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Upper Extremity Neuropathies Following Severe COVID-19 Infection: A Multicenter Case Series

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■ OBJECTIVE: **The purpose of the study is to examine presentation, injury patterns, and clinical course, for COVID-19-related peripheral nerve injury following mechanical ventilation.**

■ METHODS: **A multicenter retrospective study of patients with COVID-19 complicated by acute respiratory distress syndrome (ARDS) that required mechanical ventilation was undertaken. Patient records were reviewed for intensive care unit and intubation characteristics, prone or lateral decubitus positioning, and the onset of neuropathy diagnosis.**

■ RESULTS: **Between September 2020 and January 2022, 11 patients were diagnosed with peripheral neuropathy, including 9 with brachial plexopathy following COVID-19 infection. Each patient developed ARDS requiring mechanical ventilation for a median of 39 days. Six patients (54.5%) underwent prone positioning and 1 lateral decubitus. Neuropathies involved 5 brachial pan-plexopathies, 2 incomplete brachial plexopathies, 2 lower trunk plexopathies, 1 radial neuropathy, and 1 bilateral ulnar neuropathy. At a mean follow-up of 10.2 months, patients with brachial pan-plexopathies demonstrated signs of reinnervation proximally, and 1 resolved to a radial mononeuropathy; however, the majority have demonstrated minimal clinical improvements.**

■ CONCLUSIONS: **Our series demonstrates that peripheral neuropathies and especially brachial plexopathies have occurred following mechanical ventilation for ARDS-related COVID-19 infections. Contrary to prior COVID-19 studies, only 54.5% of these patients underwent prone positioning. Aside from a traumatic disturbance of prone positioning, the increased incidence of neuropathy may involve an atraumatic effect of COVID-19 via direct invasion of nerves, autoantibody targeting of nervous tissue, or hypercoagulation-induced microthrombotic angiopathy.**

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (Sars-CoV2) has presented unprecedented challenges to healthcare around the world. At the time of writing (April 24, 2022), there have been nearly 506 million confirmed cases of COVID-19, with 6.2 million deaths worldwide. Upon infection, the virus invades the respiratory mucosa, penetrating intracellularly and potentially inducing a cytokine storm.[1] About a third of patients with COVID-19 progress to acute respiratory distress syndrome (ARDS), and 26% of COVID-19 patients require transfer to an intensive care unit (ICU).[2-4] Experience with ARDS over the past 20 years has noted improved oxygenation and increased survival with prone

Key words
- Acute respiratory distress syndrome
- Brachial plexus
- COVID-19
- Prone positioning
- Upper extremity neuropathy

Abbreviations and Acronyms
ARDS: Acute respiratory distress syndrome
COVID-19: Coronavirus Disease 2019
ICU: Intensive care unit
Lateral: Lateral Decubitus Positioning
Prone: Prone Positioning
Sars-CoV2: Severe acute respiratory syndrome coronavirus 2

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positioning.[3,5] These studies have further noted that a minimum of 16 hours in the prone position is ideal to obtain a survival benefit.[5,6] From the initial randomized controlled trial of Prone Positioning in ARDS (ProSEVA), complications of prone positioning have been centered around pressure necrosis of the skin, followed by instances of unscheduled extubation, and endotracheal tube obstruction.[5] However, over the course of the COVID-19 pandemic, patients with COVID-19 placed in the prone position have demonstrated acute peripheral neuropathy conditions with a higher-than-expected prevalence of upper extremity peripheral neuropathies.[3,7,8]

The increase in the presentation of COVID-19 ICU-related upper extremity neuropathy, especially pan-brachial plexopathies, could potentially be related to the sheer volume of ICU-ARDS admission necessitating prone positioning. Nonetheless, it remains unknown whether there is a direct or indirect effect of the Sars-CoV2 on peripheral nerves rendering them vulnerable to injury or if there is an inflammatory or vascular pathway that is associated with severe infection that predisposes peripheral nerves to injury. To offer additional insight into these previously uncommon complications, the purpose of this multicenter, retrospective study was to examine presentation, injury patterns, and clinical course for COVID-19-related peripheral nerve injury following mechanical ventilation.

METHODS

This study was a multicenter retrospective review of patients following Institutional Review Board approval at Mayo Clinic in Minnesota (Rochester), Mayo Clinic in Florida (Jacksonville), Shirley Ryan AbilityLab, and Northwestern Memorial Hospital in Illinois (Chicago). Patients were identified by a review of each institution's peripheral nerve/brachial plexus clinic database. Inclusion criteria for analysis were patients older than 18 years, COVID-19 infection, and concern of brachial plexopathy on initial referral following treatment of severe COVID-19 infection requiring ICU level of care with mechanical ventilation. Exclusion criteria involved patients less than 18 years of age, COVID-19 infection that did not require ICU level of care, no electrodiagnostic studies, no previous peripheral nerve injury, and no evaluation by a peripheral nerve/brachial plexus specialist. For patients from the Shirley Ryan AbilityLab and Northwestern cohort, cases were reviewed after April 1, 2021, with some cases being excluded due to prior publication.[9]

Patient demographics, hand dominance, as well as comorbidities, including obesity, lung disease, diabetes, and tobacco use, were reviewed from the electronic medical record. Each patient was hospitalized for COVID-19 at institutions separate from the study centers. Inpatient records were obtained from these hospitals to confirm the timing of infection, progression to ARDS, length of intubation, institution of altered positioning such as prone or lateral decubitus, and timing to diagnosis of peripheral neuropathy or brachial plexopathy. When available from outside records, clinical findings, imaging, and electrodiagnostic studies were reviewed for initial analysis and working diagnosis.

Upon being seen at one of the study centers, each patient was evaluated by a peripheral nerve/brachial plexus specialist. Time from diagnosis to specialist evaluation, clinical exam findings, advanced imaging, electrodiagnostic findings, and diagnoses were reviewed. Treatment plans and, when available, follow-up encounters to understand clinical progression were reviewed.

Statistical Analysis

Continuous and categorical variables were reported with means, standard deviations, ranges, frequencies, and percentages. Descriptive statistics were performed by GraphPad Prism 9 (San Diego, California).

RESULTS

Demographics and COVID-19 Management

Between September 2020 and January 2022, 11 patients were diagnosed with upper extremity neuropathy following severe COVID-19 infection. The mean age of these patients was 48.7 (±12.9, range 27–68), with 9 males (81.8%). The mean body mass index was 33.8 (±7.14), with 6 patients (54.5%) considered obese with a body mass index ≥30. Seven patients (63.6%) had dominant hand-sided injuries. All patients progressed to ARDS and required mechanical ventilation, with 6 (54.5%) undergoing prone positioning for ARDS and 1 with lateral decubitus positioning (Table 1). The median length of intubation was 39 days (range 18–60 days).

Initial Diagnosis and Work-Up of Peripheral Neuropathy Prior to Referral

Initial diagnosis of peripheral nerve injury/brachial plexus injury was recognized when patients had the inability to utilize 1 or both upper extremities after being extubated. The mean time from infection to the diagnosis of neuropathy was 2.82 months (±2.04, range 1–7 months). Of the 11 patients, 5 demonstrated brachial pan-plexopathies, 2 demonstrated incomplete brachial plexopathies, 2 demonstrated lower trunk plexopathies, 1 had radial mononeuropathy, and 1 with bilateral ulnar neuropathies (Table 2). Of the 5 patients with brachial pan-plexopathy, 2 had deficits in both upper extremities. The patient who developed radial mononeuropathy was placed in lateral decubitus positioning (patient no. 10 in Table 3).

One patient (patient no. 3 in Table 3) with a brachial pan-plexopathy underwent magnetic resonance imaging (MRI) at an outside facility soon after demonstrating weakness, which found thickening and enhancements of roots and trunks of the brachial plexus consistent with brachial plexitis (Figure 1. Another patient (patient No. 2 in Table 3) obtained an electrodiagnostic study shortly after diagnosis, demonstrating a severe brachial pan-plexopathy. It was further notable that patients with incomplete, lower trunk or pan-plexopathies endorsed severe neuropathic pain.

Follow-Up and Outcomes of Patients with Neuropathy Following COVID-19 Treatment

The mean time from injury to specialist evaluation was 9.5 months (±6.96 months, range 3–28 months). Patient No. 5 (Table 3), who developed bilateral brachial pan-plexopathy, had MRI on follow-up at 9 months that demonstrated diffuse enhancement and thickening of the left brachial plexus (Figure 1). Patient No. 2 and patient no. 3 both with brachial pan-plexopathy (Table 3) each

Table 1. Patient Demographics and Intubation Characteristics

Total Patients	11
Mean Age, SD, range (years)	48.7, 12.9, 27—68
Gender	
Male (%)	9 (81.8)
Female	2 (18.2)
BMI (mean, SD range)	33.8, 7.14, 26.6—46.7
Obesity (%)	6 (54.5)
Diabetes (%)	4 (36.3)
Dominant sided injury (%)	7 (63.6)
ARDS (%)	11 (100)
Intubation for COVID-19	11 (100)
Length of intubation, days (median range)	39, 18—60
Intubation positioning	
Supine	4 (36.3)
Lateral decubitus (%)	1 (9.09)
Prone positioning (%)	6 (54.5)

ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, Coronavirus Disease 2019.

Table 2. Peripheral Neuropathy Diagnosis at Time of COVID-19 Treatment

Peripheral Nerve Complication	Number of Patients (and Percent of Cases)
Brachial pan-plexopathy	5 (45.5)
Unilateral	3
Bilateral	2
Incomplete brachial plexopathy	2 (18.2)
Unilateral	1
Bilateral	1
Lower trunk plexopathy (%)	2 (18.2)
Radial mononeuropathy (%)	1 (9.1)
Ulnar neuropathy (%)	1 (9.1)
Neuropathic pain (%)	9 (81.8)

Time from Infection to Diagnosis of Nerve Injury:mean 2.82, SD 2.82, 2.04, range (mo) 1—7.

received MRI evaluations at 6 months which noted asymmetric atrophy of the affected shoulder and chest wall muscles in varying nerve distributions (Figure 2). Concomitant electrodiagnostic studies from 6 months to 12 months noted a patchy distribution of pathology in patients with severe brachial pan-plexopathy as well as lower trunk plexopathy (Table 3, Patients 1, 2, 4, 5, 9). Patients with incomplete and lower trunk plexopathies demonstrated variable involvement of the plexus at the trunk, cord, and branch levels on electrodiagnostic studies (Table 3, Patients 6, 7, 8, 9).

The mean follow-up was 10.2 months (±6.79 months). The resolution of plexopathies and neuropathies has been variable. Patients with brachial pan-plexopathy have shown gradual improvement in function, starting proximally with shoulder function followed by elbow flexion (Table 3, Patient No. 1, 2, 3). Patient No. 4 demonstrated resolution of initial bilateral brachial pan-plexopathy, which resolved to a right radial mononeuropathy at 3 months. Patient No. 11 with initial bilateral ulnar neuropathy resolved on the left side at 6 months, but continued on the right side, currently scheduled for cubital tunnel release. Treatment of these patients have involved nonoperative measures that include hand therapy, splinting, as well as continued follow-up. A discussion with each has ensued regarding the role of nerve transfers, tendon transfers, selected joint fusions, and other potential surgical interventions.

DISCUSSION

Recognizing and understanding the sequelae of COVID-19 infection to assist with treatment modalities is imperative as the world continues to recover from this pandemic. This study presents 11 cases of peripheral neurologic complications, with 9 involving the brachial plexus that each occurred during the treatment of COVID-19 infection. Each patient in this series progressed to ARDS, requiring prolonged intubation and, for 54.5% of cases, prone position mechanical ventilation. Notably, patients with complete/partial brachial plexopathy were not all placed in the prone position. This finding gives credence to the hypothesis that there is a multifactorial compromise of the peripheral nerves secondary to a hyperinflammatory environment imposed by the viral infection, prolonged ICU courses, as well as patient comorbidities (e.g. diabetes, obesity, and age) that causes these nerves to be vulnerable to injury.

Prior to COVID-19, ICU-induced peripheral neuropathy, especially involving the brachial plexus, was not commonly reported. Of the few studies available, 1 by Goettler et al. from 2002, details brachial plexopathy in a case series of 2 patients, both associated with prone positioning in the ICU.[10] Aside from the ICU, prone positioning during spine surgery has also been described as a risk factor for brachial plexopathy.[11,12] However, within the short period of COVID-19 literature, there have been several reports of patients developing brachial plexopathy following prone positioning (Table 4). Douglas et al. studied 61 COVID-19 patients treated in the prone position for severe ARDS, finding 5 brachial plexopathies (8.2%), noting an unclear determination of whether this was due to the virus, prone positioning, or the critical illness itself.[13] Miller et al. identified 15 COVID-19 patients and 30 limbs with peripheral nerve injuries following prone positioning in the ICU, finding the most common injury being to the ulnar nerve.[14] Malik et al. reviewed 12 patients with 21 peripheral nerve injury sites, a majority being in the upper extremity.[7] High rate of neurologic injury was found at the ulnar nerve in 6 cases and the brachial plexus in 2 cases.[7] Authors of these studies do recognize the high rate of injury may be multifactorial rather

Table 3. Outcomes of Patients with Peripheral Neuropathy Following COVID-19 Infection

Patient No.	Age Gender	Neurologic Injury	Positioning	Diagnosis to Specialist Evaluation (mo)	Follow-Up (mo)	Magnetic Resonance Imaging	Electrodiagnostic Studies	Clinical Course
1	44F	Brachial pan-plexopathy	Prone	12	3		Diffuse brachial plexopathy with greatest involvement of lower trunk	
2					12		Chronic patchy pan-brachial plexopathy, most affecting ulnar nerve innervated muscles	Improvement in shoulder and elbow function, poor hand function, continued dysesthesias to fingertips
2	57M	Brachial pan-plexopathy	Supine	7	2		Severe brachial pan-plexopathy	Minimal shoulder function
4					6	Asymmetric decrease bulk of multiple muscles around left chest wall and shoulder in varying nerve distributions with chronic denervation changes.	Fibrillation potentials in a patchy distribution, severe left brachial pan-plexopathy	Shoulder abduction with deltoid 3/5
5					12		Severe diffuse brachial plexopathy, interval reinnervation of proximal muscles	Deltoid 4+, Biceps/ Brachialis 1/5, Triceps 2/5
3	37M	Brachial pan-plexopathy	Prone	6	1	Thickening and enhancements of roots and trunks consistent with brachial plexitis, no structural abnormality		
7	68M	Incomplete bilateral brachial plexopathy	Supine	12	12		Incomplete bilateral brachial pan-plexopathy affecting posterior cord and median and ulnar nerves	
8	27F	Lower trunk plexopathy	Supine	12	12		Lower trunk plexopathy	
9	53M	Lower trunk plexopathy	Prone	4	4		Patchy lower trunk plexopathy affected median, posterior interosseous, and ulnar nerves	
10	44M	Radial mononeuropathy	Lateral Decubitus	3	3		Severe right radial mononeuropathy arising proximal to branch of triceps with some reinnervation to the triceps	No finger or wrist extension
11	59M	Bilateral ulnar neuropathy resolved on left side after 6 months, persistent on right	Supine	28	28	Normal caliber and signal intensity of the right ulnar nerve	Right severe ulnar neuropathy at or about the elbow	Dense numbness and wasting of right hand

than solely position-related as their cohort demonstrates high rates of diabetes, obesity, and advanced age, which are factors for both severe COVID-19 infection as well as peripheral neuropathy.[3,17,18]

Consistent with our series of brachial plexopathy patients, the evidence against prone positioning alone was reported by Michaelson et al., where only 1 of 4 cases of brachial plexopathy was positioned prone.[19] Patients with brachial plexopathy in their

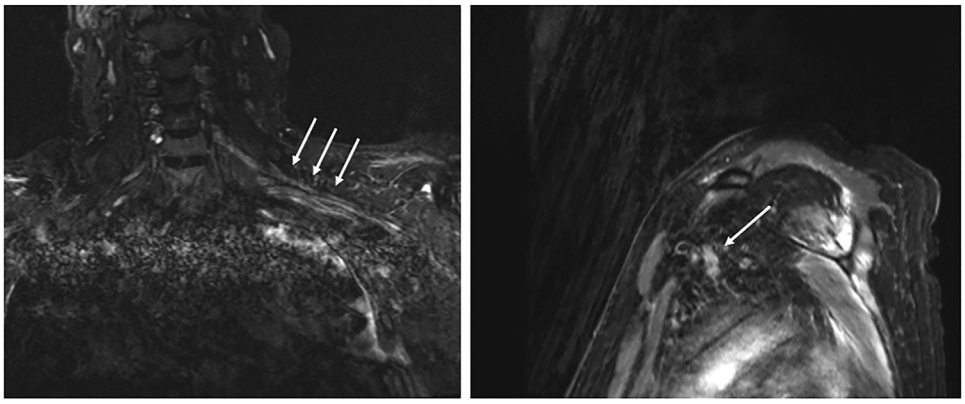

Figure 1. MRI of 46 year old male with 9 month history of bilateral brachial pan-plexopathy following COVID-19 infection with protracted hospital course including management in prone positioning for ARDS demonstrating diffuse enhancement and thickening of the left brachial plexus (*white arrows*). MRI, magnetic resonance imaging; COVID-19, Coronavirus Disease 2019; ARDS, acute respiratory distress syndrome.

series were also noted to have an incomplete plexopathy picture with sparing of axillary and suprascapular nerves. Han et al. also report on a patient with neuropathy who contracted COVID-19, requiring intubation, but did not undergo prone positioning.[20] Their patient was noted to be in a hypercoagulable state with elevated D-dimers and, on day 24, developed a rash that was consistent with thrombotic microvascular injury. Four days later, he was noted to have severe weakness of the left upper extremity, with sparing of the deltoid, infraspinatus, and pectoral muscles.[20] Similar to our patients with complete and

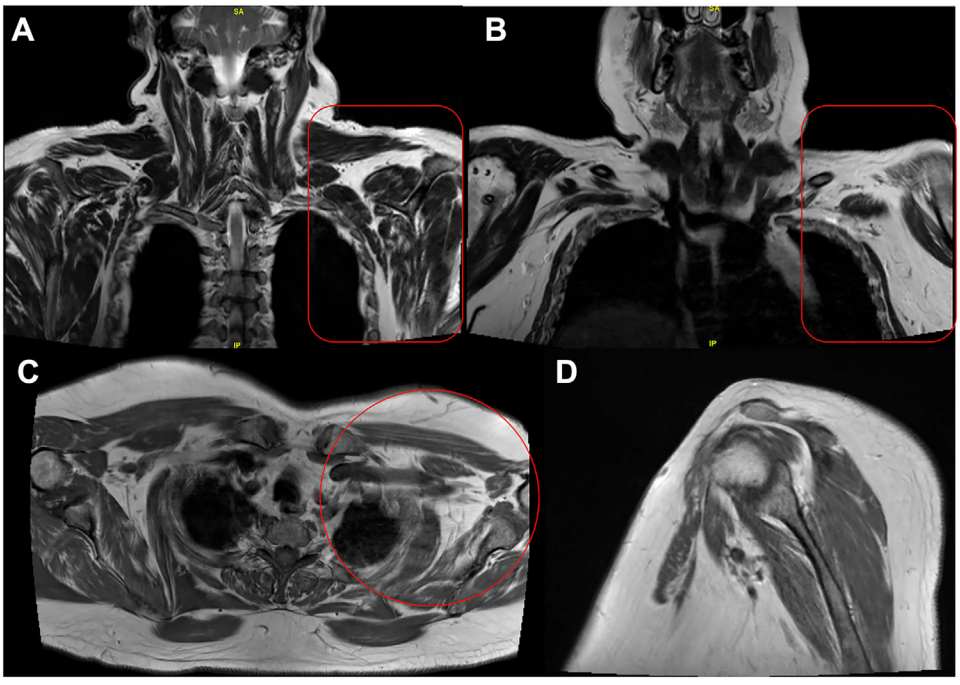

Figure 2. 57 yoM with 6-month history of brachial pan-plexopathy following COVID-19 infection. MRI demonstrates asymmetric decreased bulk of multiple muscles around left chest wall and shoulder with varying nerve distributions consistent with chronic denervation changes and/or disuse atrophy. Views: (**A**) Mid Coronal T2 Dixon_in (**B**) Anterior Coronal T2 Dixon_in (**C**) Axial TSE T1 (**D**) Affected Left Sagittal TSE T1. COVID-19, Coronavirus Disease 2019; MRI, magnetic resonance imaging.

Table 4. Literature Review of COVID-19-Related Peripheral Neuropathy Following Prone Positioning

Study	Design	Findings
Douglas et al.[13]	Single-center retrospective study	61 patients with COVID-19 treated with prone position ventilation, 5 (8.2%) brachial plexopathies
Miller et al.[14]	Single-center retrospective study	114 patients with treated with prone positioning, 15 (13.2%) patients and 30 peripheral neuropathies, most common was ulnar nerve (12/30) followed by cords of brachial plexus (10/30)
Malik et al.[7]	Single-center retrospective study	12 patients treated with prone position, 6 (50%) with ulnar neuropathy and 2 (16.7%) with brachial plexopathy
Diprose et al.[15]	Case report	55F, BMI 42.6, bilateral upper limb neuropathies with comprised of individual nerve lesions affecting axillary and suprascapular nerves, sparing brachioradialis and biceps.
Sayegh et al.[16]	Case series	Single center case series noting ulnar neuropathy in 3 patients following prone positioning

COVID-19, Coronavirus Disease 2019; BMI, body mass index.

partial plexopathies, electrodiagnostic studies from Han et al. noted a patchy pattern of axonotmesis with sparing of some fascicles and severe denervation of the other fascicles that run through the same trunks and cords.[20] With these findings, Michaelson et al. and Han et al. postulated that an uncontrolled systemic inflammation resulting in hypercoagulation may have led to the development of microthombotic angiopathy of the vasa nervorum about the brachial plexus leading to paucifascicular infarctions and subsequent plexopathy.[19] Needham et al. have also described 11 patients with a mononeuritis multiplex with pathology most similar to vasculitic neuropathies given multifocal sites alongside their associated electrodiagnostic evidence.[21] Similarly, in our series of patients, several had incomplete pan-brachial plexopathy with severe involvement of nerves at the trunk, cord, and branch level alongside both diffuse and patchy electrodiagnostic findings.

Another pathophysiologic consideration may be in relation to neuralgic amyotrophy during which, in addition to mechanical vulnerability in the intubated ICU environment, an auto-immune trigger from the viral infection, leads to neuronal injury.[22] Impact of peripheral nerves may also occur directly through the angiotensin-converting enzyme 2 receptor, which has been identified as the functional receptor for Sars-CoV2, with the expression of ACE2 on neurons.[23-26] Others have reported that COVID-19 has been associated with acute inflammatory demyelinating polyneuropathy, increasing the vulnerability of peripheral nerves to injury.[27] In addition, multifactorial considerations such as obesity, age, diabetes, hypovolemia, or ICU interventions through the use of muscle paralytic agents, long periods of sedation, and mechanical ventilation may all be involved in such peripheral neuropathy complications associated with COVID-19.[11,28-31] Taken together, a double crush phenomenon of prone positioning in addition to a systemic, metabolic, or direct viral insult to the peripheral nerve secondary to the viral infection may be more plausible as opposed to prone positioning alone in the etiology and rise of brachial plexus injuries.[20,32-34]

We recognize the limitations of this study and those inherent to retrospective analyses. The patient cohort is small, with only 11 patients identified in 3 institutions. As these patients were referred for tertiary care, documentation of their prior critical care course or details on positioning protocols were limited, with most only detailing prone positioning and no other forms of positioning (i.e., lateral decubitus, etc.). In addition, accessory information on instances of hypoxic respiratory failure, hypotension, hypovolemia, or agitation and use of restraints that all may influence the integrity of the peripheral nerves was limited. The time from recognition of the upper extremity neuropathy to evaluation by a specialist was prolonged (9.5 months) coinciding with a delay in electrodiagnostic evaluation and may have represented the difficulty of obtaining specialty care during the pandemic. We recommend specialist evaluation at the first evidence of peripheral nerve or brachial plexopathy recognition with a detailed exam and electrodiagnostic studies. These limitations notwithstanding, this multicenter series provides additional information regarding the development of neuropathies following severe COVID-19 infection.

CONCLUSION

This series provides insight that both traumatic and atraumatic causes of peripheral neuropathy may be associated with COVID-19 infections. Furthermore, there may be an interplay of traumatic and atraumatic etiologies whereby the traumatic disturbance of the plexus from prone positioning with shoulder abduction align with the physiologic vulnerability of the peripheral nerves during infection. This physiologic vulnerability stems from either a hypercoagulation state and the development of microthrombotic angiopathy with vascular compromise, a direct viral invasion, or an autoantibody targeting of the nervous tissue.[35] Ongoing treatments have been nonoperative in nature, with some patients demonstrating signs of reinnervation. As we proceed further in the recovery process for patients infected with COVID-19, recognizing long-term complications and optimal treatments for these pathologies become necessary. Ongoing follow-up with the development of larger observational and longitudinal studies is needed to understand the course and recovery of COVID-19 related neuropathies.

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