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An Insidious Clinical Picture: Optic Nerve Involvement in Patients with COVID-19

Sinsi Bir Klinik Tablo: COVID-19'lu Hastalarda Optik Sinir Tutulumu

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Abstract

Objective: Many neurological symptoms due to central nervous system, peripheral nervous system and musculoskeletal system damage have been reported in more than a third of patients with coronavirus disease-2019 (COVID-19). Although optic neuritis has been reported in patients with COVID-19, they are extremely rare. The aim of this study was screening optic nerve involvement in COVID-19 with visual evoked potential (VEP) in asymptomatic patients without a history of visual impairment.

Materials and Methods: Pattern reversal VEP measurements were made in 101 adult patients with COVID-19 without a history of visual impairment after they completed COVID-19 treatments and the quarantine period. VEPs were recorded with the 4-channel electromyography-evoked device in a dark room. P100 latencies and amplitudes were analyzed by the same neurologist.

Results: A total of 34 (33.7%) patients had P100 latency prolongation. There was no significant difference in terms of gender, age or outpatient/inpatient treatment status. There was no significant correlation between the time of polymerase chain reaction diagnosis and VEP values.

Conclusion: Contrary to previous studies, asymptomatic optic nerve involvement after COVID-19 was detected by VEP measurements. Prolongation of P100 latency shows the probable linkage between COVID-19 virus and angiotensin converting enzyme 2 receptors in human eyes.

Keywords: COVID-19 virus infection, optic nerve, VEP

Öz

Amaç: Merkezi sinir sistemi, periferik sinir sistemi ve kas-iskelet sistem hasarına bağlı nörolojik semptomlar koronavirüs hastalığı-2019'lu (COVID-19) hastaların üçte birinden fazlasında bildirilmiştir. COVID-19'da optik nöritli olgular bildirilse de oldukça nadirdir. Bu çalışmanın amacı, bilinen görme bozukluğu olmayan asemptomatik hastalarda görsel uyarılmış potansiyel (VEP) ile COVID-19'lu hastalarda optik sinir tutulumunu taramaktır.

Gereç ve Yöntem: Bilinen görme bozukluğu olmayan 101 yetişkin COVID-19'lu hastada tedavileri ve karantina sürecini tamamladıktan sonra pattern reversal VEP ölçümleri yapıldı. VEP analizi karanlık bir odada 4 kanallı elektromiyografi cihazı ile kaydedilmiş, aynı nörolog tarafından P100 latansları ve amplitüdleri incelenmiştir.

Bulgular: Toplam 34 (%33,7) hastada P100 latans uzaması vardı. Cinsiyet, yaş veya ayaktan/yatarak tedavi durumu açısından anlamlı bir fark yoktu. Polimeraz zincir reaksiyonu tanısı ile VEP çekim zamanı arasındaki süre ile elde edilen değerler arasında anlamlı bir ilişki yoktu.

Sonuç: Daha önceki çalışmaların aksine, VEP ölçümleri ile COVID-19 sonrası asemptomatik optik sinir tutulumu tespit edildi. P100 latans uzaması, insan gözündeki COVID-19 virüsü ile anjiyotensin dönüştürücü enzim 2 reseptörleri arasındaki olası bağlantıyı gösteriyor olabilir.

Anahtar Kelimeler: COVID-19 virüs enfeksiyonu, optik sinir, VEP

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Introduction

There is an increasing concern about multisystemic involvement of novel coronavirus. A concern about different neurological symptoms related to coronavirus disease-2019 (COVID-19) has been expressed since the beginning of the pandemic. Unconsciousness, myopathy, dystonia, cerebrovascular diseases, epileptic seizures, movement disorders, encephalitis, Guillain-Barré syndrome and optic neuritis are reported neurological disorders in patients with COVID-19 (1). Ageusia (taste disturbances) and anosmia (loss of smell) observed in the early stages of infection are challenging symptoms and have been associated with the involvement of angiotensin converting enzyme 2 (ACE2) receptor (2). Transmission of the virus via the conjunctiva is known and coronavirus RNAs were demonstrated in a patient with acute monosymptomatic optic neuritis (3). The presence of specific binding sites for ACE2 has been demonstrated in the capillaries of the optic nerve head. The presence of receptors for this vasoactive hormone in the optic nerve can cause spread of circulating agents to the optic disc from the choroid and affect the vascular tone, autoregulation response, and the sensitivity of the optic disc. For this reason, COVID-19 can cause optic nerve damage, just like causing loss of sense of smell and taste. Studies have shown that 50-70% of patients with multiple sclerosis without visual complaints have prolongation in P100 latency (4,5). Prolongation of P100 latency in the asymptomatic eye is a sign of subclinical optic neuritis.

Recording visual potentials with pattern reversal visual evoked potential (VEP) test is a non-invasive method that evaluates the optic nerve. Pattern reversal VEP test is considered to be useful in studying the physiology and pathophysiology of the human visual system, including the visual pathways and the visual cortex (6). This test is widely used in electrophysiology laboratories for supporting clinical diagnosis in cases such as unexplained vision loss and optic nerve damage. Pattern visual evoked potential test (pattern VEP) is an objective electrophysiological test obtained by recording the electrical responses developing in photoreceptors from the occipital region as a result of a visual stimulus. In pattern VEP test, stimuli from the occipital cortex to the visual stimulus are recorded in a time-dependent manner (7). Electrophysiological evaluation of visual pathways is accepted as a sensitive and objective method (6).

The aim of this study was screening optic nerve involvement with VEP test in patients with COVID-19. VEP test may show possible optic nerve involvement that was not clinically overtis. If such a conclusion can be made, clinicians may be guided to screen COVID-19 patients with the VEP test. Since the VEP test, is low-cost and easy to access, early treatment of patients with optic nerve damage may be possible.

Materials and Methods

This is a descriptive study in a cross-sectional design. Institutional Ethics Committee approval was obtained for the study from Canakkale Onsekiz Mart University Ethics Committee for Clinical Studies with decision number 14-27 dated December 09, 2020. All the procedures followed were in accordance with the ethical standards of the ethics committee and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent from all participants was obtained. Adult patients with COVID-19 (above 18 years of age) admitted to the COVID-19 outpatient clinic and/or hospitalized in the relevant services of the hospital were invited to participate in the study. Patients who wanted to participate in the study were referred to the neurology outpatient clinic. A total of 101 participants were included in the study. The diagnosis of COVID-19 was confirmed by quantitative reverse transcription-polymerase chain reaction (PCR) assay using samples taken by nasopharyngeal swab. Participants were selected from patients with a positive PCR test for COVID-19 who completed their outpatient or inpatient treatments and quarantine period. All patients underwent treatment in accordance with the national treatment guidelines for COVID-19. Exclusion criteria were; having a history of optic neuritis, multiple sclerosis and other demyelinating diseases, sarcoidosis, systemic lupus ertyhematousus, polyarterits nodosa and other vasculitis, and chronic diseases causing ischemic optic neuropathy such as diabetes mellitus and hypertension.

Pattern reversal VEP's were recorded at the Electrophysiology Laboratory in the Neurology Department of Canakkale Onsekiz Mart University. The same neurologist performed all VEP measurements. The VEP analysis was recorded with the 4-channel Nihon-Kohden electromyography-evoked device in a dark room, with a monocular recording sitting one meter away from the monitor, using the checkerboard method, with 1 Hz stimulus. It was recorded in 200 Hz frequency band and the analysis time was 500 milliseconds. The visual stimulus is a high contrast black-and-white checker board spanning the central 20°-30° of the visual field of which black and white squares reverse each second. The participants were instructed to focus on the red mark placed in the center of the screen. VEP is the averaged response to this reversal pattern. Pattern VEP was recorded from the occipital scalp. This zone (Brodmann zone 17) is the closest to the primary visual cortex. A 10-20 international electrode placement system is used to place electrodes (8). One of the active recording silver electrodes is placed 2 cm above the external protuberentia occipitalis, the reference electrode is placed on the vertex, and the ground electrode is placed on the forehead. All applications and evaluation of test results were made by the same technician and expert, and P100 latencies and amplitudes were examined. The peak latencies of N75, P100, and N145 potentials were measured. We recorded peak-to-peak amplitude of P100 potential calculated as the amplitude from the N75 peak to the P100 peak. Peak P100 latencies and N75-P100 amplitudes were used in the statistical analysis of each participant.

VEP consists of two negative and one positive components (negative N75 wave, large positive P100 wave and negative N135 wave), and the most prominent component is the P100 wave that occurs around 100 ms in normal individuals. VEP latency is read as the peak latency of the P100 wave, and this value is below 115 ms under 60 years of age in the normal population (9). In our study, P100 latency values above 115 ms recorded in the pattern VEP study were evaluated as prolonged.

Statistical Analysis

After the study data were digitalized and corrected, descriptive information was presented with frequency and percentage for categorical data, and with mean and standard deviation for ordinal data. Compliance of continuous data to normal distribution was analyzed and reported. P100 latency and amplitude results were

analyzed with statistical tests to be selected according to variable characteristics in terms of patients' demographic characteristics, duration of illness and treatment characteristics. Test constants and absolute p values were presented for all analyzes, $p<0.05$ was accepted significant.

Results

A total of 101 participants, 55 (54.5%) females and 46 (45.5%) males, with a mean age of 43.3±15.0 (min 19, max 81) years were included in the study. The mean age of women (42.3±14.5 years) was not different from men (44.5±15.6 years) (t=0.718; p=0.474). Seventy eight of the participants (77.2%) received outpatient treatment and 23 (22.8%) were hospitalized. Three patients (3.0%) who received inpatient treatment received intensive care treatment. VEP test was performed an average of 67.0±19.8 (min 15, max 114) days after the PCR test result. The results obtained in the VEP test is given in Table 1.

The average N75, P100 and N145 latencies and amplitude values were not significantly different between genders. There was no difference between inpatients and outpatients in terms of measurements. It was also observed that being in an intensive care unit did not make a difference. There was no significant correlation between the time of PCR diagnosis and VEP values obtained.

According to VEP results, a total of 34 (33.7%) patients [18 patients (17.8%) in both eyes, 16 (15.8%) patients in only one eye] had prolongation of P100 latency.

The proportion of patients with prolonged P100 latency according to VEP results was not significantly different between female (23.7%) and male (41.3%) patients (X^2: 2.209; p=0.137). There was no significant difference between the ages of the patients with normal or prolonged P100 latency (t=0.937; p=0.351). The proportion of patients with prolonged P100 latency was not significantly different between outpatients (34.6%) and inpatients (30.4%) (X^2: 0.139; p=0.709). There was not any prolongation in P100 latencies in 3 patients with a history of intensive care unit stay. There was no significant correlation between P100 latency and amplitude values for both eyes. In patients where measurements could be done in both eyes, there were 5 (5.0%) patients with a difference of more than 50% between the amplitudes between the eyes. Mean P100 latency values and prolonged P100 latency rates were not significantly different between those with and without an amplitude ratio difference. The graphical view of P100 latency is shown in Figure 1.

In our study, none of the COVID PCR positive patients had vision loss but prolongation of P100 latency was detected in 34.6% of the outpatients and in 30.4% of the inpatients. Our results show that optic nerve involvement in COVID-19 is not a rare finding, contrary to what has been reported in other studies.

Table 1. VEP recordings

	Left eye (mean ± SD)	Right eye (mean ± SD)
N75 latency (ms)	67.9±16.9	67.3±15.5
P100 latency (ms)	109.6±14.9	110.0±14.9
N145 latency (ms)	149.4±23.1	151.8±23.3
P100 amplitude (uV)	7.5±3.3	8.1±3.8

SD: Standard deviation, VEP: Visual evoked potential

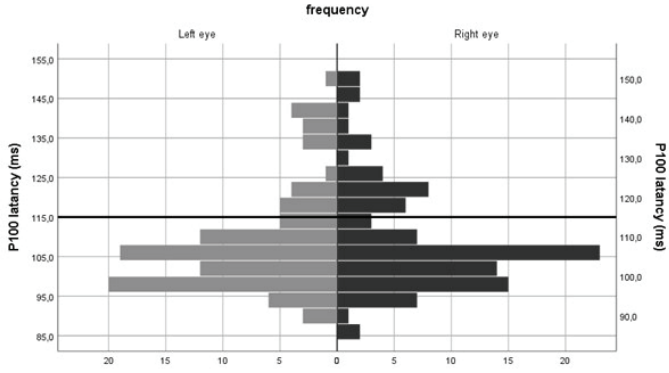

Figure 1. Histogram of P100 latency of the two eyes

Optic nerve involvement is a fairly common finding in patients who are asymptomatic in terms of visual symptoms.

Discussion

In patients with COVID-19, the optic nerve might be involved due to the systemic inflammatory response. Except for a small number of case reports, we could not find any study investigating subclinical involvement of the optic nerve. The most common and important abnormality indicating optic nerve involvement is the prolongation of latency of P100 wave. The most important electrophysiological reflection of demyelination is prolongation of latency due to conduction delay. The most important and beneficial role of VEP is that it can show these subclinical disturbances. The VEP test which is a cost-effective and non-invasive test can be used to detect the involvement of the asymptomatic anterior visual pathways, and that it reveals abnormalities in the majority of patients with non-overt visual disturbances.

The ACE2 receptors are abundant during development in the brain and peripheral tissues, but they regress after birth. Of particular interest is the potential effect of vasoactive substances such as angiotensin II (AII) on the vascular tone in the optic nerve head by diffusion from the adjacent choroid. Such externally induced tone can reduce the expansion of vessels in the optic nerve head when blood flow is strained by high intraocular pressure (IOP). There are publications showing the presence of AII binding sites in animal experiments in the retinal arterioles and in the capillaries of the optic nervehead. The presence of receptors for this vasoactive hormone in the optic nerve head indicates that circulating agents can spread from the choroid to the optic disc and affect vascular tone, alter the autoregulation response, and alter the sensitivity of the optic disc at different IOP levels. These results support the hypothesis that the microvascular tone and perhaps the autoregulation responses of the optic nerve capillaries may be affected by vasoactive substances such as locally synthesized AII or AII leaking from the choroid (10). ACE2 receptors are thought to play a role in neuroregenerative or apoptotic events and are also involved in axonal regeneration in the central nervous system. In an experimental study on optic nerve damage, a moderate increase in the RNA expression of the ACE2 receptor was reported. There are studies showing that ACE2 receptors are located at the head of optic nerve in the human eye (11). Ramipril, a potent ACE inhibitor prodrug, has been shown to significantly reduce radiation-induced optic neuropathy. To demonstrate these effects,

VEP response, a reliable and precise measure of the integrity of the visual system from the retina to the cortex, have been used (12). Optic nerve damage was reported in an active COVID-19 patient with normal ophthalmological examination findings. The optic damage mechanism was not conclusive, but posterior neuropathy was found as a possible mechanistic explanation (13). Many studies emphasize that cranial nerve involvement, mainly ocular motor paralysis, occurs in COVID-19, but optic nerve involvement is rare (14).

Study Limitations

This study was a cross-sectional observational study that included post-disease VEP measurements in patients with COVID-19, and the most important limitation was that it did not include pre-illness measurements of the participants or comparison with a similar control group. Our results should be interpreted cautiously, results of comprehensive studies should be awaited before reaching definitive conclusions about the causal link between prolongations in VEPs and COVID-19.

Conclusion

Contrary to previously published studies, we found asymptomatic optic nerve involvement by VEP measurements in COVID patients. Prolongation of P100 latencies show a putative link between novel coronavirus and ACE2 receptors in the human eye. This is the first study demonstrating asymptomatic eye involvement of COVID-19 with VEP tests. We presume that the importance of our findings will be better understood in the future, because they can be considered as a component of long COVID-19.

Ethics

Ethics Committee Approval: Canakkale Onsekiz Mart University Faculty of Medicine Institutional Ethics Committee approval was obtained for the study (project no: 2011-KAEK-27/2020-E.2000183492, approval no: 2020-14).

Informed Consent: Informed consent from all participants was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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