

# Clinical Features of Patients Referred to an Electroneurophysiology Laboratory After COVID-19 Infection: Retrospective Analysis

## COVID-19 Enfeksiyonu Sonrası Elektronörofizyoloji Laboratuvarına Yönlendirilen Hastaların Klinik Özellikleri: Retrospektif Analiz

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This study was presented as an oral presentation at 16<sup>th</sup> Virtual Congress of European Forum for Research in Rehabilitation (EFRR), September 23-25, 2021, online Ljubljana, Slovenia.

**ABSTRACT Objective:** The aim of this study was to determine the clinical features and electrophysiological diagnoses of patients referred to the electroneuromyography (ENMG) laboratory after coronavirus disease-2019 (COVID-19) infection. **Material and Methods:** Medical records of patients referred to the ENMG laboratory between March 11, 2020 and March 11, 2021 with neuromuscular signs and symptoms, preceded by a diagnosis of severe acute respiratory syndrome-CoV-2 (SARS-CoV-2), were reviewed retrospectively. Patient demographics, comorbidities, presenting complaints, date of SARS-CoV-2 infection, nature of electrophysiological investigation and ENMG outcomes were recorded. **Results:** A total of 1,274 medical records were reviewed, 62 patients were included in the study. Mean age was 50.39±17.2 years, 36 (58.1%) were male. The diagnosis of COVID-19 was made 7.29±1.59 months after the onset of the pandemic and 95.2% did not require treatment in the intensive care unit of the hospital. Patients presented with neuromuscular complaints 2.65±1.86 months after COVID-19 diagnosis. Common symptoms were paraesthesia (41.9%) and pain in the extremities (17.7%). Hypertension (22.6%) and diabetes mellitus (17.7%) were the most commonly reported comorbidities. Changes in sensation and deep tendon reflexes, and reduced muscle power were detected in 30.6%. Most common ENMG diagnosis was polyneuropathy (22.5%). ENMG findings were normal in 42.1%. **Conclusion:** COVID-19 gives rise to many neurological complications, including those involving the peripheral nervous system (PNS). Repeat ENMG and further, more sensitive electrophysiological testing should be considered in those with continued PNS complaints, despite initially normal electrophysiological findings. Further studies should establish whether SARS-CoV-2 infection is causal or coincidental in the development of PNS pathologies and related ENMG findings.

**Keywords:** SARS-CoV-2; electromyography; polyneuropathies; peripheral nervous system

**ÖZET Amaç:** Bu çalışmanın amacı, koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] enfeksiyonu sonrası elektronöromiyografi (ENMG) laboratuvarına refere edilen hastaların klinik özelliklerinin değerlendirilmesidir. **Gereç ve Yöntemler:** 11 Mart 2020-11 Mart 2021 tarihleri arasında şiddetli akut solunum sendromu-CoV-2 [severe acute respiratory syndrome-CoV-2 (SARS-CoV-2)] tanısı alan ve sonrasında nöromusküler semptom ve bulguları olan, ENMG laboratuvarına refere edilen hastaların, hastane dosyaları retrospektif olarak tarandı. Hastaların demografik bilgileri, komorbiditeleri, şikâyetleri, SARS-CoV-2 enfeksiyon tarihi, istenen elektrofizyolojik tetkik ve ENMG sonuçları kaydedildi. **Bulgular:** Bin iki yüz yetmiş dört hasta dosyası tarandı ve 62 hasta çalışmaya dâhil edildi [ortalama yaş: 50,39±17,2, %58,1 (n=36) erkek]. Hastalar, COVID-19 tanısını pandemi başlangıcından itibaren ortalama 7,29±1,59 ay sonra almış olup, çoğu yoğun bakımda tedavi edilmemişti (%95,2). Hastaların nöromusküler şikâyetleri, COVID-19 enfeksiyonundan ortalama 2,65±1,86 ay sonra başlamıştı. Sık görülen semptomlar, parestezi (%41,9) ve ekstremitelerde ağrı (%17,7) idi. En sık görülen komorbiditeler arasında ise hipertansiyon (%22,6) ve diabetes mellitus (%17,7) yer almaktaydı. Hastaların %30,6'sında duyu bozukluğu, azalmış kas kuvveti ve derin tendon refleksi değişikliği saptandı. En sık ENMG tanısı, polinöropati idi (%22,5). Hastaların %42,1'inde ise ENMG bulguları normal sınırlarda saptandı. **Sonuç:** COVID-19, periferik sinir sistemi (PSS) dâhil birçok nörolojik komplikasyona yol açabilmektedir. İlk elektrofizyolojik değerlendirmeler normal saptansa bile devam eden PSS şikâyetleri olan hastalarda, ENMG tekrarlanmalı ve daha duyarlı elektrofizyolojik testlerin de gerekliliği dikkate alınmalıdır. Gelecekteki çalışmalarda, PSS patolojilerinin oluşumunda SARS-CoV-2 enfeksiyonunun gerçek bir etkisi olup olmadığı araştırılmalıdır.

**Anahtar Kelimeler:** SARS-CoV-2; elektromiyografi; polinöropatiler; periferik sinir sistemi

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Coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome-CoV-2 (SARS-CoV-2), was first identified in China in December 2019 and declared a pandemic in March 2020.<sup>1</sup> Even though respiratory system involvement is at the forefront of clinical findings of COVID-19 infection, it now appears that these are only one part of the spectrum of possible clinical manifestations of the disease. Reports on neuromuscular complications such as myalgia, epileptic seizures and cerebrovascular disorders continue to grow as the pandemic evolves.<sup>2</sup>

Neurological manifestations following SARS-CoV-2 infection do not strictly necessitate direct involvement of the central nervous system (CNS) or peripheral nervous system (PNS); hypothesized mechanisms of neurological involvement also include a secondary hyperinflammatory syndrome, inflammatory or immune mediated disorders and systemic disorders with neurological consequences.<sup>3-5</sup> Neurological diagnoses reported to date include ischaemic stroke and meningo-encephalitis.<sup>6,7</sup> Moreover, cases of myopathy and polyneuropathy (PNP), namely Guillain-Barré syndrome (GBS), supported by electrophysiological findings, have also been reported.<sup>8-10</sup> Electrophysiological tests, including nerve conduction studies (NCS) and electromyography, are used to diagnose neuromuscular diseases, locate nerve lesions and determine their severity. To the best of our knowledge, to date there is no study on the electroneuromyography (ENMG) findings and neurophysiological diagnoses obtained in patients presenting with neuromuscular signs and symptoms following SARS-CoV-2 infection.

The aim of this study was to elicit the neuromuscular signs and symptoms and electrophysiological diagnoses of patients referred to the ENMG laboratory after COVID-19 infection.

## MATERIAL AND METHODS

A retrospective analysis of clinical and electrophysiological findings of patients referred to the ENMG laboratory of Başkent University Ankara Hospital between March 11, 2020 and March 11, 2021 was made. Medical records of patients referred with neuromuscular signs and symptoms, preceded by a diag-

nosis of SARS-CoV-2 with a positive SARS-CoV-2 polymerase chain reaction test, were evaluated. All electrophysiological studies were conducted in a single laboratory using a Medelec Synergy Multimedia electrodiagnostic device (Oxford Instruments, UK) by 2 physiatrists with a cumulative experience of 40 years in this field. Those with a history of neuromuscular disease prior to COVID-19 infection and those with missing pertinent clinical details in their medical records, were excluded from the study. Patient demographics, comorbidities, presenting neuromuscular signs and symptoms, date of SARS-CoV-2 infection, type of electrophysiological investigation conducted and ENMG outcomes were recorded.

The study was carried out according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants prior to study inclusion. Approval for the study was granted by the Turkish Health Institute (form name Selin Ozen-2021-01-11T14\_47\_42, date 14.01.2021) and Başkent University Institutional Review Board (Project no:KA21/32) and supported by Başkent University Research Fund.

## STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (IBM SPSS, United States) software version 22 was used for statistical analyses. The Kolmogorov-Smirnov test was used to test the normal distribution of each of the variables. Descriptive analyses were presented using means and standard deviations for normally distributed variables, medians for non-normally distributed and ordinal variables, and tables of frequency for ordinal variables. Associations between non-normally distributed and/or ordinal variables were assessed using the Spearman test. A p value of less than 0.05 was considered to represent statistical significance.

## RESULTS

A total of 1,274 medical records were reviewed. Of these, 62 patients had been infected with COVID-19 with a positive polymerase chain reaction test and developed neuromuscular complaints following infec-

tion. Mean patient age was  $50.39 \pm 17.2$  years and 36 (58.1%) were male. The diagnosis of COVID-19 was made on average  $7.29 \pm 1.59$  months after the onset of the pandemic and 59 (95.2%) of the patients did not necessitate intensive care unit admission. Patients presented with neuromuscular complaints  $2.65 \pm 1.86$  months after COVID-19 diagnosis.

Clinical details of patients referred to the electrophysiology laboratory are given in Table 1. Most patients were referred to the ENMG laboratory by the physical medicine and rehabilitation, and neurology departments (45.2% and 37% respectively). Most common symptoms were paraesthesia (41.9%), pain (17.7%), mostly in the limbs but also in the neck, back and shoulders, with 25.9% of patients experiencing a combination of paraesthesia and pain +/- muscle weakness (Table 1). Hypertension (HT) (22.6%) and diabetes mellitus (DM) (17.7%) were the most commonly occurring comorbidities. Neurological and musculoskeletal examination findings mostly consisted of changes in sensation and reflexes and a reduction in muscle power (30.6%). The most common preliminary diagnosis was PNP (33%) followed by a combination of differential diagnoses (17.7%), mostly PNP and carpal tunnel syndrome/ulnar tunnel syndrome/radiculopathy (Table 2). The most common neurological diagnosis based on ENMG findings was PNP (n=14, 22.5%). Two (14.3%) of the patients' had axonal PNP and were diagnosed with GBS, 12 (85.7%) had ENMG findings consistent with mixed type sensorimotor PNP. ENMG findings were normal in 42.1% (26) of the patients (Table 2).

There was a weak positive correlation between age and the presence of comorbidities ( $r_s=0.296$ ,  $p=0.020$ ), and age and neuromuscular examination findings ( $r_s=0.291$ ,  $p=0.022$ ). There was also a weak positive correlation between comorbidities and ENMG findings ( $r_s=0.290$ ,  $p=0.022$ ). There was no correlation between past medical history of DM and ENMG diagnosis of PNP. Neuromuscular examination findings were positively correlated with the preliminary diagnoses ( $r_s=0.314$ ,  $p=0.013$ ) and final diagnoses based on ENMG findings ( $r_s=0.387$ ,  $p=0.002$ ). There was also a positive correlation between preliminary diagnoses and ENMG findings ( $r_s=0.313$ ,  $p=0.013$ ).

**TABLE 1:** Clinical details of patients referred to the electrophysiology laboratory.

n=62	
<b>Referring department, n (%)</b>	
PMR	28 (45.2)
Neurology	23 (37)
Neurosurgery	4 (6.5)
Orthopaedics	5 (8.1)
ENT	1 (1.6)
Rheumatology	1 (1.6)
<b>Patient comorbidities, n (%)</b>	
Hypertension	14 (22.6)
Diabetes mellitus	11 (17.7)
Thyroid dysfunction	7 (11.3)
Chronic renal failure	1 (1.6)
Psychiatric illness	1 (1.6)
None	28 (45.2)
<b>Neuromuscular symptoms, n (%)</b>	
Paraesthesia	26 (41.9)
Muscle weakness	4 (6.5)
Difficulty in walking	2 (3.2)
Loss of balance	1 (1.6)
Pain	11 (17.7)
Ptosis	1 (1.6)
Facial muscle weakness	1 (1.6)
More than one of the above symptoms	16 (25.9)
<b>Neuromuscular examination findings, n (%)</b>	
Reduced muscle power	5 (8.2)
Abnormal sensation	10 (16.1)
Abnormal balance and coordination	1 (1.6)
Abnormal reflexes	1 (1.6)
Abnormal gait	3 (4.8)
Abnormal cranial nerve examination	2 (3.2)
More than one of above	19 (30.6)
No positive findings	21 (33.9)

PMR: Physical medicine and rehabilitation; ENT: Ear nose and throat.

## DISCUSSION

Patients referred to our neurophysiology laboratory in the first year of the COVID-19 pandemic with a history of SARS-CoV-2 infection mostly presented with symptoms of paraesthesia, muscle weakness and pain and examination findings of changes in sensation, reflexes and muscle weakness. Examination findings were positively correlated with preliminary diagnoses and ENMG findings.

**TABLE 2:** Clinical details of patients referred to the electrophysiology laboratory.

n=62	
<b>Preliminary diagnosis, n (%)</b>	
PNP	20 (33.0)
CTS	9 (14.5)
UTS	7 (11.3)
Radiculopathy	7 (11.3)
MND	1 (1.6)
Guillain-Barré syndrome	2 (3.2)
Neuromuscular junction disease	2 (3.2)
Multifocal motor neuropathy	2 (3.2)
Facial nerve palsy	1 (1.6)
More than one preliminary diagnosis	11 (17.7)
<b>ENMG diagnosis, n (%)</b>	
PNP	9 (14.5)
UTS	9 (14.5)
CTS	3 (4.8)
Radiculopathy	4 (6.5)
Facial nerve lesion	1 (1.6)
MND	4 (6.4)
PNP+nerve lesion	2 (3.2)
CTS+UTS	1 (1.6)
PNP+CTS	1 (1.6)
UTS+PNP	1 (1.6)
PNP+radiculopathy	1 (1.6)
Normal ENMG	26 (42.1)

ENMG: Electroneuromyography; PNP: Polyneuropathy; CTS: Carpal tunnel syndrome; UTS: Ulnar tunnel syndrome; MND: Motor neurone disease.

Over half of the patients had positive ENMG findings; PNP was the most common definitive diagnosis.

The wide range of CNS and PNS diseases associated with COVID-19 is unsurprising given existing knowledge of other CoVs and respiratory viruses. Based on cases reported so far, neurological disease may be increasingly seen in SARS-CoV-2-positive individuals who show few or no typical features of COVID-19.<sup>11</sup> However, the disease mechanisms resulting in neurological manifestations remain under debate. It is generally believed that neurological complications may arise as a result of direct viral invasion of nervous system tissue, immune-mediated pathogenesis and complications associated with severe illness.<sup>3,12</sup> The mechanism behind peripheral nerve invasion remains even more of a mystery; stud-

ies on PNS involvement following SARS-CoV-2 infection are sparse. One belief is that direct viral invasion of the PNS may occur due to SARS-CoV-2 targeting the blood nerve barrier (BNB) which protects the endoneurium of the peripheral nerve and facilitates axonal signal transduction. Altered permeability of the BNB may trigger events leading to demyelination and axonal degeneration, similar to that occurring in GBS, acute and chronic inflammatory demyelinating polyradiculoneuropathy and vasculitis.<sup>13</sup> However, in our study, the mean time of presentation with neuromuscular complaints was  $2.65 \pm 1.86$  months after SARS-CoV-2 infection. This may have, of course, been due to a time lag between symptom onset and first hospital presentation. On the other hand, the time delay between SARS-CoV-2 infection and onset of neuromuscular complaints may also indicate that neuromuscular complications occurred due to a post infectious immune-mediated response rather than an inflammatory response to acute illness.<sup>5</sup>

In this study, approximately half of the patients were male and most common comorbidities were HT and DM. To date, SARS-CoV-2 rate has been comparable in males and females, and HT and DM have been identified as the most common comorbidities.<sup>14,15</sup> Interestingly, neurological examination was normal in 33.9% of the patients and 42.1% had a normal ENMG despite the presence of neuromuscular symptoms, mainly paraesthesia (41.9%) and pain (17.7%). Nerve pain has previously been described in a study of 214 patients with 4.5% (n=4) and 0.8% (n=1) of cases occurring in those with severe and non-severe COVID-19 respectively.<sup>9</sup> Once again, such PNS symptoms may indicate that SARS-CoV-2 is responsible for dysregulating the systemic immune response which is believed to give rise to PNS manifestations after the acute phase of infection.<sup>16,17</sup> Neuronal involvement in those with normal ENMG findings may not have been enough to result in a change in neuromuscular physiology; moreover changes in neuromuscular activity may have been too mild to detect using ENMG. Repeat ENMG and further, more sensitive electrophysiological testing in those with continued PNS complaints, despite normal initial electrophysiological findings, should be

considered. In addition, other diagnoses, such as small fibre neuropathy (SFN), which characteristically produces symptoms of pain and paraesthesia, may not have been detected by ENMG.<sup>18</sup> It is believed that COVID-19 may cause SFN.<sup>19</sup> Once again, in these cases, a definite causal relationship between COVID-19 and development of SFN could not be established.<sup>20,21</sup>

The most common neurological diagnosis based on ENMG findings was PNP. Cases of PNP, and especially GBS, following COVID-19 infection have been reported in the literature.<sup>22</sup> However, the majority have been serious cases of COVID-19, with lower respiratory tract involvement, requiring intensive care treatment.<sup>23,24</sup> Even though it is difficult to decipher whether the cases of PNP in our study were a consequence of SARS-CoV-2 infection, the symptoms associated with PNP commenced after COVID-19 infection. Therefore, these patients may have had a mild form of post-COVID PNP with a post-infective physiopathological mechanism.<sup>25</sup> Similar findings have been described in a recent case series of five patients with mild neurological symptoms developing 2-4 weeks after a mild course of COVID-19 infection in whom neurophysiological findings supported a diagnosis of PNP.<sup>26</sup> In 4 out of 5 of the cases described, sensory and motor NCS were normal; however, an increase in F wave latency and absence of sympathetic skin responses were detected.<sup>26</sup> In another case series of 4 patients hospitalised due to COVID-19 infection with a history of DM, new onset of neuropathic symptoms including numbness in the feet and sensory neuropathy characterised by changes in vibration and heat sensation were diagnosed using quantitative sensory testing.<sup>27</sup>

There were some limitations to this study. Firstly, it was impossible to establish whether SARS-CoV-2 infection was causal or coincidental in the development of neuromuscular signs and symptoms, and ENMG diagnoses. Case-control studies are necessary to establish this relationship. In addition, follow-up of the patients and repeated ENMG studies would have been useful in monitoring disease progression in those diagnosed with PNP. Furthermore, other quantitative tests could have been considered in those with persisting neuropathic complaints despite persistently normal ENMG findings.

## CONCLUSION

This study provides insight on the main neuromuscular complaints and ENMG diagnoses of patients infected with SARS-CoV-2 within the first year of the COVID-19 pandemic. Based on this data, one tentative conclusion which may be drawn, is that even in mild cases of COVID-19, mild to moderate post-COVID PNS complications can occur. Although SARS-CoV-2 infection complications involving the PNS may not be the most common or life-threatening, they can result in lifelong disability, an increase in long term care needs and cost. In addition, even though the proportion of patients with PNS manifestations may be much smaller than those with respiratory disease, if 50-80% of the world's population will be infected with SARS-CoV-2 before herd immunity develops, then the number of people with PNS and CNS complications will become significantly greater. The findings of this study suggest that the relationship between SARS-CoV-2 infection and neuromuscular complications involving the PNS need to be better identified and established for improved healthcare planning.

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