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Nerve Conduction Studies in post COVID-19 Patients Without Neuropathic Complaints

Derya Özdoğru[1], Miray Erdem[1], Halit Fidanci[2], Zülfikar Arlier[1]

1 Department of Neurology, Adana City Training and Research Hospital, University of Health Sciences, Adana, Turkey

2 Department of Neurology, Division of Clinical Neurophysiology, Adana City Training and Research Hospital, University of Health Sciences, Adana, Turkey

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Abstract

Objective: Neurological diseases related to the coronavirus disease (COVID-19) are known. In this study, it was aimed to find out whether the peripheral nervous system is affected in patients with a history of COVID-19 (post COVID-19) without neurological findings.

Methods: Patients with a positive history of the nose swap polymerase chain reaction test and clinical signs of COVID-19 (post COVID-19 patients), and controls who have not had COVID-19 were included in this retrospective cohort study. Neurological examinations of post-COVID-19 patients and controls should have been normal. Nerve conduction studies including median, ulnar, posterior tibial and peroneal nerves were applied to all participants.

Results: Thirty controls (14 males, 16 females) and 32 post COVID-19 patients (19 males, 13 females) were included. The mean ages of postCOVID-19 patients and controls were 49.7±10.9 and 38.0±7.6 years, respectively. Age and gender were not different between post COVID-19 patients and controls (p=0.122, p=0.316122). Nerve conduction study findings of median, ulnar, posterior tibial and sural nerves were not different between the two groups (p>0.05).

Conclusion: This study may show that routine nerve conduction studies are not subclinically affected in post COVID-19 patients without neurological findings.

Keywords: COVID-19, nerve conduction study, peripheral neuropathy

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Correspondence / Yazışma Adresi: *Derya Özdoğru, Department of Neurology, Adana City Training and Research Hospital, University of Health Sciences, Adana, Turkey e-mail: deryaozdogru@hotmail.com*

Nöropatik Şikayetleri Olmaksızın COVID-19 Geçiren Hastalarda Sinir İletim Çalışmaları

Öz

Amaç: Coronavirüs hastalığına (COVID-19) bağlı nörolojik hastalıklar bilinmektedir. Bu çalışmada, nörolojik bulgusu olmayan COVID-19 (COVID-19 sonrası) öyküsü olan hastalarda periferik sinir sisteminin etkilenip etkilenmediğinin ortaya çıkarılması amaçlanmıştır.

Yöntemler: Bu retrospektif kohort çalışmasına, sürüntü polimeraz zincir reaksiyonu testi öyküsü pozitif ve COVID-19 klinik belirtileri (COVID-19 sonrası hastalar) öyküsü olan hastalar ve COVID-19 olmayan kontroller dahil edildi. COVID-19 sonrası hasta ve kontrollerin nörolojik muayeneleri normal olmalıydı. Tüm katılımcılara median, ulnar, posteriortibial ve peroneal sinirleri içeren sinir iletim çalışmaları uygulandı.

Bulgular: Otuz kontrol (14 erkek, 16 kadın) ve 32 COVID-19 sonrası hasta (19 erkek, 13 kadın) dahil edildi. COVID-19 sonrası hastaların ve kontrollerin ortalama yaşları sırasıyla 49.7±10.9 ve 38.0±7.6 yıldı. COVID-19 sonrası hastalar ve kontroller arasında yaş ve cinsiyet farklı değildi (p=0,122, p=0,316). Median, ulnar, posteriortibial ve sural sinirlerin sinir iletim çalışması bulguları iki grup arasında farklı değildi (p>0.05).

Sonuç: Bu çalışma, nörolojik bulgusu olmayan COVID-19 sonrası hastalarda rutin sinir iletim çalışmalarının subklinik olarak etkilenmediğini gösterebilir.

Anahtar kelimeler: COVID-19, sinir iletim çalışması, periferik nöropati.

INTRODUCTION

The coronavirus disease (COVID-19), which emerged in 2019 caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), affected almost the whole world. The disease often causes fever, cough and respiratory system related symptoms[1,2]. Neurological disorders caused by COVID-19 are also being reported with increasing frequency[2-4]. Although the pathophysiology of neurological disorders that may be associated with COVID-19 has not been fully elucidated, it has been reported that the central or peripheral nervous system may be affected in COVID-19[4-6].

It has been suggested that disorders involving the peripheral nervous system, such as cranial neuropathies and Guillain-Barré syndrome, may be associated with COVID-19 [4-6]. Although the cause of peripheral nervous system involvement in COVID-19 is not clearly known, the development of Guillain-Barre syndrome during severe acute COVID-19 in some patients suggested that peripheral nervous system involvement may occur with a cause such as cytokine storm[2,3,5]. On the contrary, the development of Guillain-Barre syndrome after acute COVID-19 in some patients shows that peripheral nervous system involvement may develop after an immune process[2,3,5]. Whether the cause is an immune process or a cytokine storm, ultimately COVID-19 can affect the peripheral nervous system.

Subclinical peripheral nervous system involvement can be seen in some chronic diseases or infectious diseases[7,8]. Subclinical involvement of peripheral nerves can be described as abnormality in nerve conduction studies without symptoms associated with peripheral nervous system involvement[7,8]. Subclinical peripheral nervous system involvement can be demonstrated by nerve conduction studies. In this study, it was aimed to find out whether the peripheral nervous system is affected subclinically in COVID-19 using nerve conduction study.

METHODS

Study design and subjects

The participants over the age of 18 admitted to neurology department and clinical neurophysiology laboratory of Adana City

Training and Research Hospital (ACTRH) between April 2020 and June 2021 were included in this retrospective cohort study. Ethics committee approval was obtained from the ACTRH ethics committee (number: 1438). All participants should have clinical features and neurological examination findings, nerve conduction study findings in the clinical neurophysiology laboratory and neurology clinic archives. In order to determine the peripheral nervous system involvement, the patients needed to be compared with controls. Therefore, participants were divided into two groups as controls and post COVID-19 patients.

Patients with the following characteristics were included in the group that included post COVID-19 patients: 1) History of the nose swap polymerase chain reaction (PCR) test positivity 2) Clinical features during acute infection compatible with COVID-19 (fever or cough or generalized pain or dyspnea). Patients were not considered as post-COVID-19 patients if they had: 1) Clinical or neurological examination findings suggestive of polyneuropathy or cranial neuropathy during or after acute infection 2) A disease that can cause polyneuropathy, such as diabetes mellitus. The control group did not consist of completely healthy participants. It consisted of patients who applied to the clinical neurophysiology laboratory due to knee / shoulder / neck / low back pain. Participants in the control group were excluded from the study if they had the following features: 1) Clinical history consistent with COVID-19 2) History of the nose swap PCR positivity 3) Having a disease that can cause polyneuropathy, such as diabetes mellitus 4) Clinical or neurological examination findings suggestive of polyneuropathy or peripheral neuropathy. The neurological examination was performed by an experienced neurologist and a professor of neurology.

Nerve conduction study

The Cadwell Sierra Summit EMG unit (Cadwell Laboratories, Kennewick, Washington, USA) was used for nerve conduction study. Nerve conduction studies was performed by a clinical neurophysiologist and two neurophysiology technicians. Nerve conduction study lasted approximately 30 minutes in each patient. Nerve conduction study was performed if the temperature of the extremities was 32 degrees. If cold extremity was present, it was warmed. Stimulation and recording were performed with superficial electrodes. Stimulation was applied supramaximally. Band filters for sensory and motor nerve conduction studies were 20Hz-2kHz and 20Hz-10kHz, respectively. For the sensory nerve conduction study, the sensitivity and sweep speed were set as 10 uV/division and 1 ms/division, respectively. Sensitivity and sweep speed for motor nerve conduction study were 2 mV/division and 5 ms/division, respectively. Compound muscle action potential (CMAP) and compound nerve action potential amplitudes (CNAP) were measured from peak to peak. Sensory nerve conduction studies were performed antidromically. Sensory nerve conduction velocity was calculated using peak latency. For distal stimulation of the median, ulnar, and posterior tibial motor nerves, the distances between the stimulation points and the recording electrodes were 5 cm, 5 cm, and 10 cm, respectively. The latency of the shortest F-waves obtained with ten supramaximal stimulations was recorded.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, and numerical variables as mean ±standard deviation (SD), min-max. Categorical variables were analyzed using Pearson's Chi-square test. Mann-Whitney U test was used to compare numerical variables between groups. It was considered statistically significant if the p value was < 0.05. SPSS 22.0 was used for statistical analysis.

RESULTS

The mean ages of 30 controls (14 males, 16 females) and 32 post COVID-19 patients (19 males, 13 females) were 38.0±7.6 (range 20-53) and 49.7±10.9 (range 20-72) years, respectively. Age and gender were not different between groups (p=0.122, p=0.316). Fever, sore throat, headache, loss of taste, inability to smell, widespread pain, diarrhea, cough, dyspnea were reported in 8 patients (25%), 8 patients (25%), 16 patients (50%), 7 patients (22%), 11 patients (34%), 14 patients (44%), 1 patient (3%), 12 patients (38%), and 4 patients (13%), respectively. Thoracic CT was performed in 21 patients. The findings of thorax CT in 11 of these 21 patients were compatible with COVID-19. There were no patients hospitalized due to COVID-19. Post COVID-19 patients and controls were not vaccinated for COVID-19. The controls did not have a chronic disease. Table 1 shows the chronic diseases of post-COVID-19 patients.

Table I: Chronic diseases of post COVID-19 patients

Chronic disease	**Number of patients (%)**
Hypertension	9 (28)
Coronary artery disease	4 (12)
Hyperlipidemia	5 (16)
Chronic obstructive pulmonary disease	2 (6)

A total of 62 upper extremity and 62 lower extremity nerve conduction studies were performed in 30 controls and 32 post-COVID-19 patients. The interval between the time the nerve conduction study was performed in post COVID-19 patients and the onset of COVID-19 complaints was 3.0±1.9 (range 1-7.5) months. The right upper and lower extremities were studied in 25 and 24 of controls and post COVID-19 patients, respectively (p=0.421). Comparisons of nerve conduction study findings in the upper and lower extremities between controls and post COVID-19 patients are shown in Table 2. Median, ulnar, posterior tibial, and sural nerve conduction studies findings were not different between post-COVID-19 patients and controls.

Table II: Comparison of extremity nerve conduction study findings between controls and post COVID-19 patients

Nerve conduction study parameter	**Controls** Mean±SD (min-max)	**Post COVID-19 patients** Mean±SD (min-max)	**P value**
Upperextremity			
MedianNerve			
Distal CMAP amplitude (mV)	16.2±6.6 (5.1-29.7)	15.8±5.0 (5.1-24.7)	0.812
Distal CMAP latency (ms)	3.0±0.4 (2.2-3.7)	3.1±0.6 (2.2-4.7)	0.292
Motor NCV acrosswrist-elbow segment (m/s)	61.1±5.0 (50-71)	58.8±4.1 (50-68)	0.072
F-wavelatency (ms)	25.7±1.9 (22.6-30.0)	25.0±2.9(21.9-32.7)	0.228
CNAP amplitude – 2nd finger-wrist segment (μV)	43.9±16.1(19.0-79.4)	43.3±17.6(14.2-75.6)	0.784
Sensory NCV across 2nd finger-wrist segment (m/s)	46.8±5.1 (39-58)	44.1±4.5 (30-50)	0.095
Ulnarnerve			
Distal CMAP amplitude (mV)	14.8±3.1 (8.9-20.4)	13.2±3.2 (8.0-18.9)	0.090
Distal CMAP latency (ms)	2.2±0.2 (1.9-2.7)	2.4±0.3 (2.0-3.2)	0.180
Motor NCV acrosswrist-belowelbowsegment (m/s)	62.9±4.8 (52-71)	63.3±7.1 (50-75)	0.682
F-wavelatency (ms)	26.5±2.2 (23.0-32.0)	25.6±2.5(20.3-32.0)	0.137
CNAP amplitude – 5th finger-wrist segment (μV)	50.1±14.4(27.7-95.2)	51.3±20.1(12.1-98.2)	0.579
Sensory NCV across 5th finger-wrist segment (m/s)	46.9±4.1 (41-57)	45.4±5.4 (38-57)	0.202
Lower extremity			
Posterior tibial Nerve			
Distal CMAP amplitude (mV)	14.0±4.4 (5.8-25.7)	12.5±5.0 (4.3±23.6)	0.214
Distal CMAP latency (ms)	3.9±0.6 (2.9-5.2)	3.6±0.9 (2.8-5.8)	0.143
Motor NCV acrossankle-popliteal segment (m/s)	49.1±6.5 (40-65)	46.6±5.3 (39-61)	0.139
F-wave latency (ms)	47.9±4.1 (40.1-59.0)	50.2±4.8(44.1-62.0)	0.105
Sural nerve			
CNAP amplitude (μV)	18.3±4.7 (8.1-27.2)	23.5±12.2(11.3-59.1)	0.291
Sensory NCV (m/s)	44.3±6.9 (35-58)	47.2±5.8 (38-60)	0.087

CMAP: compound muscle action potential; CNAP: compound nerve action potential; NCV: nerve conduction velocity; SD: standard deviation.

DISCUSSION

Neurological disorders that may be associated with COVID-19 have been reported[2-4]. In addition to disorders that may affect the central nervous system such as ADEM, there are those who suggest that the peripheral nervous system

may be affected by COVID-19[4-6]. The presence of symptoms such as headache, anosmia, and taste loss in patients may indicate that COVID-19 affects the nervous system[2,9,10,11]. Anosmia may be an important symptom to support peripheral nervous system involvement in COVID-19. Although the pathophysiology of anosmia associated with COVID-19 is unknown, there are those who suggest that pathophysiological processes such as olfactory spreading play a role in anosmia[12,13]. Angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serine 2 (TMPRSS2) are reported to be important for SARS-CoV-2[12,13]. The presence of ACE2 and TMPRSS2 in the olfactory nerve may suggest that the olfactory nerve is affected in COVID-19. The fact that the olfactory nerve may be affected in this hypothesis may mean that other peripheral nervous system elements may also be affected. In addition, some cranial neuropathies associated with COVID-19 may indicate that the peripheral nervous system may be affected in COVID-19[14,15]. In this study, the peripheral nervous system was examined by performing the routine nerve conduction studies in post COVID-19 patients with normal neurological examination and no neurological complaints. We found that there was no subclinical involvement in the peripheral nervous system in postCOVID-19 patients without neurological symptoms. According to some, this may contradict the knowledge that the peripheral nervous system may be affected in COVID-19 patients. However, it should be kept in mind that post COVID-19 patients without neurological symptoms were included in this study. Also, according to some, the cause of anosmia in COVID-19 may not be due to olfactory nerve involvement. There are those who argue that ACE2 and TMPRSS2 are located in the epithelial sustentacular cells rather than the olfactory nerve[16]. This may support the finding in our study that peripheral nerves are not subclinically affected in COVID-19 patients without neurological symptoms. In this study, we included patients without neurological symptoms, but we think that electrodiagnostic studies on patients with continuing neurological symptoms such as anosmia after COVID-19 will contribute to the understanding of the neuropathophysiology of COVID-19.

Guillain Barre-Syndrome associated with COVID-19 has been reported[5,17]. Although the pathophysiology of this condition is not clearly known, it can be thought that excessive cytokine release in COVID-19 may contribute to Guillain-Barre syndrome[18,19]. The patients included in this study had mild or moderate clinical signs of COVID-19 and were not hospitalized. This may mean that there was no excessive cytokine release in the patients included in the study. This may explain why there was no subclinical involvement of the peripheral nervous system in post COVID-19 patients in our study. However, it has been reported that Guillain-Barre may develop in asymptomatic individuals with positive SARS-CoV-2 test[19,20]. This finding was in contrast to the results of our study and the hypothesis that cytokine storm would predispose to Guillain-Barre syndrome. We find it difficult to explain this situation. However, PCR test in cerebrospinal fluid (CSF) was negative in one asymptomatic patient, and it should be noted that PCR analysis could not be performed in CSF in another patient. We think that future studies on asymptomatic post COVID-19 patients with neurological symptoms are necessary.

Reporting of cranial nerve neuropathies associated with COVID-19 may also support peripheral nervous system involvement, such as COVID-19 associated with Guillain-Barré syndrome[14,15,19]. It is not known which patients have cranial nervous system or peripheral nervous system involvement. The previously mentioned cytokine storm or ACE2 or hypercoagulopathy may explain peripheral nervous system involvement[1-3,12,13]. As

mentioned earlier, the fact that the patients included in this study did not have severe COVID-19 suggests that the patients do not have an excessive cytokine storm. These findings may explain the absence of peripheral nervous system involvement in our study. However, there is a need to confirm this situation with further studies on the peripheral nervous system in patients with severe COVID-19.

In addition to its retrospective design, this study had some limitations. Controls did not consist of healthy individuals. However, it should be kept in mind that the controls only have neck or knee pain and that the neurological examinations of the controls are normal. Neck pain may be a result of a cause such as cervical radiculopathy, which may affect upper extremity nerve conduction study findings. Peroneal motor nerve conduction study findings were not included in the study, as peroneal motor nerve conduction study findings were not available in all participants. This situation can also be considered a limitation. Another limitation was the variable interval between the time the nerve conduction study was performed in post COVID-19 patients and the time the patients started to complain of COVID-19. Finally, routine nerve conduction study provides information about the physiology of large myelinated nerves. Therefore, unmyelinated fibers could not be evaluated in this study. However, there were no neurological complaints such as burning, indicating small nerve fiber neuropathy in the patients.

In conclusion, these study findings may indicate that there is no abnormality in routine nerve conduction study in asymptomatic post COVID-19 patients. These may mean that the peripheral nervous system is not subclinically affected in post COVID-19 patients.

Ethics Committee Approval: In this study, national and international ethical rules are observed. Ethic Board: Adana city training and research hospital ethic committee, 02.06.2021/1438.

Conflict of Interest: The authors declared no conflicts of interest.

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