the mean P100 amplitude was 8.0 ± 3.0. P100 latency was significantly prolonged in the RRMS group than the NMOSD group, and amplitude was significantly lower in the NMOSD group than the RRMS group.

Discussion: Differentiating NMOSD patients with optic neuritis from MS in the early period is very important for preventing permanent visual damage, initiating appropriate treatment, planning treatment, and predicting prognosis. VEP findings in early-stage acute optic neuritis can be used to differentiate clinically challenging both seropositive and seronegative NMOSD patients from patients with MS.

Keywords: Neuromyelitis optica spectrum disorders, relapsing-remitting multiple sclerosis, Pattern reversal visual evoked potentials, P100 latency, P100 amplitude.

ÖZ

Akut Optik Nöritli Multipl Skleroz ve Nöromiyelitis Optika Spektrum Bozuklukları Hastalarında VEP Parametrelerinin Karşılaştırılması

Giriş: Multipl skleroz (MS) ve nöromiyelitis optika spektrum bozuklukları (NMOSD), merkezi sinir sisteminin idiyopatik, otoimmün ve inflamatuar hastalıklarıdır. Her iki hastalığın klinik seyrindeki benzerlik ayırıcı tanıda güçlükler yaratır. Bu aşamada desen görsel uyarılmış potansiyeller (VEP) kullanılır. Bu çalışmanın amacı, hastalar akut optik nörit ile başvurduğunda MS ve NMOSD ayırıcı tanısında VEP'nin rolünü araştırmaktır.

Yöntem: Bulanık görme ile başvuran ve akut optik nörit tanısı alan 15 relapsing-remitting MS hastası (RRMS) ve 10 NMOSD hastasının (1 seropozitif hasta) verileri geriye dönük olarak incelendi. Hastaların demografik, hastalık ve VEP özellikleri kaydedildi.

Bulgular: NMOSD hastalarından elde edilen retrospektif verilere göre, ortalama P100 latansı 117.3 ± 12.3 ve ortalama amplitüd 6.1 ± 3.5 idi. 15 RRMS hastasından elde edilen VEP özellikleri değerlendirildiğinde, P100 latansı 131.7 ± 17.3 ve ortalama P100 amplitüdü 8.0 ± 3.0 idi. NMOSD grubuna kıyasla RRMS grubunda P100 gecikmesi önemli ölçüde uzamış ve amplitüd, NMOSD grubunda RRMS grubuna kıyasla önemli ölçüde daha düşük saptanmıştır.

Tartışma: Optik nöriti olan NMOSD hastalarını erken dönemde MS'den ayırmak, kalıcı görsel hasarı önlemek, uygun tedaviyi başlatmak, tedaviyi planlamak ve prognozu öngörmek için çok önemlidir. Erken evre akut optik nöritte VEP bulguları, klinik olarak ayırımı zorlayıcı olan seropozitif ve seronegatif NMOSD hastalarını MS hastalarından ayırt etmek için kullanılabilir.

Anahtar Sözcükler: Nöromiyelitis optika spektrum bozuklukları, relapsing remitting multipl skleroz, desen görsel uyarılmış potansiyeller, P100 latansı, P100 amplitüdü.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system that can cause neurological disability in young adults. While 1/3 of MS patients present with optic neuritis (ON), it is known that ON develops in almost 70% of patients during the disease.[1]

Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune inflammatory diseases, mainly involving the optic nerve and spinal cord, which has been difficult to distinguish from MS in recent years.[2] In both diseases, ON occurs acutely with variable remission and relapses, but visual dysfunction in NMO tends to be more severe and is usually bilateral.[3]

The clinical use of evoked potential recordings that can detect clinically silent lesions in the visual, auditory, sensory and motor pathways has been developed and improved over the years.[2] Pattern reversal visual evoked potentials (VEP) is a non-invasive method used in daily practice for evaluating visual pathways.[4] Since 1970, VEPs have been used for diagnostic, follow-up and prognostic evaluation of visual transmission. In 1994, when Baseler et al. described the multi-focus VEP technique testing separate parts of the visual field, VEPs began to be used in the assessment of optic neuropathies and neurological conditions, including MS.[1] Preserved waveform morphology and prolonged latency in the VEP examination are signs that are indicative of the demyelinating process and are considered particularly typical for MS patients.[5] VEP technique is also used to detect subclinical asymptomatic involvement of the visual pathway. Early studies have shown that VEP latency is prolonged in 50-70% of MS patients without visual complaints. Recent studies have shown that VEP sensitivity is between 20-50% in patients without ON history. It is known that VEPs are widely used to predict the degree of optic nerve injury and hence the long-term outcome, predict the risk of MS development in clinically isolated syndrome patients and predict future disability in patients already diagnosed with MS.[1] Clinical symptoms of NMO patients are not specific for NMO disease. These symptoms are also common in MS patients, and this clinical similarity explains why NMO has long been considered a variant of MS. However, this changed with AQP4-IgG detection in NMO patients, removed NMO from being a sub-type of MS and led to the expansion of serum AQP4-IgG-mediated astrocytopathy spectrum, also called NMOSD. The primary target of these antibodies is astrocyte AQP4, a water channel protein, and the amount of AQP4-IgG in the cerebrospinal fluid has been found to correlate significantly with astrocyte damage. However, even in the most sensitive analyses, 10-40% of patients clinically diagnosed with NMOSD may show seronegative results for serum AQP4-IgG. Therefore, a significant number of seronegative patients are misdiagnosed as MS, and the correct diagnosis can be made after disease progression despite disease-modifying treatments. Since immunopathogenesis and immunomodulatory treatment responses are different for these two diseases, it is important to make a differential diagnosis between NMOSD, seronegative NMOSD, and MS and to prevent permanent visual impairment.[6]

In this study, we aimed to determine the VEP characteristics obtained during optic neuritis episode in NMOSD patients and to determine whether VEP can be used in the differential diagnosis of both diseases when compared with the VEP characteristics of MS patients.

METHODS

Ten patients who were admitted to our outpatient clinic between January 2010 and January 2018 with blurred vision complaint and diagnosed as NMOSD according to 2015 diagnostic criteria and 15 patient who were admitted to our outpatient clinic between January 2017 and January 2018, diagnosed as relapsing-remitting MS (RRMS) according to 2010 revised McDonald criteria and who had blurred vision complaint were included in the study and their data were retrospectively reviewed. Written consent was obtained from all patients. Age, sex, age of disease onset, EDSS (Extended Disability Status Scale), duration of disease, the eye with optic neuritis, frequency of ON and VEP characteristics of the patients were recorded. The VEP recordings obtained from 20 eyes of 10 patients with NMOSD and 30 eyes of 15 patients with RRMS were examined and comparisons were made between the two groups. Patients with the retinal, optic nerve, or any other type of optic neuropathy and other neurological diseases affecting the visual system, including optic atrophy without a known cause, were excluded from the study. Patients with refractive errors were examined with their glasses. Ethical committee approval was obtained for the study, data privacy and security were ensured in line with the recommendations of the ethics committee, and the study was conducted by the ethical standards of the 1964 Helsinki Declaration.

VEP recordings were made in the neurophysiology laboratory by the same technician blinded to the study and the diagnoses. Technical parameters were determined by the American Clinical Neurophysiology Society (ACNS).[7] The recordings were made in a Nihon Kohden device. International 10-20 system placement was used for all the VEP recordings. The patients were placed 100 cm from the stimulus screen. While looking at the fixation point, the electrical VEP potentials appearing in the occipital cortex against black-and-white checkerboard stimuli with check size of 60 min arc and rate of 2 m/s were recorded. The highest latency and amplitude size of each average wave were measured, and response changes in the latency and amplitude of the first positive waves were taken. The values were obtained with 200 stimuli per response monocularly. That is, P100 wave latencies and P100 wave amplitudes were measured.

The normal values of our laboratory were determined by evaluating 52 eyes, 16 females and 10 males between the ages of 25-69. <115 ms was accepted as the cut-off value for P100 latency and ≥ 5 μV was accepted as the cut-off value for P100 amplitude. These threshold limits represent values that were previously determined by internal validation measurements and were beyond 2 standard deviations from the mean.

The collected data was entered in Microsoft Excel spreadsheets and analyzed with SPSS for Windows, version 20.0. The tables shown contain mean values and standard deviation, or medians followed by minimum and maximum value. Differences among groups of patients were analyzed with the Student's t-test or Mann-Whitney U-test, with p-value being considered statistically significant when $p < 0.05$.

RESULTS

Of the 10 NMOSD patients included in the study, 6 (60%) were male and 4 (40%) were female. The mean age of the patients was 51.2 ± 7.4 years and the mean age of disease onset was 46.7 ± 8.2 years. The mean EDSS of the patients was 3.25 ± 1.1, the mean duration of disease was 4.3 ± 4.0 years and the mean number of ON episodes was 1.7 ± 0.8. All patients were oligoclonal band negative, one patient was AQP4-IgG positive, and AQP4-IgG was not studied in one patient. According to retrospective data obtained from 20 eyes of 10 NMOSD patients during acute optic neuritis episode, VEP response was not obtained in 6 eyes (30%), prolonged latency was detected in 8 eyes (40%) and decreased amplitude was detected in 6 eyes (30%). Prolonged subclinical latency was detected in 2 (10%) eyes. The mean P100 latency was 117.3 ± 12.3 and the mean P100 amplitude was 6.1 ± 3.5.

Of the 15 patients who were followed up with the diagnosis of

RRMS, 2 (13.3%) were male and 13 (86.6%) were female. The mean age of the patients was 37.8 ± 8.6 years and the mean age of disease onset was 31.2 ± 8.0 years. The mean EDSS value of the patients was 2.4 ± 1.3, the mean duration of disease was 6.6 ± 4.5 years, and the mean number of ON episodes was 1.5 ± 0.6. When all the data obtained during an acute optic neuritis attack were examined, no eye without VEP response was detected. Prolonged subclinical latency was observed in 5 (16.6%) eyes. When the VEP characteristics obtained from 30 eyes of 15 RRMS patients were evaluated, the mean P100 latency was 131.7 ± 17.3 and the mean P100 amplitude was 8.0 ± 3.0.

When the characteristics of both groups were compared, it was found that NMOSD group was older, the mean age of disease onset was higher than the RRMS group, and there was no significant difference between the two groups in terms of EDSS, disease duration and number of ON episodes. It was found that the patients in the RRMS group exhibited more subclinical response. P100 latency was significantly prolonged in the RRMS group compared to the NMOSD group, and amplitude was significantly lower in the NMOSD group compared to the RRMS group (Table 1). The VEP responses obtained from both eyes of a patient with NMOSD have been shown in Figure 1, and the VEP responses of a patient with RRMS have been shown in Figure 2.

Figure 1. Pattern reverse VEP response to full-filled stimulation of a patient with NMOSD, check size of 60 min arc and rate 2 m/s. A. Pattern reverse VEP response could not be obtained in the right eye, B. Pattern reverse VEP response (P100 latency: 132.3 and amplitude:6.0) of the left eye is shown.

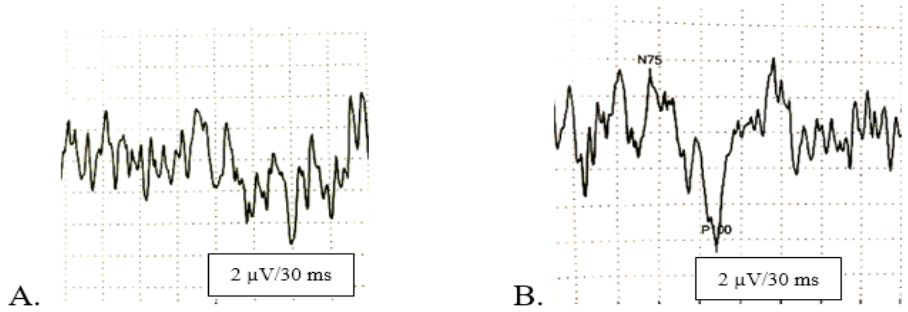
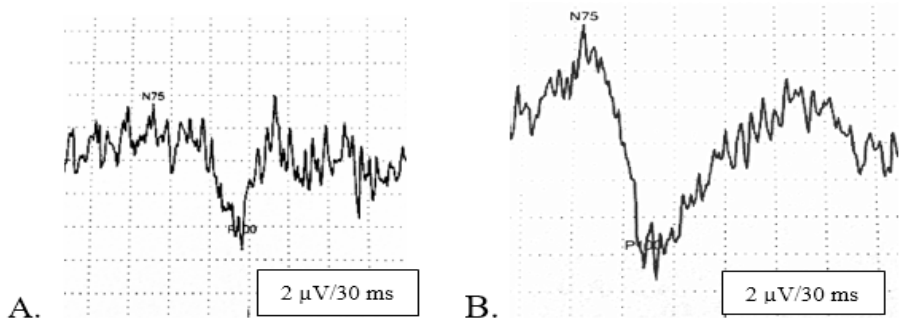


Figure 2. Pattern reverse VEP to full-filled stimulation of a patient with RRMS, check size of 60 min arc and rate 2 m/s. A. Pattern reverse VEP response (P100 latency: 144.9 and amplitude: 5.93) of the right eye is shown, B. Pattern reverse VEP response (P100 latency:102.6 and amplitude:10.0) of the left eye is shown.



DISCUSSION

MS and NMOSD patients with optic neuritis show similar clinical symptoms, and it is often not possible to differentiate these two diseases based solely on bedside neurological examinations. Therefore, additional clues are needed to differentiate between NMOSD and MS.[2] Dissemination of VEP use in NMOSD patients and the definition of VEP characteristics can be considered as a specific parameter that may help in the differentiation of this disease from MS.[3] In this study, VEP characteristics of patients with optic neuritis presenting with blurred vision were examined to determine whether the VEP characteristics obtained during the episode can be used in the differential diagnosis of both diseases. It was found that RRMS patients had significantly prolonged P100 wave latency compared to NMOSD patients. At the same time, P100 wave amplitudes of NMOSD patients were significantly lower than those of RRMS patients. Symptoms of NMOSD patients started at a later age and these patients were diagnosed at later ages. There was no significant difference between the two groups in terms of EDSS, disease duration, and frequency of ON.

In a study conducted in 34 NMOSD patients and 10 opticospinal MS patients, no significant difference was observed between the two groups in terms of age, but consistent with our results, there was no significant difference between disease duration and EDSS score. In 22 patients with NMOSD, antibody positivity was found and seropositivity was not associated with disability.[8] Due to the small number of antibody-positive patients in our study, no comparison was made in terms of disability. Consistent with our findings, another study reported that the disease symptoms of the patients in the NMOSD group appeared at a later age compared to the RRMS group and that there was no statistically significant difference between the duration of the disease.[2] In a study of 27 NMOSD patients and 54 MS patients (10 of which had active ON), there was no significant difference between the two groups in terms of EDSS and frequency of ON in accordance with our study. However, contrary to our results, the duration of disease was longer in the MS group and there was no difference between the groups in terms of age.[9] Our results on the age that is contrary

Table 1. Characteristic features and VEP parameters in NMOSD and RRMS patient groups

	NMOSD		RRMS		
Sex (Male/Female)	6/4		2/13		
	Mean	SD	Mean	SD	P value
Age (years)	51.2 (42-66)	7.4	37.8 (23-55)	8.6	0.001[a]
Age of onset (years)	46.7 (36-63)	8.2	31.2 (16-47)	8.0	< 0.001[b]
EDSS	3.25 (2-6)	1.1	2.4 (0.5-6)	1.3	> 0.05[b]
Duration of the disease (years)	4.3 (1-15)	4.0	6.6 (2-19)	4.5	> 0.05[b]
Frequency of ON	1.7 (1-3)	0.8	1.5 (1-3)	0.6	> 0.05 [b]
P100 latency (ms)	117.3 (97.2-134.4)	12.3	131.7 (102.9-177)	17.3	0.008 [b]
P100 amplitude (µV)	6.1 (2.67-14.4)	3.5	8.0 (3.47-15.9)	3.0	0.049[a]

NMOSD: Neuromyelitis optica spectrum disorders, RRMS: Relapsing-remitting multiples sclerosis, EDSS: Expanded Disability Status Scale, ON: optic neuritis; SD: standard deviation, [a]: T-test, [b]: Mann-Whitney U-test

to the literature can be attributed to the fact that secondary and primary progressive MS patients were also included in the MS group.

In a study conducted by Matthews et al. to evaluate response pattern differences in 223 definite, probable, and possible MS and healthy individuals, VEP responses were evaluated and it was found that there was a prolonged VEP latency in the definite MS group.[10] In a study conducted by Andrade et al.,[11] 39.6% of 24 patients with MS had normal VEP response, 52.07% had delayed P100 wave latency, and 8.33% had no response to stimuli. It was thought that the lack of response was not associated with the expected VEP pattern in MS. In our study, prolonged latency findings, a demyelinating finding in MS patients, were found and it was seen that the results of both other studies were consistent with our study. In a study of 19 patients followed with the diagnosis of NMOSD, VEP response was not obtained in 18 (47.4%) of the 38 eyes examined and, decreased P100 wave amplitude with normal latency was detected in 13 patients (34.2%).[3] In their study, Vabanesi et al.[12] reported that the VEP response in NMOSD after optic neuritis was significantly absent compared to MS; most of the eyes of NMOSD patients showed prolonged latency, but excessive prolonged latency was observed more frequently in MS patients in accordance with our study. On MS and NMOSD patients, Ohnari et al.[2] found prolonged latencies in VEP measurements of RRMS patients and observed that prolonged latencies disappeared in NMOSD patients. Ringelstein et al.[4] analyzed VEPs in a predominantly Caucasian cohort of 43 patients with definite NMO and 61 healthy controls. They observed decreased amplitude in 12.3% and prolonged latency in 41.9% of the eyes of NMO patients, and no VEP response in 14% of patients in their study. They suggested that prolonged P100 latencies in eyes without a history of optic neuritis were a subclinical effect.[4] In our study, VEP response was not obtained in 30% of NMOSD patients and prolonged latency was found in 40% of patients, although this was not statistically significant. It is not surprising that amplitude loss in visually evoked potentials is more pronounced than P100 latency prolongation since NMOSD is considered to be associated with a destructive astrocytopathy, which primarily causes neuronal loss and secondary demyelination. Prolonged latency in MS patients is typically more prominently affected than amplitude unless a serious ON event occurs.[13] Another similar feature with the study of Ringelstein et al.[4] is the P100 latency prolongation detected in the eyes of NMOSD patients without a history of neuritis. However, in the study of Shen et al.,[6] eyes with a history of optic neuritis in NMOSD patients were found to have more severe axonal damage than MS patients. Subclinical P100 latency prolongation was detected in eyes without a history of optic neuritis in MS patients, but no subclinical effect was detected in NMOSD patients. This subclinical effect observed in MS patients was associated with the optical radiation lesion burden observed in the neuroimaging of MS patients.[6] Previous studies reported that there was no significant difference between seropositive and seronegative NMO patients in terms of VEP analyses and disability rates.[3,4] At the same time, in another study, no significant difference was observed between the two groups in terms of disability.[7] Therefore, the comparison results of NMOSD and RRMS groups in our study, which have a high number of seronegative patients, show that VEP can be used for differentiating both seropositive and seronegative NMOSD patients from MS patients.

The limitations of this study include the inclusion of patients with ON history in the RRMS group of patients with optic neuritis and the analysis of VEP values of both eyes with and without ON episodes. This may have led to the inclusion of both subclinical VEP characteristics and impaired values after previous episodes of optic neuritis in both groups. Therefore, measurements should be performed prospectively only during the first ON episode of both NMOSD and RRMS patients and only on the eye with complaints, and further large-scale multi-center studies should be planned.

Visual impairment in NMOSD tends to be more severe. VEP amplitude in NMOSD patients was different from that of MS patients and was characterized by reduced amplitude with prolonged latency. VEP findings are very valuable for differential diagnosis of demyelinating disease, management of the treatment, and predicting prognosis in patients with acute optic neuritis. This study is critical as it demonstrates that VEP findings can be used to differentiate both seropositive and seronegative NMOSD patients from patients with MS during acute optic neuritis in an early stage.

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