Focal Peripheral Neuropathies Observed in Patients Diagnosed With COVID-19

A Case Series

Eric A. Liu, DO, Tomas Salazar, MD, Elisa Chiu, DO, Talya K. Fleming, MD, Leslie Bagay, MD, David P. Brown, DO, and Sara J. Cuccurullo, MD

Abstract: A growing number of studies have documented a wide variety of neurological manifestations associated with the novel SARS-CoV-2 (COVID-19). Of the available literature, cranial neuropathies and central nervous system disorders, such as encephalopathy and ischemic strokes, remain the predominant discussion. Limited investigations exist examining peripheral neuropathies of those with COVID-19. This case series discusses eight patients who tested positive for COVID-19 and presented with localized weakness after a prolonged course of mechanical ventilation (>21 days). We retrospectively reviewed all patients' charts who received electrodiagnostic evaluation between March and November 2020 in the outpatient clinic or in the acute care hospital at the JFK Medical Center/JFK Johnson Rehabilitation Institute and Saint Peter's University Hospital of New Jersey. A total of eight COVID-19–positive patients were identified to have a clinical presentation of localized weakness after a prolonged course of mechanical ventilation. All patients were subsequently found to have a focal peripheral neuropathy of varying severity that was confirmed by electrodiagnostic testing. Patient demographics, clinical, and electrodiagnostic findings were documented. The findings of local weakness and focal peripheral neuropathies after diagnosis of COVID-19 raise significant questions regarding underlying pathophysiology and overall prognosis associated with COVID-19.

Key Words: Coronavirus Disease 2019 (COVID-19), Peripheral Nerve Injury, Neuropathy, Neurological Manifestations

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Originally identified late 2019 within Wuhan, China, the novel coronavirus was declared a pandemic by the World Health Organization on March 11, 2020.[1] Within the United States, approximately 44,000,000 cases and more than 700,000 deaths have been reported to date.[2]

Because of its novelty and widespread morbidity and mortality, the coronavirus disease of 2019, commonly known as COVID-19, has remained a significant challenge for health care professionals. Although primarily known to affect the respiratory system, there has been increasing evidence of neurological manifestations after COVID-19 infection. Clinical symptoms, such as cough and shortness of breath, have been further expanded to include fatigue, headache, nausea, vomiting, and anosmia, which suggests greater neural involvement.

A literature review of PubMed has supported this notion, demonstrating an emerging number of patients presenting with neurological disorders associated with COVID-19. Within the central nervous system, encephalopathy and encephalitis have been documented.[3,4] Case series are starting to identify younger and previously healthy patients presenting with ischemic strokes, a possible complication attributed to the hypercoagulable and prothrombotic states commonly found with COVID-19.[5,6] Peripherally, cranial neuropathies such as olfactory and gustatory nerve dysfunction have been frequently cited.[7,8] There have also been growing number of case reports and case series of Guillain-Barré syndrome and polyneuropathies in those positive for COVID-19.[3,9–11]

Several mechanisms have been proposed to explain this phenomenon in the setting of COVID-19. Similar to Guillain-Barré syndrome and other viral diseases, SARS-CoV-2 infection may illicit a postinfectious inflammatory neuropathy via immune-mediated processes.[12] Neuropathies can also occur as a consequence of extended COVID-19 hospitalization. Profoundly ill patients in the intensive care unit (ICU) are more likely to develop critical illness neuropathy due to sepsis and systemic inflammatory response syndrome.[13,14] Finally, prolonged periods on mechanical ventilation in the ICU and proning therapy can lead to increased risk for developing entrapment neuropathies.[15]

The aim of this case series is to examine and discuss eight patients who were hospitalized after COVID-19 infection and subsequently found to have a focal peripheral nerve injury on electrodiagnostic testing.

METHODS

This study was conducted at the JFK Medical Center, JFK Johnson Rehabilitation Institute, and Saint Peter's University Hospital of New Jersey. We performed a retrospective review of all patients' charts who received electrodiagnostic evaluation from March to November 2020 in the outpatient clinic or acute care hospital. Nerve conduction studies (NCSs) and electromyography (EMG) results of more than 500 patients were

From the Department of Physical Medicine and Rehabilitation, JFK Johnson Rehabilitation Institute, Rutgers Robert Wood Johnson Medical School, Hackensack Meridian School of Medicine, Edison, New Jersey.

All correspondence should be addressed to: Eric A. Liu, DO, JFK Johnson Rehabilitation Institute, 65 James St, Edison, NJ 08820.

All cases submitted in this manuscript are original. Verbal informed consent was obtained from the patients for their information to be published under anonymity.

Eric A. Liu, Tomas Salazar, and Elisa Chiu are in training.

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reviewed to identify cases of focal peripheral neuropathies after a COVID-19 diagnosis. Inclusion criteria also included patients with a prolonged course of mechanical ventilation (greater than 21 consecutive days of mechanical ventilation for more than 6 hrs/d as defined by the National Association for Medical Direction of Respiratory Care).[16] Patients' charts with an uncertain COVID-19 status were excluded. Eight patients were found to have a focal peripheral neuropathy confirmed by NCSs and EMG with a preceding diagnosis of COVID-19. For the group of eight patients, data were gathered including demographics, medical comorbidities, and hospital course details. Specifically, key clinical details were identified as length of hospitalization, duration of mechanical ventilation, and whether prone positioning was used. The physical examination objective measure of muscle strength, based on the Medical Research Council Grading Scale, was also recorded to ensure EMG findings correlated appropriately. Considering the timeline of Wallerian degeneration and that findings such as fibrillations and positive waves may take 10–14 days after injury to be detected,[17] electrodiagnostic testing was done at least 2 wks after detection of weakness to minimize the chance of misleading results. Last, institutional review board approval was not obtained as all care was performed to the standard medical practice and that these patterns were then noticed retrospectively. All eight patients included in this study did provide informed consent. This study conforms to all CARE guidlines (for CAse REports) and reports the required information accordingly (see Supplementary Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B434).

RESULTS

Case 1: Right Femoral Neuropathy

A 73-yr-old Asian man with a history of hypertension and type 2 diabetes mellitus was mechanically ventilated because of COVID-19 pneumonia for 23 days without the use of prone therapy. After extubation, the patient complained about right leg weakness with associated burning and tingling. Physical examination was notable for right hip flexion and knee extension weakness but strength intact distally. There was sensory impairment in the right L2-L3 dermatome distribution. Patellar and Achilles reflexes were diminished bilaterally. Laboratory results were negative for coagulopathy. A1c was 11.9. Because of the patient's positive COVID-19 status, imaging was not able to be performed. Electromyography showed fibrillations and positive sharp waves (PSWs) in the right rectus femoris, vastus lateralis, vastus medialis, and iliopsoas; no motor units were seen firing in the femoral nerve innervated muscles. He was diagnosed with right femoral neuropathy.

Case 2: Bilateral Sciatic Neuropathy

A 46-yr-old Asian man with a history of morbid obesity underwent mechanical ventilation for COVID-19 pneumonia for 59 days without the use of prone positioning. Examination was notable for bilateral knee flexion and ankle dorsiflexion weakness, impaired sensation to light touch in a glove and stocking pattern, and impaired proprioception in the bilateral lower limbs. Strength was intact in the upper limbs. Imaging of the brain, abdomen/pelvis, and lower limbs were negative. Nerve conduction studies showed absent left sural and bilateral superficial fibular sensory nerve action potentials, absent bilateral fibular motor responses, absent left tibial motor response, and reduced compound muscle action potential (CMAP) amplitude of the right tibial motor response. Electromyography showed fibrillations, PSWs, and polyphasic potentials in the bilateral tibialis anterior (TA), peroneus longus (PL), gastrocnemius medial head, gastrocnemius lateral head, biceps femoris long head (BFLH), and biceps femoris short head with left worse than right. There was distal reinnervation bilaterally with decreased recruitment except in the left TA. Myopathic findings were not observed. The patient was diagnosed with bilateral sciatic neuropathy.

Case 3: Bilateral Sciatic Neuropathy

A 40-yr-old Hispanic man with a history of morbid obesity, hyperlipidemia, and type 2 diabetes mellitus was mechanically ventilated for COVID-19 pneumonia for 60 days with prone therapy. Examination was notable for bilateral knee flexion and ankle dorsiflexion weakness and impaired sensation in a stocking pattern. Strength was intact in the upper limbs. Electromyography demonstrated fibrillations and PSWs in the bilateral TA, PL, gastrocnemius medial head, extensor digitorum longus, and BFLH. No motor units were seen firing in the muscles innervated by the sciatic nerve. Myopathic findings were not observed. He was diagnosed with likely bilateral sciatic neuropathy, with the caveat that bilateral sacral plexopathy was unable to be completely excluded.

Case 4: Right Lumbar Plexopathy

A 70-yr-old Asian woman with a history of hypertension and hyperlipidemia was mechanically ventilated for COVID-19 pneumonia for more than 44 days with prone therapy used. She was found to have right hip flexion, knee extension, and ankle dorsiflexion and plantarflexion weakness. Imaging of the abdomen/pelvis was negative for retroperitoneal hemorrhage or mass. Nerve conduction studies showed an absent right sural sensory response and decreased CMAP amplitudes of the right fibular and tibial motor responses. Electromyography showed fibrillations, PSWs, and polyphasic waves in the right TA, PL, vastus lateralis, rectus femoris, BFLH, and biceps femoris short head. Lumbar paraspinals were normal, whereas there was decreased recruitment in the lumbar plexus innervated muscles. She was diagnosed with a right lumbar plexopathy.

Case 5: Left Incomplete Radial Neuropathy Distal to the Innervation of the Triceps

A 66-yr-old White woman with a history of obesity and anxiety underwent mechanical ventilation for COVID-19 pneumonia for at least 29 days with the use of prone therapy. She had left wrist and finger extension weakness on examination. Nerve conduction studies showed an absent left radial sensory response with a reduced CMAP at the forearm, elbow, and below spiral groove sites. Sensory nerve action potentials and CMAPs of the median and ulnar nerves were normal. Electromyography revealed fibrillations and PSWs in the left extensor carpi radialis longus, extensor carpi ulnaris, extensor digitorum communis, and extensor indicis proprius. There was evidence of an incomplete

left radial neuropathy distal to the innervation of the triceps with reinnervation to the brachioradialis, extensor carpi radialis longus, and extensor digitorum communis.

Case 6: Left Fibular Neuropathy at the Fibular Head

A 74-yr-old White man with COVID-19 pneumonia was mechanically ventilated for 43 days without prone therapy. Examination was notable for left ankle dorsiflexion weakness. Nerve conduction studies showed absent bilateral sural sensory responses and decreased fibular-extensor digitorum brevis and fibular-TA CMAPs above the fibular head. There was also decreased amplitudes and slowing of the bilateral tibial motor responses. Electromyography showed fibrillations of the left TA with decreased recruitment in the TA and fibularis longus. Myopathic findings were not observed. He was diagnosed with a left fibular neuropathy at the fibular head superimposed on a generalized peripheral lower limb polyneuropathy.

Case 7: Right Incomplete Fibular Neuropathy at the Fibular Head

A 64-yr-old Hispanic man with a history of hypertension, hyperlipidemia, type 2 diabetes mellitus, and asthma was mechanically ventilated for 23 days because of COVID-19 pneumonia. Prone therapy was used. He was found to have right ankle dorsiflexion weakness. Electromyography demonstrated fibrillations and PSWs in the right TA, with decreased recruitment in the right TA and PL. He was diagnosed with an incomplete right fibular neuropathy at the fibular head.

Case 8: Right Incomplete Fibular Neuropathy at the Fibular Head

A 48-yr-old Asian man with a history of hypertension, diabetes, and asthma was mechanically ventilated for 63 days because of COVID-19 pneumonia without the use of prone therapy. He developed right ankle dorsiflexion weakness. Electromyography showed fibrillations and PSWs in the right TA and PL. He was diagnosed with an incomplete right common fibular neuropathy at the fibular head.

Patient characteristics and clinical course were analyzed (Table 1). The mean age among the identified patients was 60.13 yrs, and most patients were male (75%). Of the eight peripheral neuropathies identified, the majority were located in the lower limb (87.5%) and were primarily unilateral (75%).

DISCUSSION

The pathophysiology has yet to be fully understood and current literature remains sparse regarding COVID-19–related peripheral neuropathies. Several theories have been postulated. Initial investigations have identified the SARS-CoV-2 high affinity for the angiotensin-converting enzyme 2 receptor and neuroinvasion via the olfactory tracts as responsible for central nervous system manifestations.[18,19] In contrast, progression of peripheral neuropathies may be more immune mediated. Through shared sequences with human shock proteins, SARS-CoV-2 infection may illicit autoantibody formation and nerve insult by mechanism of molecular mimicry.[12] This idea has been linked more closely to Guillain-Barré syndrome and may not be applicable to other types of peripheral neuropathies.

Comorbidities such as diabetes mellitus, hypertension, obesity[20] and hyperlipidemia[21] have been well established to cause neuropathy via multiple mechanisms. Inflammatory pathways, oxidative stress, and ischemia[22] can provoke neural injury. Unsurprisingly, almost all patients in this study had a history of multiple underlying conditions including one who had findings of a chronic neuropathy but was undiagnosed at the time. Considering the numerous comorbidities and advanced age, these certainly could explain the patients' increased susceptibility for developing peripheral nerve injuries. Adding to this risk, the presence of these comorbidities has been linked with a greater severity of COVID-19 infection, and consequently, a greater likelihood of prolonged mechanical ventilation and ICU care, which is discussed later in the article.[23,24]

This process may be most evident in case 1 with the patient presenting with a right femoral neuropathy. Anterior thigh pain, sensory disturbances along the L2-L3 dermatomes, and right hip flexion and knee extension weakness are typical signs and symptoms seen in diabetic amyotrophy, or diabetic lumbosacral radiculoplexus neuropathy. However, it is difficult to definitively attribute the presentation as diabetic lumbosacral radiculoplexus neuropathy. Although the patient did have poorly controlled diabetes with a significantly elevated A1c, the risk of developing diabetic lumbosacral radiculoplexus neuropathy has no relation to the length or severity of glycemic dysregulation. No observable atrophy was noted in the affected limb, another sign typically seen in those with diabetic lumbosacral radiculoplexus neuropathy. Furthermore, although proximal involvement often predominates early, there will still be distal weakness later in the disease course with foot drop being a common consequence.[25,26] As highlighted earlier in case 1, this patient had no clinical or electrodiagnostic findings distally.

Other reports have examined patients with severe COVID-19 illness requiring ICU stays and were found to have critical illness polyneuropathy.[27] Critical illness polyneuropathy is an axonal sensory and motor polyneuropathy, which may develop in acutely ill patients, such as those in the ICU. Many of these patients experience systemic inflammatory response syndrome, and this is suspected to contribute to the development of this polyneuropathy.[13] Commonly diagnosed in patients with symmetric and flaccid paralysis, 25%–45% of patients admitted to the ICU are diagnosed with critical illness polyneuropathy or myopathy.[14] Although studies are documenting findings of critical illness polyneuropathy in patients with severe illness due to COVID-19, it is not yet known whether the causes are exactly the same.[10,11] In addition, because of the novel nature of the SARS-CoV-2 virus, the rate of peripheral neuropathy has yet to be determined for a population similar to the subjects represented in this case series.

Substantial attention has been given to improper patient positioning as a contributor to nerve injuries, especially in the perioperative period.[28,29] Greater awareness in conjunction with optimal positioning techniques has decreased the overall incidence of perioperative peripheral nerve injuries to 0.03%.[28] This concept of patient malpositioning has been well documented in the ICU as the risk of sustaining a compression neuropathy increases with prolonged immobilization, generalized anesthesia, neuromuscular blocking agents, and malpositioning.[15] Radial neuropathies typically occur because of direct compression at the spiral groove of the humerus when the arm is abducted

TABLE 1. Characteristics of eight COVID-19–positive patients diagnosed with focal neuropathy on electrodiagnostic testing

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, yr	73	46	40	70	66	74	64	48
Sex	M	M	M	F	F	M	M	M
Race/ethnicity	Asian	Asian	Hispanic	Asian	White	White	Hispanic	Asian
BMI	22.1	50.3	63.8	26.8	34.7	23.3	32.0	23.8
Medical comorbidities	HTN, DMII	Morbid obesity	Morbid obesity, HLD, DMII	HTN, HLD	Obesity, Anxiety	None	HTN, HLD, DMII, Asthma	HTN, DMII, Asthma
Length of stay, d	37	72	74	50	32	45	36	80
Duration of mechanical ventilation, d	23	59	60	>44	>29	43	23	63
Prone therapy	No	No	Yes	Yes	Yes	No	Yes	No
Time between COVID-19 infection and onset of clinical symptoms, d	44	31	72	≈ 69	≈ 43	≈ 70	80	84
Time between clinical symptoms and initial EDX testing, d	30	98	24	≈ 18	≈ 42	≈ 39	72	43
Main objective findings—Medical Research Council Grading Scale for Muscle Strength	Right–hip flexion 0/5, knee extension 0/5	Bilateral–knee flexion 0/5, dorsiflexion 0/5	Bilateral–knee flexion 1/5, dorsiflexion 0/5	Right–hip flexion 3/5, knee extension 2/5, ankle dorsiflexion 1/5, plantarflexion 4/5	Left–elbow extension 5/5, wrist and finger extension 1/5	Left–dorsiflexion 1/5	Right–dorsiflexion 1/5	Right–dorsiflexion 1/5
Working diagnosis	Right femoral nerve injury	Bilateral sciatic nerve injury	Bilateral sciatic nerve injury	Right lumbar plexus injury	Left radial nerve injury	Left fibular nerve injury	Right fibular nerve injury	Right fibular nerve injury
Location of fibrillations and PSWs on EMG	Right RF, VL, VM, and IP	Bilateral TA, FL, GMH, GLH, BFLH, BFSH, left worse than right.	Bilateral TA, FL, GMH, EDL, BFLH.	Right TA, FL, VL, RF, BFLH, BFSH.	Left ECRL, ECU, EDC, and EIP.	Left TA	Right TA	Right TA and FL
Other pertinent EMG findings	No motor units seen firing in the femoral nerve innervated muscles	Reinnervation noted distally bilaterally with the exception of no motor units seen firing in the left TA	No motor units seen firing in the sciatic nerve innervated muscles. Bilateral sacral plexopathy cannot be totally excluded	Lumbar paraspinals showed normal activity. Decreased recruitment in the lumbar plexus innervated muscles	Reinnervation noted to the BR, ECR, and EDC	Findings are consistent with a left fibular neuropathy at the fibular head on a superimposed generalized peripheral lower polyneuropathy	Decreased recruitment in the right TA and FL	Evidence of a severe incomplete right common fibular neuropathy at the fibular head

BFSH, biceps femoris short head; BR, brachioradialis; DMII, diabetes mellitus type 2; ECRL, extensor carpi radialis longus; ECU, extensor carpi ulnaris; EDC, extensor digitorum communis; EDL, extensor digitorum longus; EIP, extensor indicis proprius; EDX, electrodiagnostic testing; F, female; FL, fibularis longus; GLH, gastrocnemius lateral head; GMH, gastrocnemius medial head; HLD, hyperlipidemia; HTN, hypertension; IP, iliopsoas; M, male; RF, rectus femoris; TA, tibialis anterior; VL, vastus lateralis; VM, vastus medialis.

and pushed against a hard surface.[30] Common fibular neuropathies occur because of direct compression at the fibular head when the leg is externally rotated or when the patient is placed in a lateral decubitus position. Both femoral and sciatic compression neuropathies are rare in the literature but have been documented as a postsurgical complication from intraoperative positioning. Femoral compression neuropathies are thought to occur when the legs are abducted and externally rotated, such as in a lithotomy position. This extreme positioning subjects the femoral nerve to severe angulation and compression beneath the inguinal ligament.[31] Femoral nerve compression can also occur more proximally because of compression in the retroperitoneal space, such as from a retroperitoneal or intramuscular hematoma.[32] COVID-19 patients admitted to the ICU may be particularly susceptible to hematoma formation because of ongoing coagulopathy, anticoagulation management, or need for vascular/interventional access via the femoral vessels. Finally, sciatic nerve compression commonly occurs as it exits the greater sciatic foramen. Entrapment of the sciatic nerve can develop secondary to lithotomy positioning, but it can also occur from compression between a hard surface and the ischial tuberosity when in semilateral position.[31]

Interestingly, several case series have speculated an association between prone positioning for management of COVID-related acute respiratory distress syndrome and peripheral nerve injuries. Prone positioning has been overwhelmingly used as a technique to improve oxygenation in patients severely affected by COVID-19 requiring intensive care. Malik et al.[33] found that a significant majority (83.3%) of their patients who were identified with a focal neuropathy had a history of at least one prone positioning session in the acute care hospital. Chang et al.[34] presented patients who presented with unilateral ankle dorsiflexion weakness to their acute rehabilitation facility were all managed with ICU proned ventilation. Finally, Brugliera et al.[15] described a variety of peripheral nerve injuries in patients after extended prone position ventilation. By comparison, only half of the patients in this series were found to have records of prone therapy during acute hospital management. An important caveat to note would be the limited sample sizes with the above studies, analyzing a total of 12, 5, and 7 patients, respectively. Furthermore, some of the patients discussed in this case series exhibited neuropathies that are difficult to explain from prone positioning or prolonged immobilization alone. Sciatic neuropathies and lumbar plexopathies have not been associated with prone positioning in the literature and seem difficult to explain by positioning alone. Hence, it is likely premature to postulate prone positioning as the sole cause of COVID-related peripheral neuropathies and further investigation may be warranted.

Prognosis after nerve injury will be a significant topic to address within the physiatry field. Three patients (patients 1, 3, and 8) were able to follow up in the outpatient clinic for repeat electrodiagnostic testing. All electrodiagnostic testing was done approximately 3 mos after the initial test. Of the three, all showed moderate to significant improvement clinically (at least a two-grade increase on muscle strength examination) and in self-reported activities of daily living. This progress translated well to improvements on EMG with motor units seen firing in muscles that showed no units firing on previous examination. Considering all three patients had a strong desire to return to driving, this improvement carried significant weight in their overall quality of life. As further data emerges, it will be intriguing to see whether patients diagnosed with focal neuropathies after COVID infection will have similar rates of recovery.

CONCLUSIONS

A growing number of reports have revealed a wide array of neurological injuries after COVID-19 infection in hospitalized patients. This has added not only to the challenges presented to health care providers but also to the overall burden of disability for patients. With the emergence of COVID-19 rehabilitation aftercare programs, evidence-based guidelines will need to be established that fully identify and target secondary comorbidities such as peripheral nerve injuries to better use treatment strategies within a rehabilitation framework. This case series highlights focal peripheral neuropathies as another neurological manifestation associated with COVID-19.

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