Introduction

The global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its emerging variants has led to considerable morbidity and mortality, even more than 2 years following the initial identification of coronavirus disease 2019 (COVID-19). COVID-19, the disease caused by SARS-CoV-2, is frequently associated with neurological symptoms [1]. These manifestations may involve the peripheral nervous system (PNS), presenting as myalgia, loss of taste and smell, or visual disturbances, or the central nervous system (CNS), resulting in symptoms such as dizziness, headaches, seizures, ataxia, stroke, and altered consciousness [2].

Several pathophysiological mechanisms have been suggested for the neurological symptoms associated with COVID-19, which could stem from a strong immune response to the viral infection or from direct effects of COVID-19 on the PNS or CNS [3]. Furthermore, it has been noted that neurological symptoms can persist or emerge weeks to months after the initial infection.

These post-acute sequelae of SARS-CoV-2 can manifest as headaches, fatigue, chronic dysosmia and dysgeusia, dysautonomia, dizziness, and peripheral sensory abnormalities. Additionally, symptoms indicative of peripheral neuropathy, such as paresthesia, myalgia, and nerve pain, have been reported in patients who have had COVID-19 [4].

This review focuses on the application of standard neurophysiological diagnostic modalities in assessing neurological signs and symptoms that are related to the acute phase of COVID-19, as well as those associated with the post-acute condition known as "long COVID." Additionally, this manuscript will examine neurological disorders that have been reported to have a temporal association with vaccination against SARS-CoV-2.

Indications for Electrodiagnostic Studies

First, we examine the guidelines regarding indications for electrophysiological testing in patients with COVID-19, as presented by the American Association of Neuromuscular and Electrodiag...
nostic Medicine [5]. The presence of an acute or rapidly progressing peripheral neurological condition, which develops over a period of days to a maximum of 2 weeks, warrants immediate electrodiagnostic (EDX) testing. Such testing can lead to precise and conclusive management and provide a confirmatory diagnosis. Neglecting to perform EDX evaluations can be detrimental, as it may delay both diagnosis and treatment. These conditions are relatively uncommon and are characterized by symptoms such as bulbar dysfunction, gait abnormalities, respiratory insufficiency, and extensive weakness that is potentially indicative of a neuromuscular disorder. Examples of these conditions include suspected Guillain-Barré syndrome (GBS) and newly diagnosed myasthenia gravis (MG), for which a precise EDX assessment could substantially alter the treatment approach. In these instances, EDX studies are justified, provided that appropriate personal protective equipment and other infection control protocols are observed in line with institutional guidelines.

Requests for non-urgent EDX studies can be categorized based on the severity of symptoms, their progression, or both. These requests encompass conditions such as mild, localized symptoms—for example, numbness in the fingers of one hand—long-standing weakness or sensory symptoms that are either nonprogressive or progressing slowly, or situations where the diagnosis is relatively certain clinically and treatment can commence without the immediate need for EDX testing. In these instances, it is advisable to postpone EDX studies until the benefits of conducting the tests outweigh the risks posed by the COVID-19 pandemic. Conditions categorized as “possibly urgent” present the greatest challenge for classification. Urgency is contingent upon various factors, including the level of impairment, the rate of progression of the condition, the intensity of pain, and the likelihood of identifying a treatable condition. Here, the purpose of EDX testing is two-fold: to exclude treatable conditions that might be mistaken for those without a known cure, and to confirm a clinical diagnosis before initiating treatment.

1) Electromyography and nerve conduction studies

Few studies have utilized electrophysiology to confirm and quantify the extent of peripheral nerve dysfunction in individuals with COVID-19, despite numerous studies and systematic reviews documenting neurological symptoms in these patients [2,3].

A comprehensive review of six studies examined data regarding electromyography and nerve conduction studies (EMG/NCS). Of the 195 individuals assessed, only 175 underwent EMG/NCS evaluation. Among these, seven individuals (4%) exhibited abnormal sensory NCS, while 44 (25.1%) displayed abnormal EMG findings, and 54 (30.8%) presented with abnormal motor NCS. The electrophysiological evaluations of the remaining patients were normal [6]. All of the studies included in this review reported that NCS findings, including sensory nerve conduction velocity (NCV), were not significantly altered in patients with COVID-19 relative to healthy controls. This aligns with previous research that revealed either no or very slight NCS abnormalities [7]. Studies of COVID-19 severity, considering factors such as intubation, weaning from mechanical ventilation, and pneumonia, have identified substantial variation in EMG/NCS between more and less severe cases [8]. Early EDX testing is therefore essential for patients with COVID-19, especially those with severe illness, as evidenced by the significant fluctuation in EMG/NCS results in these cases. In one study, patients in the intensive care unit presented with flaccid quadriplegia—a muscle weakness affecting both the upper and lower limbs—and were categorized as having “critical illness neuropathy or myopathy” [9]. Other patients were referred for neurological evaluation, primarily for confusional syndrome associated with neuromuscular disorder [10].

Previous research has not yet provided evidence of direct viral invasion leading to the degeneration or inflammation of peripheral nerves and motor neurons, as is the case with certain viral infections [11]. Therefore, indications for EMG/NCV studies include PNS diseases that are suspected to be associated with COVID-19 or related to recent SARS-CoV-2 vaccination. These conditions encompass myopathies, neuromuscular junction disorders, Bell palsy, autoimmune mononeuropathies, and neuropathies, the majority of which are autoimmune [12].

(1) Acute inflammatory demyelinating polyneuropathy

In a previous report, 24 cases involving acute inflammatory demyelinating polyneuropathy (AIDP) variants were identified, of which 18 were classified as demyelinating. There were five cases of acute motor sensory axonal neuropathy, five cases of the Miller Fisher variant, one case of acute motor axonal neuropathy, and two cases that were not classified [13]. Another study indicated that most patients with GBS exhibited EDX features consistent with AIDP. Additionally, no difference was evident in the distribution of axonal versus demyelinating variants between SARS-CoV-2 and other viruses known to be associated with GBS. Notably, a comparison of 48 AIDP cases associated with COVID-19 and 49 control AIDP cases revealed that patients with COVID-19 were more likely to exhibit increased latency in distal compound muscle action potentials, and F waves were more frequently absent [14]. Consequently, EMG and NCV...
studies are useful in diagnosing GBS; however, neither COVID-19 infection nor the side effects of SARS-CoV-2 vaccination present a unique electrophysiological signature.

(2) Critical illness neuropathy or myopathy

The most common symptoms of SARS-CoV-2 infection are myalgias, followed by inflammatory myopathies and critical illness syndromes such as critical illness neuropathy or myopathy. These complications have been documented in the literature [4]. The first report of critical illness myopathy associated with severe COVID-19 revealed that individuals with severe cases of the disease often suffer from both critical illness myopathy and neuropathy [15]. Specifically, myopathy was detected in several patients with COVID-19 who were on mechanical ventilation, primarily through needle EMG findings that showed motor unit action potentials with low amplitude and short duration [16]. These patients were typically very ill and required extended stays in the intensive care unit. In the same study, critical illness neuropathy was found to be more prevalent among COVID-19 patients than among a control group without COVID-19 [17]. Notably, a study involving 12 non-ventilated COVID-19 patients found that half of them exhibited subclinical myopathy [18].

(3) Bell palsy

In a study of 20 individuals who tested positive for COVID-19, Gupta et al. [19] discovered that Bell palsy was the only significant neurological symptom to emerge shortly after infection, despite the lack of EDX testing of the facial nerve. The link between Bell palsy and the SARS-CoV-2 vaccine is currently a subject of debate. Some studies suggest no association between Bell palsy and the vaccine. These conclusions were based on clinical observations and did not incorporate EDX testing among the criteria for diagnosing Bell palsy [20]. To date, research has not identified any specific EDX criteria that can distinguish Bell palsy caused by SARS-CoV-2 from that caused by other factors. Consequently, future studies are required to determine the incidence and prognosis of Bell palsy, as well as to develop reliable electrophysiological methods for detecting facial palsy in patients with COVID-19.

(4) Myasthenia gravis

A case report documented a 21-year-old woman who became infected with the SARS-CoV-2 virus and subsequently developed MG. She had no previous history of autoimmune diseases and did not undergo EDX testing [21]. Additional reports have noted the exacerbation of symptoms in individuals with previously diagnosed MG following COVID-19 infection [22]. These observations are consistent with numerous prior instances where myasthenic crises or exacerbations were precipitated by an enhanced immune response, often occurring in the context of a recent infection. None of the studies in question used EDX testing as a criterion for inclusion or as a defining characteristic of their cases. Similarly, a single case report has described the onset of MG following vaccination against SARS-CoV-2 [23].

These authors did not highlight the EDX findings as especially remarkable; rather, they observed that repetitive nerve stimulation testing of the right orbicularis oculi muscle revealed a significant decremental response. In the case of Bell palsy, no specific EDX features are associated with MG precipitated by SARS-CoV-2, nor has a definitive connection been drawn between vaccination for this virus and the subsequent development of MG.

(5) Long COVID-19

Patients experiencing myalgias, chronic fatigue, persistent sensory abnormalities, and dysautonomia following acute COVID-19 have undergone EMG/NCV evaluation. In one study, 20 individuals with sensory symptoms following acute COVID-19 were assessed for neuropathy using quantitative EMG (qEMG) and NCV. On average, 210 days after contracting COVID-19, 55% of these patients (11 individuals) exhibited myopathic changes in one or more muscles on qEMG, despite the absence of electrophysiological signs of neuropathy. Among these patients, 73% reported myalgias, and all experienced fatigue. The authors of the study suggested that the fatigue observed in patients with prolonged COVID-19 could be attributed to myopathy [24]. Supporting this hypothesis, another study analyzed qEMG and muscle biopsy findings in 16 patients who experienced fatigue, myalgia, or weakness for up to 14 months following COVID-19. In this group, 75% displayed electromyographic evidence of myopathy, such as brief and low-amplitude motor unit action potentials, while all showed histopathological alterations, including inflammation, capillary damage, muscle fiber atrophy, and mitochondrial changes [25].

Evidence suggests that some patients exhibit small fiber involvement and dysautonomia, as indicated by skin biopsy results and autonomic function test findings.

(6) Post-vaccine complications

Regarding vaccination against SARS-CoV-2, the literature includes a solitary case report of dermatomyositis [26] and another of rhabdomyolysis [27]. However, neither of these studies provided EDX findings specifically associated with the SARS-CoV-2 vaccine, nor did they confirm a connection between the vaccine and these conditions in the medical literature. Separately,
GBS is a rare yet serious immune-mediated neurological disorder that affects the PNS. A previous extensive study on the epidemiology of GBS following vaccination indicated that the condition was more frequently observed in men and in individuals aged between 40 and 60 years, with an average age of 56.8 ± 16.1 years. The most common form identified was AIDP. Most patients responded well to treatment. Evidence suggests that the administration of vector vaccines for COVID-19 may increase the risk of developing GBS. The characteristics of GBS following vaccination were found to be consistent with those of GBS cases prior to the COVID-19 pandemic [28].

2) Evoked potentials

Evoked potential studies are commonly used to evaluate extensive myelinated pathways that originate in the PNS and extend through the CNS. A review of the scientific literature indicates that COVID-19 lacks specific evoked potential signatures. Nevertheless, evoked potentials across visual, auditory, somatosensory, and olfactory modalities have been used to investigate symptoms associated with COVID-19.

Visual evoked potentials (VEPs) are primarily utilized to identify lesions in the optic tract up to the chiasm, but they can also be employed to assess the entire visual pathway from the cornea to the occipital cortex. In a prior study, no significant differences were observed between 44 healthy controls and 76 patients who had recovered from COVID-19. This was the case even though 12 of the patients with COVID-19 exhibited delayed P100 latency, which may suggest subclinical damage to the anterior visual pathway [29]. Nevertheless, it seems that VEPs cannot be used to differentiate myelin dysfunction/demyelination caused by COVID-19 infection or vaccination from myelin dysfunction resulting from other CNS demyelinating diseases.

Vecchio et al. [30] examined brainstem auditory evoked responses (BAERs) among 10 patients experiencing difficulties weaning from mechanical ventilation. These authors observed increased delays between the interpeak III–V waves in four participants, suggesting lesions between the caudal pons and midbrain. This observation could support the hypothesis that the brainstem plays a role in severe cases of COVID-19 [30]. Netravathi et al. [31] evaluated 29 individuals with CNS demyelination following administration of the AstraZeneca replication-deficient adenoviral vector vaccine against COVID-19 (ChAdOx1-S) (n = 27) and Bharat Biotech COVAXIN vaccine against COVID-19 (BBV152) (n = 2) COVID-19 vaccines. Of these, seven patients underwent BAER testing, which yielded normal results. Overall, BAERs appear to be a relatively insensitive diagnostic tool for detecting demyelination related to immunization or probable COVID-19 infection.

Additionally, somatosensory evoked potentials can be used to detect abnormalities within the large fiber sensory pathways. However, no signature has been identified that is exclusive to COVID-19 or to demyelination events temporally associated with vaccination [10].

3) Autonomic function testing

Small fiber neuropathy (SFN) and dysautonomia have been found in a subset of long-term COVID-19 patients who present with peripheral sensory or autonomic symptoms, which often occur simultaneously. In a study conducted by Abrams et al. [32], skin biopsies were obtained from 13 individuals within 2 months following the onset of acute COVID-19 symptoms. These symptoms were considered mild for all but one of the participants. Among these individuals, seven reported autonomic symptoms. Six patients exhibited signs of SFN, and within this group, two also demonstrated evidence of autonomic dysfunction when subjected to autonomic function tests [32]. In a separate study, high incidence rates of SFN and dysautonomia were reported—89% and 100%, respectively—in a cohort of nine patients with long COVID-19. These patients reported symptoms such as fatigue, brain fog, and orthostatic intolerance [33].

One study focused on the results of autonomic function tests in 27 patients experiencing prolonged COVID-19 symptoms indicative of dysautonomia. Abnormal test results were observed in 63% of the participants. These abnormalities included issues with cardiovascular adrenergic function (7%), cardiac vagal response (27%), and the quantitative sudomotor axon reflex (36%). Additionally, 22% of the cases met the diagnostic criteria for postural orthostatic tachycardia syndrome. Notably, the majority of patients who self-reported symptoms of orthostatic hypotension did not exhibit any clinical signs of hypotension or postural tachycardia [34].

Conclusion

Numerous illnesses of the CNS and PNS, both acute and chronic, can be triggered by SARS-CoV-2. The bulk of research available suggests that the neurological symptoms associated with COVID-19 are more likely due to a parainfectious response rather than direct invasion of the nervous system. The electrophysiological profile that would uniquely identify SARS-CoV-2 as the cause of neurological issues is neither specific nor diagnostic. Nevertheless, EDX studies are the optimal approach for determining which areas of the nervous system are affected by SARS-CoV-2 or its associated parainfectious response. Disorders
that are suspected to relate to recent SARS-CoV-2 vaccination should be investigated using a similar strategy.

Neurophysiological methods can provide objective confirmation of a patient's reported symptoms and may therefore be useful in the evaluation of "long COVID-19." EDX studies are beneficial for assessing symptoms associated with COVID-19 or the side effects of the SARS-CoV-2 vaccine.

**Conflict of Interest**

Hyun Im Moon is an editorial board member of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts.

**ORCID**

Hyun Im Moon, https://orcid.org/0000-0003-3430-1824
Hee Kyu Kwon, https://orcid.org/0000-0002-6230-2907

**REFERENCES**


https://doi.org/10.18214/jend.2023.00143

https://doi.org/10.18214/jend.2023.00143