Radiology

Imaging Review of Peripheral Nerve Injuries in Patients with COVID-19

Article Type: Review

Claire E. Fernandez[1]

Colin K. Franz MD/PhD[2,3,4]

Jason H. Ko MD, MBA[5]

James M. Walter MD[6]

Igor J. Koralnik MD[4]

Shivani Ahlawat MD[7]

Swati Deshmukh MD[8]

[1]Northwestern University Feinberg School of Medicine, 420 E Superior St Chicago, IL, USA 60611

[2]Shirley Ryan Ability Lab (Formerly the Rehabilitation Institute of Chicago), 355 E Erie St Chicago, IL, USA 60611

[3]Department of Physical Medicine and Rehabilitation, Northwestern University Feinberg School of Medicine, 420 E Superior St Chicago, IL, USA 60611

[4] Department of Neurology, Northwestern University Feinberg School of Medicine, 420 E Superior St Chicago, IL, USA 60611

[5]Division of Plastic and Reconstructive Surgery, Northwestern University Feinberg School of Medicine, 420 E Superior St Chicago, IL, USA 60611

[6]Division of Pulmonary and Critical Care, Department of Medicine, Northwestern University Feinberg School of Medicine, 420 E Superior St Chicago, IL, USA 60611

[7]Department of Radiology, Johns Hopkins Hospital, 1800 Oleans St Baltimore, MD, USA 21287

[8]Department of Radiology, Northwestern University Feinberg School of Medicine, 420 E Superior St Chicago, IL, USA 60611

Corresponding author:

Swati Deshmukh MD

676 N Saint Clair, Suite 800, Chicago IL USA 60611

swati.deshmukh@northwestern.edu

Funding: none

Abbreviations: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; MR = magnetic resonance; US = ultrasound; ARDS = adult respiratory distress syndrome; AIDP = acute inflammatory demyelinating polyneuropathy; CIDP = chronic inflammatory demyelinating polyneuropathy;

Essentials

- Neuromuscular complications of COVID-19 are increasingly being observed, particularly as survivors undergo rehabilitation care.
- Imaging aids evaluation of peripheral nerve injury in COVID-19 patients and may directly impact patient care.
- Differential diagnosis of peripheral nerve injury in the setting of COVID-19 includes post-infectious inflammatory neuropathy, prone positioning-related stretch/compression injury, systemic neuropathy, and nerve entrapment secondary to hematoma.

Summary Statement

Peripheral nerve imaging aids diagnosis and may guide management in patients with COVID-19 with neuromuscular symptoms arising from the infectious disease, hospitalization course, or secondary to a complication of treatment.

Abstract

With surging numbers of coronavirus disease 2019 (COVID-19) patients throughout the world, neuromuscular complications and rehabilitation concerns are becoming more apparent. Peripheral nerve injury can occur in COVID-19 patients secondary to post-infectious inflammatory neuropathy, prone positioning-related stretch/compression injury, systemic neuropathy, or nerve entrapment from hematoma. Imaging of peripheral nerves in COVID-19 patients may help characterize nerve pathology, identify site and severity of nerve damage, and potentially elucidate mechanisms of injury thereby aiding the medical diagnosis and decision-making process. This review article aims to provide a first comprehensive summary of the current knowledge of COVID-19 and peripheral nerve imaging.

Introduction

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China in December 2019 and quickly spread across the world, with the World Health Organization officially declaring it as a pandemic on March 11th 2020. While the respiratory system is primarily affected in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, neurological complications affecting both the central and peripheral nervous systems have been reported (1-3). An observational investigation of 214 patients with COVID-19 reported peripheral nervous system involvement in up to 8.9 % of people (4). As the number of COVID-19 survivors surges, long-term sequela and rehabilitation concerns related to neuromuscular pathology are becoming more apparent (2, 3).

While mechanisms of COVID-19-related neuropathy are yet to be fully understood, the receptor for SARS-CoV-2 (angiotensin converting enzyme 2) has been found to be expressed in the nervous system (5). The possibility of SARS-CoV-2 as a new neuropathogen has been postulated, but is as of yet unproven (5). Infectious peripheral neuropathy is known to occur secondary to other viruses such as hepatitis C, human immunodeficiency virus (HIV), and

varicella zoster (6). Similarly, immune-mediated neuropathies, such as Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP), are known to occur in the setting of viral infection (7). Prolonged hospitalization can in itself lead to peripheral nerve pathology due to critical illness polyneuropathy (CIP) or secondary to prolonged patient positioning (Figure 1) (3, 8-9). Over the past several months, cases of neurological complications in COVID-19 patients such as Guillain-Barre syndrome and prone positioning-related peripheral neuropathy have been reported (1, 5, 10-15).

Advanced imaging techniques, including magnetic resonance (MR) neurography and high-resolution ultrasound (US), are well-established diagnostic tools for assessment of peripheral nerve injury (16-24). Imaging of peripheral nerves in COVID-19 patients and survivors may characterize nerve pathology, may identify the site and severity of nerve damage, and may potentially elucidate mechanisms of injury (Table). In collaboration with clinical counterparts in the fields of pulmonary and critical care medicine, physical medicine and rehabilitation, peripheral nerve surgery, and neurology, radiologists can aid medical decision-making and guide rehabilitative care for COVID-19 patients through optimized acquisition and accurate interpretation of advanced peripheral nerve imaging. To the best of our knowledge, there is no dedicated overview or publication of this topic to date. Thus, this review article aims to provide a comprehensive summary of the current knowledge of COVID-19, peripheral neuropathy, and peripheral nerve imaging.

Basics on Nerve Anatomy and Imaging

Peripheral nerve anatomy can be visualized to the fascicular level on high resolution MR and ultrasound imaging. Peripheral nerves consist of individual nerve fibers (axons) that are each enclosed in a connective tissue sheath known as the endoneurium. Multiple axons are bundled together within a second connective tissue sheath termed the perineurium to form a nerve fascicle. Multiple fascicles are then enclosed in a fibrous sheath known as the

epineurium to form the peripheral nerve. An internal system of blood vessels within the epineurium, perineurium, and endoneurium provides oxygen and nutrients to the nerve (17, 25).

MRI

High resolution MRI of peripheral nerves, known as MR neurography, can accurately depict both macro- and micro- structural changes in the nerve as well as secondary findings of peripheral nerve injury such as skeletal muscle denervation (18, 19, 24). A normal peripheral nerve demonstrates uniform round or ovoid contour and expected continuous anatomic course on MRI, without evidence of discontinuity, displacement, focal thickening, focal narrowing, or mass lesion. Signal intensity of a normal peripheral nerve is isointense to slightly hyperintense to skeletal muscle on fluid sensitive sequences. The expected honeycomb appearance of the fascicular architecture of a normal nerve may be identified in the cross-sectional plane (17-19). Advancements in MR technology now allow for visualization of even small pure sensory peripheral nerves (18).

Primary MR neurography findings of peripheral nerve injury include signal hyperintensity on fluid-sensitive sequences, change in nerve caliber, architectural distortion (loss of fascicular architecture), nerve discontinuity, mass effect/external compression, and perineural scarring (17, 19). MR neurography findings can be correlated with the Seddon and Sunderland nerve injury classification schemes (26). Signal hyperintensity of a peripheral nerve on MRI corresponds to Sunderland grade 1 or neuropraxia. Neuropraxia entails a short-term nerve conduction block resulting in clinical symptoms with expected recovery and good prognosis. Imaging is typically not obtained in cases of neuropraxia. The additional MR findings of peripheral nerve thickening and fascicular enlargement indicate Sunderland grade 2 or axonotmesis. Axonotmesis involves axonal loss resulting in symptoms of nerve dysfunction, abnormal electrophysiologic studies, and potential muscle denervation (26). In early reports, COVID-19 related peripheral nerve injury appear to be largely axonotmesis injuries (11, 27).

Grade 3 injury or neurotmesis can be detected on MR neurography as a complete nerve gap as would be seen in the case of traumatic laceration (17, 19).

Secondary MR neurography findings of peripheral nerve injury include signs of muscle denervation such as intramuscular edema-like signal in the acute/subacute setting and fatty infiltration and atrophy in the chronic setting. MR neurography readily depicts muscle changes in both superficial and deep locations and provides comprehensive evaluation of skeletal muscle due to the large field of view. Furthermore, MR neurography can detect skeletal muscle changes earlier than electromyography (EMG) – as soon as 4 days after injury (19). In the setting of chronic peripheral nerve injury, MR is an ideal diagnostic tool for evaluation of extent of nerve injury and end-organ damage (17).

Of note, muscle injury/myalgia is a common neuromuscular symptom associated with COVID-19 (28). Currently, there are no prospective original articles available regarding the differentiation between muscle abnormalities directly associated with COVID-19 and secondary muscle abnormalities due to COVID-19-related neuropathy. While there is no current evidence in the literature for specificity of MRI in terms of depicted muscle abnormalities in COVID-19 patients, MRI is generally well known to have high sensitivity for depiction of both muscle and nerve pathology. We believe that the hypothesis is justified that if muscle and nerve abnormalities are both seen on MRI, the findings likely represent COVID-19 associated nerve injury with secondary muscle damage when the muscle changes follow the specific innervation pattern of the affected nerve.

Ultrasound

High resolution ultrasound can readily visualize peripheral nerves throughout the extremities and portions of the brachial plexus (16, 22, 23). A normal peripheral nerve demonstrates uniform round or ovoid contour in the short axis with a characteristic honeycomb appearance reflecting intact fascicular architecture. Normal nerve fascicles are hypoechoic on ultrasound and surrounded by the hyperechoic epineurium. Both short and long axis imaging is

obtained to demonstrate normal nerve continuity and anatomic course. Advancements in ultrasound and transducer technology now allow for visualization of even small peripheral nerves (16, 22).

Primary ultrasound findings of peripheral nerve injury include nerve enlargement, hypoechogenicity, and loss of fascicular architecture. Nerve discontinuity, mass effect/eternal compression, and perineural scarring are also readily identified on ultrasound. Secondary ultrasound findings of peripheral nerve injury include evidence of muscle denervation such as increased echogenicity and reduction of muscle size. Ultrasound can detect muscle denervation in the subacute timeframe, as soon as 2 weeks after nerve injury (16, 22).

MR versus Ultrasound

Advantages of ultrasound over MR neurography include cost benefit, portability, dynamic imaging, and contralateral side comparison. Ultrasound can also be performed in patients who are unable to tolerate MRI. Metallic artifact from hardware, which may be severely limiting on MRI despite metal artifact reduction techniques, is typically not problematic on ultrasound. Disadvantages of ultrasound include potential lack of a suitable acoustic window and limitations of nerve visualization due to excessive body habitus or overlapping anatomical structures (i.e. the clavicle limits evaluation of a portion of the brachial plexus). MR neurography is also superior for comprehensive large field-of-view assessment of skeletal muscle (16, 22, 23). In hospitalized patients with a COVID-19 positive test, ultrasound has the advantage of portability but the disadvantage of requiring close-contact of the sonographer or radiologist with the patient during scanning. Overall, both high resolution MR neurography and ultrasound are excellent non-invasive tools for assessment of peripheral nerve injury and have the ability to accurately localize pathology and determine extent of injury.

Imaging Techniques

MR neurography protocols generally include a combination of high resolution (2-3 mm section thickness) 2-dimensional (2D) and 3-dimensional (3D) anatomic sequences such as T1WI SE/T1WI FLAIR (T1 weighted spin-echo/T1 weighted fluid-attenuated inversion recovery) and fluid-sensitive sequences such as T2WIFS SE/SPAIR/STIR (T2 weighted fat saturated spin-echo/spectral attenuated inversion recovery/short-T1 inversion recovery) in multiple planes. 3D pulse sequences with multiplanar reconstructions are excellent for depicting peripheral nerves along their longitudinal course. MR neurography is typically performed on a 3-Tesla magnet for higher signal-to-noise ratio and better special resolution, unless there is a validated reason for imaging at a lower magnetic field strength such as metallic hardware in the region of interest (20, 21). Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) are advanced MR techniques that have yet to be widely utilized clinically for evaluation of peripheral nerves (17). While there are no current universally-accepted practice guidelines for the use of intravenous contrast in MR neurography, prior literature has shown mild to no added benefit in the majority of cases (20). In COVID-19 patients where peripheral nerve injury is suspected due to compression/stretch injury, intravenous contrast is not mandatory for diagnosis in the author's point of view. An exception is the utility of intravenous contrast for vascular suppression techniques that have been described for MRI of the brachial plexus (20). MR neurography protocols should be tailored on a case-by-case basis in COVID-19 patients to include the appropriate field of view of the nerve(s) in question and relevant skeletal muscle.

High resolution ultrasound of peripheral nerves should be performed with high-frequency, linear-array transducers (14-24 MHz). Lower frequency transducers may be necessary for larger patients and/or deeper nerves (16, 22). Both short and long axis imaging of the peripheral nerve should be obtained as well as imaging of relevant skeletal muscle. Dynamic imaging (i.e. of the ulnar nerve at the cubital tunnel) and comparison to the contralateral side may be indicated. In some instances, preliminary point-of-care ultrasound may be performed by clinicians in the physician's office with portable ultrasound machines.

Radiologists, however, should utilize high-end ultrasound machines with state-of-the-art scanner and transducer designs in order to obtain high resolution imaging of even small peripheral nerves. As ultrasound is highly operator-dependent, peripheral nerve sonography should be interpreted by radiologists with specific training in nerve ultrasound. In some settings, peripheral nerve ultrasound may be limited or non-existent in which case referral to advanced imaging facilities and/or MRI should be considered.

Imaging Considerations in COVID-19 Patients

While many patients who sustain peripheral nerve injury during their COVID-19 illness will present to imaging centers in a delayed fashion after COVID-19 test results become negative, some patients with a positive result on their most recent COVID-19 test may require urgent imaging. At this time, the American College of Radiology (ACR) recommends minimized use of MR in patients with known COVID-19 positive test or Persons Under Investigation for COVID-19 unless absolutely necessary. Imaging of peripheral neuropathy in patients with a COVID-19 positive test should therefore be performed only if the results will potentially impact imminent clinical management. Both patient and health care personnel safety measures must be undertaken, including use of personal protective equipment and room cleaning and disinfecting protocols (28.30). For MR neurography, the use of known MR Safe masks is advised; if not possible, then metallic components from the face mask must be removed prior to arrival to the MR suite. While non-MR Conditional masks are strongly discouraged, protocol modification can be implemented if absolutely necessary including lowering specific absorption rate values and/or shortening radiofrequency transmission durations and/or introducing cool-down periods between scans (29). As guidelines and policies change over time, radiologists must ensure that they are up-to-date with current recommendations.

For patients with COVID-19-related peripheral nerve injury meeting criteria for imaging evaluation, MR neurography and ultrasound protocols may be tailored for patient

comfort/tolerability and healthcare worker protection. For instance, shortened MR neurography protocols may entail 2 sequence axial plane-only imaging of the extremities (axial T2 weighted fat saturated or short tau inversion recovery (STIR) and axial T1 weighted or proton density (PD) sequences). For MR neurography of the brachial plexus, 2 sequence unilateral imaging of the affected side (sagittal and coronal T2 weighted fat saturated or STIR) may provide sufficient diagnostic information. Ultrasound imaging can be focused to the suspected site of nerve injury based on clinical evaluation and any available electrophysiologic studies. Of note, electrophysiologic laboratories may be operating in a limited capacity in light of the COVID-19 pandemic - which potentially could result in increased requests for imaging of peripheral nerve injury. Communication between providers and radiologists is key for optimizing diagnostic performance of shortened protocols.

Peripheral nerve injury in COVID-19 patients

Peripheral nerve injury in COVID-19 patients can occur as a manifestation of SARS-CoV-2 infection (post-infectious inflammatory neuropathy), as a sequela of hospitalization for COVID-19 (positioning-related neuropathy, distal symmetric polyneuropathy), or as a consequence of a complication of treatment for COVID-19 (nerve entrapment secondary to hematoma in the setting of anticoagulation treatment).

Post-Infectious Inflammatory peripheral nerve injury

Post-infectious inflammatory peripheral nerve injury is thought to occur secondary to immune-mediated mechanisms and can occur in the setting of multiple different viruses (6, 7). Post-infectious inflammatory peripheral nerve injury secondary to SARS-CoV-2 infection is therefore a theoretical differential consideration, and indeed several cases of COVID-19 patients presenting with peripheral neuropathy and Guillain-Barre syndrome have been reported in the clinical literature (31, 32). The rarity of thus far reported post-COVID-19 possibly immune-mediated cases should be considered, however, when interpreting imaging of peripheral nerves

(1). Of note, imaging features of post-infectious inflammatory peripheral nerve injury are not specific to the infectious agent and therefore correlation with viral testing history is advised in COVID-19 patients.

Guillain-Barre syndrome is an immune-mediated neuropathy that is the most common cause of acute flaccid paralysis throughout the world (33). Multiple case reports of Guillain-Barre Syndrome following COVID-19 infection have been reported in recent months (5, 13, 26). Patients with Guillain-Barre Syndrome typically demonstrate symptoms a few weeks following infection (33). Acute inflammatory demyelinating polyneuropathy (AIDP) is a common subtype of Guillain-Barre in COVID-19 patients. Clinical features of AIDP includes numbness and tingling in the hands and feet followed by progressive weakness (33). Generally, AIDP has a good prognosis. Imaging findings include signal hyperintensity, enlargement, and mild to moderate contrast enhancement of the cauda equina, nerve roots/plexus, and peripheral nerves (26). Contrast enhancement of the cauda equina is a typical MR finding of Guillain-Barre Syndrome. Albuminocytologic dissociation is seen in the CSF in the majority of Guillain-Barre Syndrome patients (33). Immunotherapy (steroids, plasmapheresis, or intravenous gammaglobulin) accelerates recovery. Functionally significant residual deficits are observed in approximately 15% of Guillain-Barre Syndrome patients (33).

Chronic inflammatory demyelinating polyneuropathy is a chronic analog to Guillain-Barre syndrome with a poor prognosis. Chronic symptoms (greater than 8 weeks) of muscle weakness, sensory loss, and areflexia are presenting features, typically with an insidious onset. Albuminocytologic dissociation with high cerebrospinal fluid protein is found on lumbar puncture (26, 33). CIDP is more common in the lower extremity (17, 26). Imaging findings are similar to that of AIDP and include focal or diffuse enlargement and signal hyperintensity of the peripheral nerves, nerve roots/plexus, and cauda equina. Contrast enhancement is usually not present. As with other acquired neuropathies, asymmetric nerve abnormalities can be seen (17, 26). Nerve root hypertrophy in the lumber spine may result in crowding and entrapment, and patients

may demonstrate symptoms of cauda equina dysfunction and lumbar stenosis (33). Treatment with immunotherapy has been shown to be beneficial for most patients with CIDP (33).

Parsonage-Turner syndrome, first described in the 1940s, is a stress-mediated acute brachial plexitis that can occur after a number of conditions including trauma, pregnancy, and viral infections and hence could theoretically occur in the setting of COVID-19 (8, 25). Clinical presentation of Parsonage-Turner Syndrome includes delayed-onset severe shoulder pain that develops rapidly and can result in muscle atrophy (8, 25). Parsonage-Turner Syndrome is more common in men and demonstrates unilateral pathology in 70% of patients (34). On imaging, Parsonage-Turner Syndrome is identified as a diffuse brachial plexitis with thickening and signal hyperintensity of the affected nerves of the plexus (Figure 2) (8, 21, 34). MR neurography correlate of high grade constrictions ("bullseye sign" or hourglass morphology) are additional imaging indicators of Parsonage-Turner Syndrome, likely the result of localized intraneural compartment syndrome/ischemia (35). Commonly involved nerves include the suprascapular nerve, upper trunk, axillary nerve, and long thoracic nerve (34). Intramuscular edema-like signal may be seen in the acute phase of Parsonage-Turner Syndrome (34). While clinical symptoms and imaging findings of Parsonage-Turner Syndrome may mimic positioning peripheral nerve injury of the brachial plexus in COVID-19 patients, the diagnosis of Parsonage-Turner Syndrome is one of exclusion and the rarity of thus far reported post-COVID-19 immune-mediated cases (aside from Guillan-Barre syndrome and its variants) should be considered (8). As Parsonage-Turner Syndrome is self-limiting, treatment is conservative (21).

Positioning-related peripheral nerve injury

Peripheral nerve injury is a known potential complication of patient positioning that has been well reported in the surgical and anesthesia literature (8, 25, 36). Recently, peripheral nerve injury in COVID-19 patients and survivors has been described in the literature following the use of prone positioning for COVID-19-related ARDS (9, 11, 27). Prone positioning is an evidenced-based therapy for optimization of oxygenation in patients with ARDS that has been

applied to hospitalized COVID-19 patients throughout the world (37-45). While direct causality between prone positioning and peripheral nerve injury is difficult to prove, the timing of onset of clinical symptoms and the plethora of prior surgical literature on positioning peripheral nerve injury is highly suggestive of a correlation (Figure 3). Knowledge of positioning utilized during patient care can facilitate identification of potential complications and inform imaging interpretation of peripheral nerve injury.

Prone positioning protocols may vary between institutions and over time, as medical understanding of COVID-19 evolves. While some authors advocate prone positioning with shoulders at 90 degrees of abduction and the elbows bent thereby allowing the hands to lie adjacent to the head, others recommend keeping the arms straight down by the sides of the body. Application of prone positioning for at least 12-16 consecutive hours daily is generally advised (38-39). Periodic movement of the limbs and head/neck has been suggested (8, 38, 46). As there may be multiple re-positioning efforts during the course of a COVID-19 patient's hospitalization, it is important to account for the theoretical possibility that peripheral nerve injury may result from traction injury during lifting/repositioning and/or stretch/pressure injury from prolonged prone positioning. Severity of positioning-related peripheral nerve injury can range from low-grade compression resulting in temporary interruption of blood supply, to moderate-grade stretching associated with damage of intraneural blood vessels, to severe nerve injury with axonal loss and Wallerian degeneration (8, 25). Factors that may predispose patients to positioning peripheral nerve injury include both thin and obese patients, pre-existing peripheral neuropathy (i.e. diabetes), smoking history, and alcoholism (8, 25, 36).

Prone positioning places patients at high risk for injury of the brachial plexus and the ulnar nerve at the level of the elbow (Figures 4 and 5) (8, 36). Variable arm placement (i.e. superman or swimmers position versus arms down by the side with supination of the hands) and external equipment (i.e. padding, blood pressure cuff) influence the location and extent of nerve injury (8). Brachial plexus positioning injury can be due to compression between the

clavicle and the ribs, compression at the level of the scalene muscles, or stretching across the humeral head (25). Ulnar neuropathy can occur in the setting of external compression at the level of the cubital tunnel (25). Male gender is thought to be a risk factor for ulnar neuropathy due to anatomical differences between men and women at the level of the cubital tunnel (25). Other individual anatomic variants (i.e. cervical ribs, anconeus epitrochlearis) may also predispose patients to positioning peripheral nerve injury (8).

Prone positioning can less commonly result in peripheral nerve injuries involving the radial, median, and common peroneal (fibular) nerves (Figures 6 and 7). Compression of the radial nerve can occur from external factors along the posterior aspect of the arm at the level of the spiral groove (8, 25). Similarly, external factors may cause compression of the proximal median nerve within the upper arm (8). Wrist hyperextension for prolonged periods can lead to distal median nerve injury at the level of the wrist (25). External compression and stretch injury of the common peroneal nerve can occur at the level of the fibular head due to suboptimal knee positioning (8). Lateral femoral cutaneous nerve neuropathy, also known as meralgia paresthetica, can uncommonly occur in the setting of prone position with inadequately padded bolsters that compress the nerve at the level of the thigh (8, 36). Isolated positioning-related axillary nerve injury is rare but has been reported in association with the prone position (Figure 8) (8).

Positioning-related peripheral nerve injury typically results in neuropraxia or axonotmesis (36). Corresponding MR neurography findings include nerve signal hyperintensity, thickening, and in some cases fascicular enlargement (Figures 3-5) (17). High resolution ultrasound findings include nerve hypoechogenicity, thickening, and in some cases fascicular enlargement (Figure 6) (16, 22). Of note, electrophysiologic studies may be falsely negative in cases of neuropraxia (17). Additional imaging features that may suggest positioning-related peripheral nerve injury include localization of nerve pathology in correlation with expected biomechanics of potential positioning related peripheral nerve injury (i.e. ulnar nerve at the cubital tunnel,

common peroneal nerve at the fibular head) with matching clinical history and in some cases adjacent soft tissue contusion or edema (Figure 8).

Imaging findings atypical for positioning peripheral nerve injury include diffuse multi-focal nerve pathology, nerve discontinuity, and evidence of advanced chronic end-organ damage inconsistent with timing of onset of suspected positioning peripheral nerve injury. When interpreting MR neurography in COVID-19 patients, it is important to consider that COVID-19 patients with prolonged hospital courses may have positioning peripheral nerve injury with superimposed critical illness myopathy resulting in a multi-focal muscle edema pattern that may not perfectly correlate with expected innervation distribution patterns of the suspected peripheral nerve (Figure 3). Consideration of all potential confounding factors and correlation with clinical history of prone positioning (including positioning protocol and duration) as well as timing of onset of symptoms is important when making an imaging diagnosis of positioning-related peripheral nerve injury. As more and more patients are evaluated in rehabilitation facilities and/or outpatient COVID-19 follow-up clinics, peripheral nerve injury secondary to prone positioning for COVID-19-related adult respiratory distress syndrome (ARDS) may be increasingly observed (11). Treatment options range from conservative rehabilitation measures to surgical intervention.

Distal Symmetric Polyneuropathy

Distal symmetric polyneuropathy is the most common subtype of peripheral neuropathy and can be due to a variety of causes including diabetes, nutritional deficiencies, toxic etiologies, and infectious/inflammatory conditions (47). In diabetic polyneuropathy, diffuse bilateral signal hyperintensity of peripheral nerves can be seen (17). As many COVID-19 patients with neuromuscular symptoms may have underlying conditions such as diabetes, pre-existing distal symmetric polyneuropathy should be accounted for when evaluating imaging of peripheral nerve injury (Figure 9).

Critical illness polyneuropathy is a distal symmetric polyneuropathy associated with prolonged hospital course typically within the intensive care unit. Clinical symptoms of muscle weakness are most pronounced in the lower extremities and may be severe with positive associated electrophysiological findings (48). While imaging is typically not obtained in critical illness polyneuropathy, MRI may demonstrate diffuse symmetric nerve signal hyperintensity and associated muscle denervation edema (Figure 10). Critical illness myopathy is a separate entity from critical illness polyneuropathy that presents with muscle weakness in patients with a prolonged hospital course typically within the intensive care unit. Critical illness myopathy represents a primary myopathy (ie. muscle necrosis) and hence the pattern of intramuscular edema-like signal is not expected to follow the innervation distribution of any particular peripheral nerve (48). While imaging is typically not obtained in critical illness myopathy, MRI may demonstrate multi-focal intramuscular edema-like signal in the acute setting and fatty infiltration and atrophy in the chronic setting.

Nerve entrapment

Nerve entrapment results in focal compression of a peripheral nerve due to an adjacent space-occupying lesion (hematoma, tumor, bony callous) and/or in the setting of an anatomical tunnel (17, 49). Nerve entrapment can potentially develop in COVID-19 patients during their hospital course secondary to a large hematoma or other drainable fluid collection. Emerging research suggests that SARS-CoV-2 may predispose patients to thrombotic complications (50-51). As many COVID-19 patients may be treated with anti-coagulation medications during their hospital course, the potential for development of soft tissue hematoma should be considered (Figure 11). Ultrasound and MRI can ready diagnose hematomas and assess for mass effect on adjacent peripheral nerves (Figures 12 and 13). Ultrasound features of nerve entrapment include hypoechogenecity, disruption of fascicular architecture, and caliber change at the site of entrapment. MR neurography features of nerve entrapment include nerve signal hyperintensity and caliber change at the site of entrapment (17).

Management of peripheral nerve injury

Depending on location and extent of nerve damage, peripheral nerve injury can cause patient morbidity and affect quality of life in COVID-19 survivors (1-5, 11-15). The reference standard for neuropathy diagnosis has traditionally been electrophysiology; however, in more recent years, imaging has played a greater role in evaluation of peripheral nerve injury. Peripheral nerve injury can serve as a non-invasive alternative or as an adjuvant diagnostic test to electromyography and nerve conduction studies for localization and evaluation of peripheral nerve injury. Limitations of electrophysiology include false negative results in the setting of neurapraxia, invasive nature and physical discomfort to the patients, and difficulty in precise localization of nerve pathology (17). In many cases, imaging can serve as a complement tool to electrophysiology for evaluation of peripheral nerve injury, allowing for precise localization of nerve pathology and early comprehensive assessment of associated muscle damage. Studies have shown that imaging of peripheral nerves impacts clinical decision-making and guides therapeutic plans (52-53). Imaging of peripheral nerves, however, remains underutilized (53). During these unprecedented times where healthcare practices have been modified by the COVID-19 pandemic and social distancing has become the norm, radiologists must reach out to clinical counterparts to discuss imaging options and collaborative patient care.

Treatment options for peripheral nerve injury include conservative measures such as pain medications and physical therapy, steroid injections (potentially image guided with ultrasound), and surgery in more severe cases (8, 36). Immunotherapy may be helpful for post-infectious inflammatory peripheral nerve injury (33). Surgical options for peripheral nerve injury include neurolysis, resection and nerve grafting, and possibly nerve transposition as in the case of ulnar neuropathy at the level of the elbow (8). Distal nerve transfers may be an option for proximal injuries. Early diagnosis and referral to a peripheral nerve surgeon is important in cases that may necessitate surgery. Imaging may help guide important treatment decisions in

COVID-19 patients through diagnosis of site and severity of peripheral nerve injury and identification of etiology of peripheral nerve injury (ie. conservative measures and primary care follow-up for mild stretch injury versus consultation of a peripheral nerve surgeon for severe positioning-related peripheral nerve injury versus administration of immunotherapy for post-infectious inflammatory peripheral nerve injury). Awareness of imaging features of peripheral nerve injury in COVID-19 patients is therefore crucial for radiologists to optimally contribute to patient care.

Attention to potential nerve compression and stretching while implementing life-saving proning measures during the care of COVID-19 patients may reduce the likelihood of positioning peripheral nerve injury. Given the utmost importance of respiratory management during COVID-19-induced ARDS, however, as well as the theoretical potential of underlying co-morbidities and virus-induced hyperinflammation increasing nerve vulnerability, cases of peripheral nerve injury may be inevitable. As COVID-19 survivors recover from a variety of pulmonary, neuromuscular, neurological, and cognitive complications, attention to peripheral nerve injury is an important component of both inpatient and outpatient rehabilitation (54-55). Management of peripheral nerve injury in COVID-19 survivors therefore should be included in future COVID-19-specific rehabilitation programs, with appropriate integration of peripheral nerve imaging and potential follow-up imaging to aid clinical decision-making.

Conclusion

The global pandemic of COVID-19 has challenged the healthcare system and many questions remain in regards to our understanding of the virus, its sequelae, and long-term outcomes. Mechanisms of peripheral nerve injury in COVID-19 patients may be multifactorial including complications of systemic disease, direct neuro-invasion, and autoimmune response. Further research is necessary to elucidate pathophysiology of peripheral nerve injury in COVID-19 patients including the possibility of SARS-CoV-2 as a new neuropathogen and the

relationship with prone positioning in the setting of COVID-19-related ARDS. Along those lines, further research is needed to determine if COVID-19 patients are at higher risk for peripheral nerve injury - potentially due to co-morbidities such as diabetes, obesity, and older age or plausibly secondary to a virus-induced state of hyper-inflammation.

MR neurography and high resolution ultrasound are excellent diagnostic tools for peripheral nerve injury and can be tailored to the specific needs and potential limitations of COVID-19 patients with consideration to their most current COVID-19 test results. As practice guidelines may rapidly change, radiologists must ensure that they are up-to-date with current recommendations. With appropriate expertise, radiologists can offer insight as to the etiology of peripheral nerve injury in COVID-19 patients which may directly impact patient management and treatment decisions. For COVID-19 patients and survivors with neuromuscular complications, imaging of peripheral nerves can aid medical decision-making, rehabilitative care, and patient/family counseling.

Acknowledgments: None

References

1. Koralnik IJ, Tyler KL. COVID-19: A Global Threat to the Nervous System. Ann Neurol 2020;88(1):1-11. doi: 10.1002/ana.25807

2. Lahiri D, Ardila A. COVID-19 Pandemic: A Neurological Perspective. Cureus 2020;12(4):e7889. doi: 10.7759/cureus.7889

3. Tsivgoulis G, Palaiodimou L, Katsanos AH, Caso V, Köhrmann M, Molina C, Cordonnier C, Fischer U, Kelly P, Sharma VK, Chan AC, Zand R, Sarraj A, Schellinger PD, Voumvourakis KI, Grigoriadis N, Alexandrov AV, Tsiodras S. Neurological manifestations and implications of COVID-19 pandemic. Ther Adv Neurol Disord 2020;13:1756286420932036. doi: 10.1177/1756286420932036

4. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, Li SB, Wang HY, Zhang S, Gao HN, Sheng JF, Cai HL, Qiu YQ, Li LJ. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606. doi: 10.1136/bmj.m606

5. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. Clin Neurol Neurosurg 2020;194:105921. doi: 10.1016/j.clineuro.2020.105921

6. Sindic CJ. Infectious neuropathies. Curr Opin Neurol 2013;26(5):510-515. doi: 10.1097/WCO.0b013e328364c036

7. Katona I, Weis J. Diseases of the peripheral nerves. Handb Clin Neurol 2017;145:453-474. doi: 10.1016/b978-0-12-802395-2.00031-6

8. Winfree CJ, Kline DG. Intraoperative positioning nerve injuries. Surg Neurol 2005;63(1):5-18; discussion 18. doi: 10.1016/j.surneu.2004.03.024

9. Le MQ, Rosales R, Shapiro LT, Huang LY. The Down Side of Prone Positioning: The Case of a COVID-19 Survivor [published online ahead of print, 2020 Jul 9]. Am J Phys Med Rehabil. 2020;10.1097/PHM.0000000000001530. doi:10.1097/PHM.0000000000001530.

10. Alberti P, Beretta S, Piatti M, Karantzoulis A, Piatti ML, Santoro P, Viganò M, Giovannelli G, Pirro F, Montisano DA, Appollonio I, Ferrarese C. Guillain-Barré syndrome related to COVID-19 infection. Neurol Neuroimmunol Neuroinflamm 2020;7(4). doi: 10.1212/nxi.0000000000000741

11. Malik GR, Wolfe AR, Soriano R, Rydberg L, Wolfe LF, Deshmukh S, Ko JH, Nussbaum RP, Jayabalan P, Walter JM, Franz CK. Injury-Prone: Peripheral nerve injuries associated with prone positioning for COVID-19-related acute respiratory distress syndrome. medRxiv 2020:2020.2007.2001.20144436. doi: 10.1101/2020.07.01.20144436

12. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77(6):1-9. doi: 10.1001/jamaneurol.2020.1127

13. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci 2020;76:233-235. doi: 10.1016/j.jocn.2020.04.062

14. Wang L, Shen Y, Li M, Chuang H, Ye Y, Zhao H, Wang H. Clinical manifestations and evidence of neurological involvement in 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis. J Neurol 2020:1-13. doi: 10.1007/s00415-020-09974-2

15. Padroni M, Mastrangelo V, Asioli GM, Pavolucci L, Abu-Rumeileh S, Piscaglia MG, Querzani P, Callegarini C, Foschi M. Guillain-Barré syndrome following COVID-19: new infection, old complication? J Neurol2020; p. 1877-1879.

16. Brown JM, Yablon CM, Morag Y, Brandon CJ, Jacobson JA. US of the Peripheral Nerves of the Upper Extremity: A Landmark Approach. Radiographics 2016;36(2):452-463. doi: 10.1148/rg.2016150088

17. Chhabra A, Madhuranthakam AJ, Andreisek G. Magnetic resonance neurography: current perspectives and literature review. Eur Radiol 2018;28(2):698-707. doi: 10.1007/s00330-017-4976-8

18. Deshmukh S, Carrino JA, Feinberg JH, Wolfe SW, Eagle S, Sneag DB. Pins and Needles From Fingers to Toes: High-Resolution MRI of Peripheral Sensory Mononeuropathies. AJR Am J Roentgenol 2017;208(1):W1-w10. doi: 10.2214/ajr.16.16377

19. Deshmukh SD, Samet J, Fayad LM, Ahlawat S. Magnetic resonance neurography of traumatic pediatric peripheral nerve injury: beyond birth-related brachial palsy. Pediatr Radiol 2019;49(7):954-964. doi: 10.1007/s00247-019-04401-9

20. Harrell AD, Johnson D, Samet J, Omar IM, Deshmukh S. With or without? A retrospective analysis of intravenous contrast utility in magnetic resonance neurography. Skeletal Radiol 2020;49(4):577-584. doi: 10.1007/s00256-019-03321-x

21. Thawait SK, Chaudhry V, Thawait GK, Wang KC, Belzberg A, Carrino JA, Chhabra A. High-resolution MR neurography of diffuse peripheral nerve lesions. AJNR Am J Neuroradiol 2011;32(8):1365-1372. doi: 10.3174/ajnr.A2257

22. Yablon CM, Hammer MR, Morag Y, Brandon CJ, Fessell DP, Jacobson JA. US of the Peripheral Nerves of the Lower Extremity: A Landmark Approach. Radiographics 2016;36(2):464-478. doi: 10.1148/rg.2016150120

23. Griffith JF. Ultrasound of the Brachial Plexus. Semin Musculoskelet Radiol 2018;22(3):323-333. doi: 10.1055/s-0038-1645862

24. Deshmukh S, Fayad LM, Ahlawat S. MR neurography (MRN) of the long thoracic nerve: retrospective review of clinical findings and imaging results at our institution over 4 years. Skeletal Radiol 2017;46(11):1531-1540. doi: 10.1007/s00256-017-2737-z

25. Kamel I, Barnette R. Positioning patients for spine surgery: Avoiding uncommon position-related complications. World J Orthop 2014;5(4):425-443. doi: 10.5312/wjo.v5.i4.425

26. Ahlawat S, Chhabra A, Blakely J. Magnetic resonance neurography of peripheral nerve tumors and tumorlike conditions. Neuroimaging Clin N Am 2014;24(1):171-192. doi: 10.1016/j.nic.2013.03.035

27. Needham E, Newcombe V, Michell A, et al. Mononeuritis multiplex: an unexpectedly common feature of severe COVID-19. medRxiv; 2020. DOI: 10.1101/2020.07.19.20149898.

28. Pinzon RT, Wijaya VO, Buana RB, Al Jody A, Nunsio PN. Neurologic Characteristics in Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis. Front Neurol 2020;11:565. doi: 10.3389/fneur.2020.00565

29. ACR Guidance on COVID-19 and MR Use. ACR American College of Radiology. https://www.acr.org/Clinical-Resources/Radiology-Safety/MR-Safety/COVID-19-and-MR-Use. Published 2020.7/14/20.

30. Gogna A, Yogendra P, Lee SHE, Aziz A, Cheong E, Chan LP, Venkatanarasimha N. Diagnostic Ultrasound Services During the Coronavirus Disease (COVID-19) Pandemic. AJR Am J Roentgenol 2020:1-6. doi: 10.2214/ajr.20.23167

31. Abdelnour L, Eltahir Abdalla M, Babiker S. COVID 19 infection presenting as motor peripheral neuropathy. J Formos Med Assoc 2020;119(6):1119-1120. doi: 10.1016/j.jfma.2020.04.024

32. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020;19(5):383-384. doi: 10.1016/s1474-4422(20)30109-5

33. Chung T, Prasad K, Lloyd TE. Peripheral neuropathy: clinical and electrophysiological considerations. Neuroimaging Clin N Am 2014;24(1):49-65. doi: 10.1016/j.nic.2013.03.023

34. Upadhyaya V, Upadhyaya DN, Bansal R, Pandey T, Pandey AK. MR neurography in Parsonage-Turner syndrome. Indian J Radiol Imaging 2019;29(3):264-270. doi: 10.4103/ijri.IJRI_269_19

35. Sneag DB, Saltzman EB, Meister DW, Feinberg JH, Lee SK, Wolfe SW. MRI bullseye sign: An indicator of peripheral nerve constriction in parsonage-turner syndrome. Muscle Nerve 2017;56(1):99-106. doi: 10.1002/mus.25480

36. DePasse JM, Palumbo MA, Haque M, Eberson CP, Daniels AH. Complications associated with prone positioning in elective spinal surgery. World J Orthop 2015;6(3):351-359. doi: 10.5312/wjo.v6.i3.351

37. Gattinoni L, Busana M, Giosa L, Macrì MM, Quintel M. Prone Positioning in Acute Respiratory Distress Syndrome. Semin Respir Crit Care Med 2019;40(1):94-100. doi: 10.1055/s-0039-1685180

38. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L, Group PS. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159-2168. doi: 10.1056/NEJMoa1214103

39. Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, Uleryk E, Mancebo J, Pesenti A, Ranieri VM, Fan E. Prone Position for Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc 2017;14(Supplement_4):S280-s288. doi: 10.1513/AnnalsATS.201704-343OT

40. Scholten EL, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS With Prone Positioning. Chest 2017;151(1):215-224. doi: 10.1016/j.chest.2016.06.032

41. Coppo A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P, Cairo M, Mori S, Messinesi G, Contro E, Bonfanti P, Benini A, Valsecchi MG, Antolini L, Foti G. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. Lancet Respir Med 2020. doi: 10.1016/s2213-2600(20)30268-x

42. Elharrar X, Trigui Y, Dols AM, Touchon F, Martinez S, Prud'homme E, Papazian L. Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. JAMA 2020. doi: 10.1001/jama.2020.8255

43. Lindahl SGE. Using the prone position could help to combat the development of fast hypoxia in some patients with COVID-19. Acta Paediatr 2020;109(8):1539-1544. doi: 10.1111/apa.15382

44. Meng L, Qiu H, Wan L, Ai Y, Xue Z, Guo Q, Deshpande R, Zhang L, Meng J, Tong C, Liu H, Xiong L. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. Anesthesiology 2020;132(6):1317-1332. doi: 10.1097/ALN.0000000000003296

45. Thompson AE, Ranard BL, Wei Y, Jelic S. Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure. JAMA Intern Med 2020. doi: 10.1001/jamainternmed.2020.3030

46. Goettler CE, Pryor JP, Reilly PM. Brachial plexopathy after prone positioning. Crit Care 2002;6(6):540-542. doi: 10.1186/cc1823

47. Callaghan BC, Price RS, Feldman EL. Distal Symmetric Polyneuropathy: A Review. JAMA 2015;314(20):2172-2181. doi: 10.1001/jama.2015.13611

48. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol 2011;10(10):931-941. doi: 10.1016/S1474-4422(11)70178-8

49. Garwood ER, Duarte A, Bencardino JT. MR Imaging of Entrapment Neuropathies of the Lower Extremity. Radiol Clin North Am 2018;56(6):997-1012. doi: 10.1016/j.rcl.2018.06.012

50. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. Thromb Res 2020;192:152-160. doi: 10.1016/j.thromres.2020.05.039

51. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, Cushman M, Quéré I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH.

COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75(23):2950-2973. doi: 10.1016/j.jacc.2020.04.031

52. Fisher S, Wadhwa V, Manthuruthil C, Cheng J, Chhabra A. Clinical impact of magnetic resonance neurography in patients with brachial plexus neuropathies. Br J Radiol 2016;89(1067):20160503. doi: 10.1259/bjr.20160503

53. Newhart H, Patterson J, Gunasekaran A, Pandey T, Kumar M, Kazemi N. The Incremental Value of Magnetic Resonance Neurography for the Neurosurgeon: Review of the Literature. World Neurosurg 2019;122:331-341. doi: 10.1016/j.wneu.2018.10.212

54. Lew HL, Oh-Park M, Cifu DX. The War on COVID-19 Pandemic: Role of Rehabilitation Professionals and Hospitals. Am J Phys Med Rehabil 2020;99(7):571-572. doi: 10.1097/phm.0000000000001460

55. Sheehy LM. Considerations for Postacute Rehabilitation for Survivors of COVID-19. JMIR Public Health Surveill 2020;6(2):e19462. doi: 10.2196/19462

Table

Table. Differential Diagnosis of Peripheral Nerve Injury in Patients with COVID-19.

Etiology	Recommended Imaging	MR characteristics	US characteristics	Pertinent Clinical Features
Inflammatory neuropathy[21,26]	1. MR 2. US	Diffuse signal hyperintensity of cauda equina/nerve roots/plexus, often asymmetric Nerve enhancement if acute	Thickening of the affected nerve	Progressive weakness, following infection (acute and chronic forms)
Parsonage-Turner syndrome[17,21,34,+]	1. MR *(better evaluation of muscle)* 2. US *(for small nerves not well seen on MR)*	Signal hyperintensity, thickening, often of multiple plexus nerves Muscle edema-like signal	Hypoechogencity, thickening of affected nerve (i.e. suprascapular, long thoracic nerve)	Sudden and rapid onset, following infection
Positioning-related Peripheral Nerve Injury of extremities[11,16,17]	MR or US *(MR = better evaluation of muscle; US = dynamic imaging, well tolerated)*	Signal hyperintensity of affected nerve +/- muscle edema-like signal if acute, fatty atrophy if chronic	Hypoechogencity, thickening of affected nerve; +/-subluxation on dynamic maneuvers +/- muscle atrophy, hyperechogenicity if chronic	Weakness/sensory deficit acquired during hospital course; often asymmetric Use of prone positioning
Positioning-related Brachial Plexus Injury[11,16,17]	1. MR 2. US *(limited by clavicle)*	Signal hyperintensity, thickening of upper or lower plexus +/- muscle edema-like signal if acute, fatty atrophy if chronic	Hypoechogencity, thickening of upper or lower plexus +/- muscle atrophy, hyperechogenicity if chronic	Weakness/sensory deficit acquired during hospital course; often asymmetric Use of prone positioning
Distal symmetric polyneuropathy[17]	Typically not performed for diagnostic purposes	Diffuse signal hyperintensity of nerves +/- Multi-focal muscle edema-like signal/fatty atrophy based on etiology and chronicity	Thickening of the affected nerve +/- Multi-focal muscle atrophy if chronic	Pre-existing polyneuropathy + co-morbidity (i.e. diabetes) vs acquired polyneuropathy and myopathy in critical illness
Nerve Entrapment[16-18]	MR or US	Signal hyperintensity of affected nerve, nerve compression or altered course due to mass effect +/- adjacent hematoma	Hypoechogencity, thickening of affected nerve, nerve compression or altered course due to mass effect +/- adjacent hematoma	Weakness/sensory deficit acquired while on anti-coagulation; +/- swelling/palpable mass

+ The diagnosis of Parsonage-Turner Syndrome is one of exclusion and the rarity of thus far reported post-COVID-19 immune-mediated cases (aside from Guillan-Barre syndrome and its variants) should be considered (8).
**Abbreviations: MR = magnetic resonance; US = ultrasound*

Figures

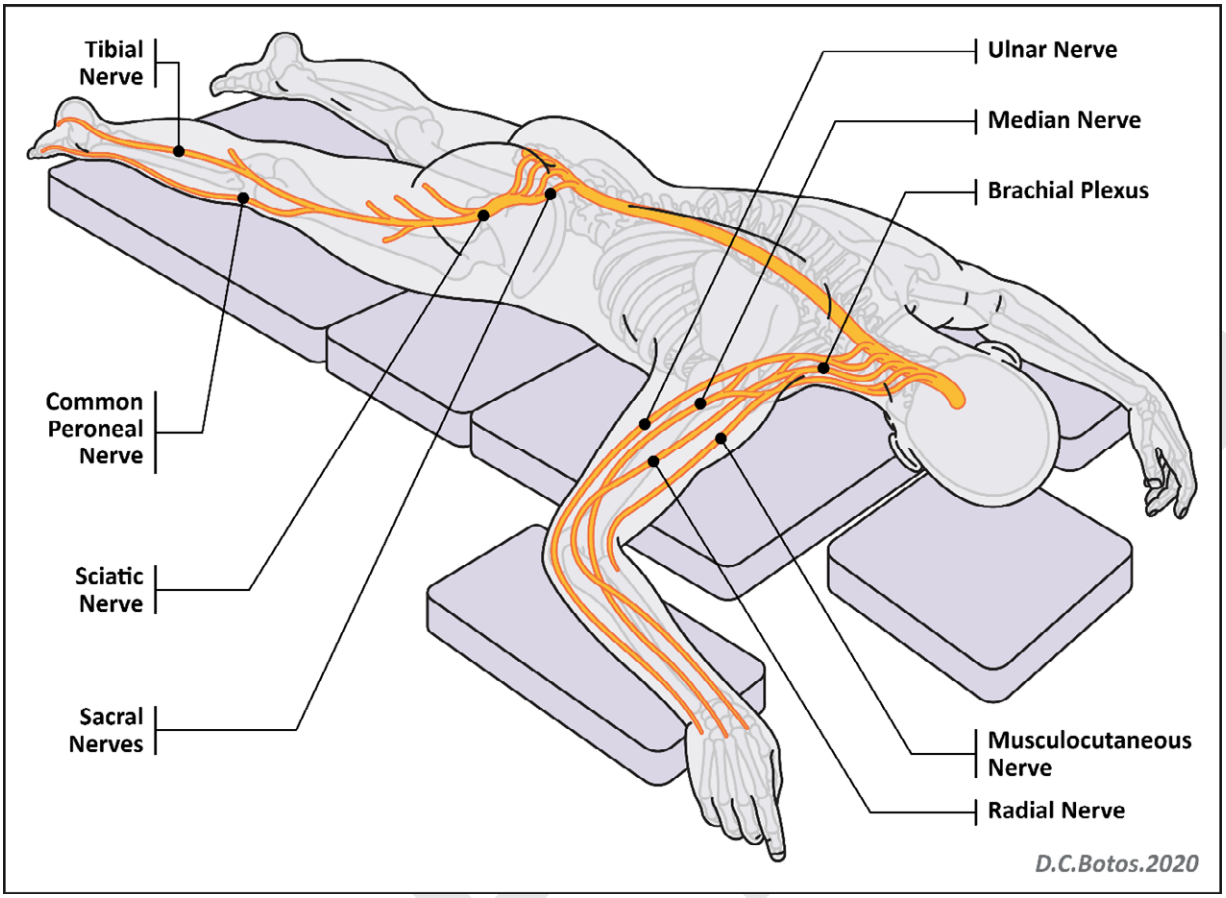
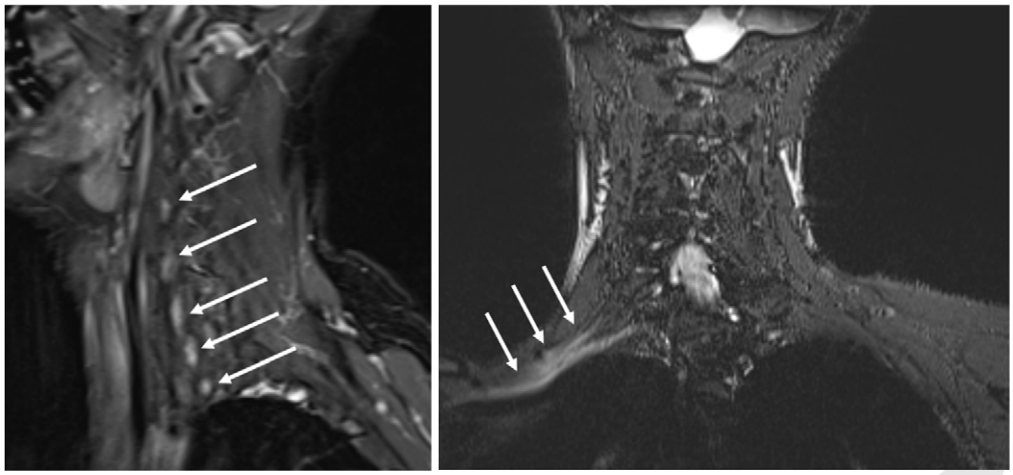
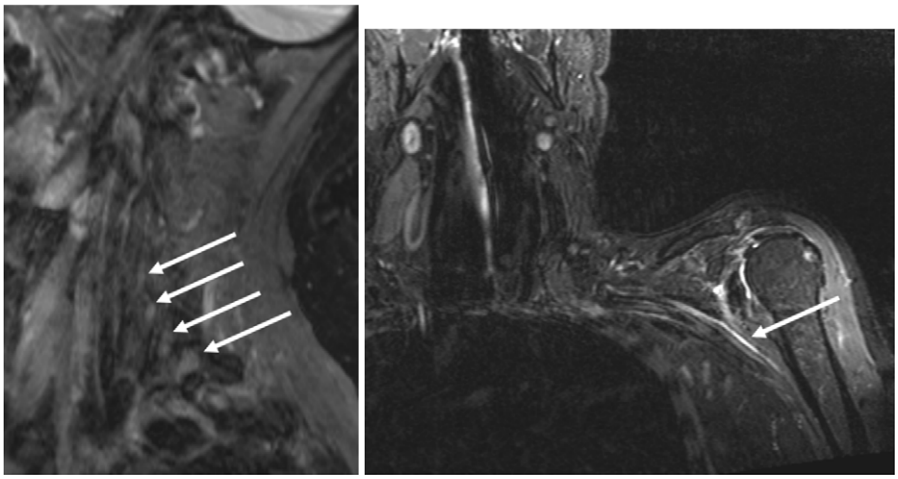


Figure 1: Illustration of peripheral nerve anatomy in the prone position. Original artwork by David Botos.

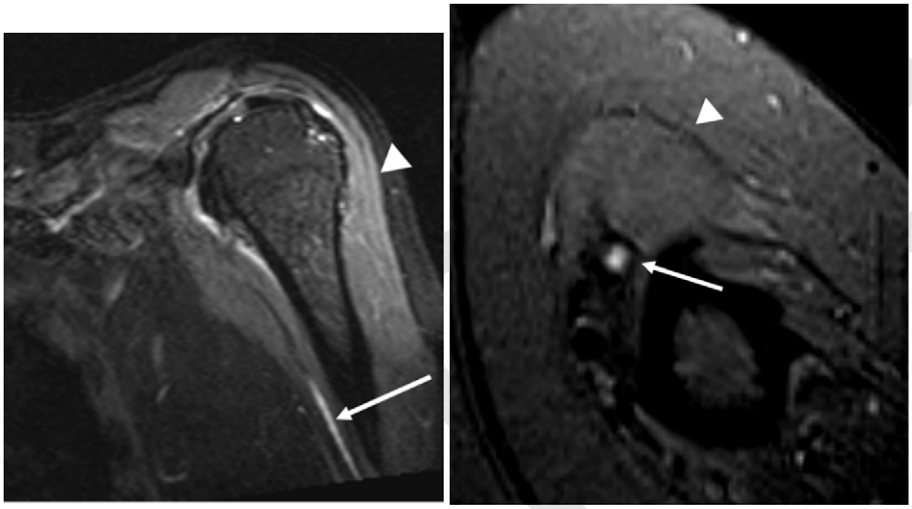


a. **b.**

Figure 2: 58-year-old female with sudden-onset severe right upper extremity pain and weakness. She reports history of two episodes of respiratory viral infection in the month preceding onset of symptoms (COVID testing not performed). Electrodiagnostic studies were normal. Clinical suspicion was for Parsonage-Turner syndrome and MR neurography of the brachial plexus was performed. **(a)** Sagittal T2 weighted fat saturated image demonstrates diffuse signal hyperintensity of the brachial plexus nerve roots (arrows). **(b)** Coronal T2 SPACE STIR post-contrast for vascular suppression image demonstrates diffuse signal hyperintensity and thickening of the right brachial plexus (arrows). MR neurography findings supported the clinical diagnosis of Parsonage-Turner syndrome, and the patient was treated with gabapentin.



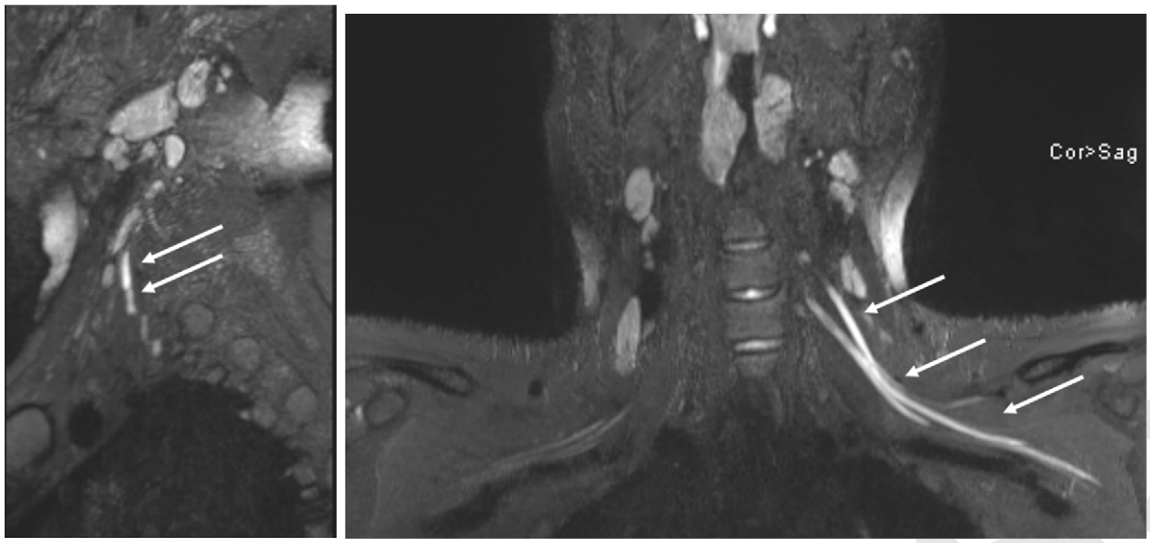
a. **b.**



c. **d.**

Figure 3: 61 year-old-male with prolonged hospital course due to COVID-19 requiring intubation and prone positioning, who developed new-onset left upper extremity weakness and decreased range of motion as an in-patient. He was evaluated by neurology, with clinical suspicion for positioning-induced brachial plexus injury with potential component of critical illness myopathy and non-exclusion of diffuse infiltrative COVID-related inflammatory injury to the brachial plexus. EMG was incomplete but suggested an upper trunk brachial plexopathy with axonal degeneration. MR neurography of the brachial plexus was performed but terminated early due to patient's inability to tolerate the full protocol. **(a)** Sagittal T2 weighted fat saturated image,

while motion degraded, demonstrates normal signal intensity of the brachial plexus nerve roots (arrows). **(b,c)** Coronal STIR images demonstrates signal hyperintensity of the musculocutaneous nerve as it transverses through the coracobrachialis muscle (arrows). Mild nonspecific deltoid muscle edema is noted (arrowhead). The patient was brought back for axial imaging of the left upper extremity. **(d)** Axial STIR image of the humerus demonstrates signal hyperintensity of the musculocutaneous nerve throughout the upper arm (arrow) and mild intramuscular edema of the biceps muscle (arrowhead). Imaging findings in correlation with clinical history favor a positioning-related injury of the musculocutaneous nerve.



a. **b.**

Figure 4: 21-year-old male with no past medical history who was diagnosed with COVID-19 with a prolonged hospital course for ARDS requiring intubation and prone positioning. During his hospital course, he developed left shoulder weakness with abduction and acquired position-related brachial plexus injury was suspected clinically. MR neurography of the brachial plexus was performed. **(a)** Sagittal T2 SPACE STIR post-contrast for vascular suppression image demonstrates signal hyperintensity of the C5 and C6 nerve roots (arrows). **(b)** Coronal T2 SPACE STIR post-contrast for vascular suppression image demonstrates signal hyperintensity of both the lateral and posterior cords as well as the suprascapular nerve (arrows). MR neurography findings are compatible with neuropathy (axonotmesis).

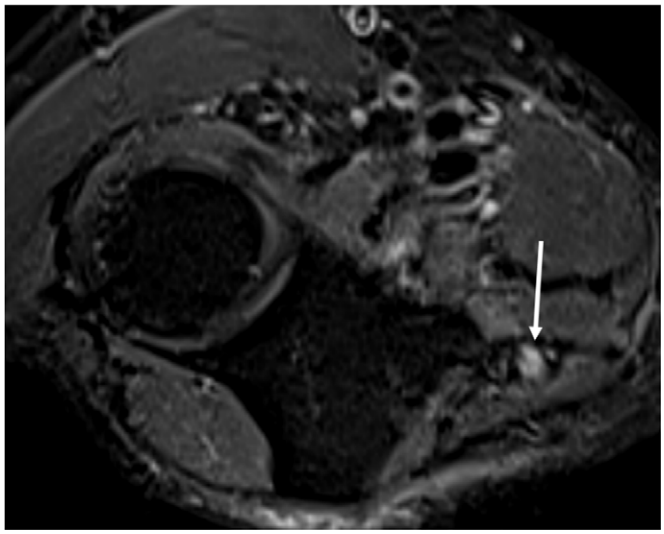
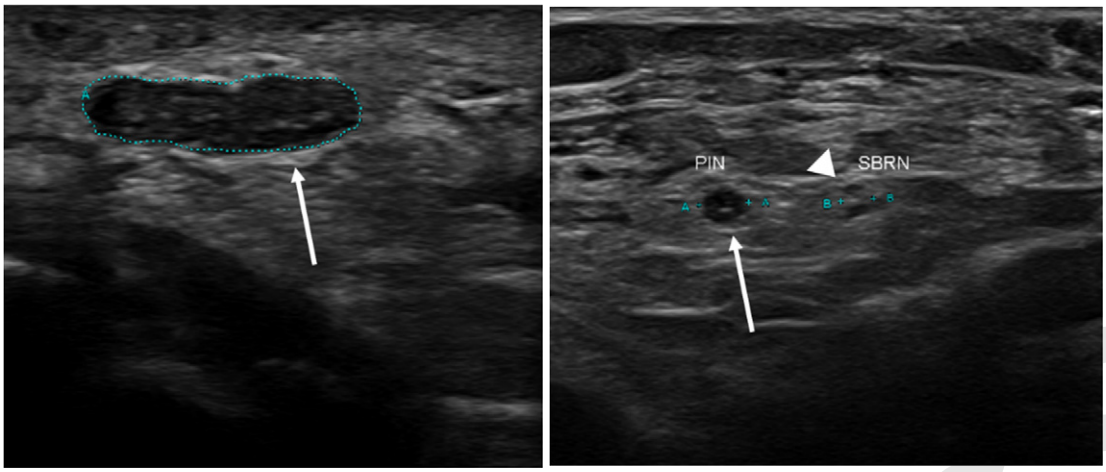
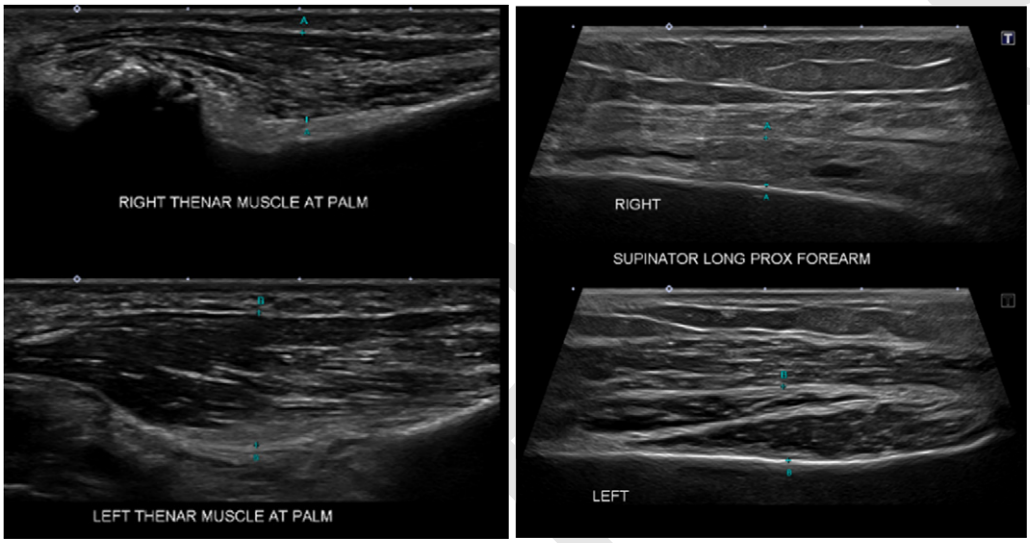


Figure 5: 45-year-old male with history of gout and diabetes mellitus who was admitted for acute inpatient rehabilitation after a prolonged hospital course due to COVID-19 infection. He noted new onset numbness in digits 4-5 in both hands as well as weakened grip that developed during his hospital course. He was found to have reduced pin prick sensation on the ulnar side of hand and fingers (splitting 4th digit). There was electrophysiologic evidence of bilateral, incomplete ulnar mononeuropathies with axonal loss and no reinnervation seen. Due to the severity and axonal nature of injury, EMG could not well localize the sites of injury and MR neurography of the humerus was performed. Axial STIR image of the right elbow demonstrates signal hyperintensity of the ulnar nerve just distal to the elbow (arrow). MR neurography findings are compatible with neuropathy (axonotmesis) of the ulnar nerve.



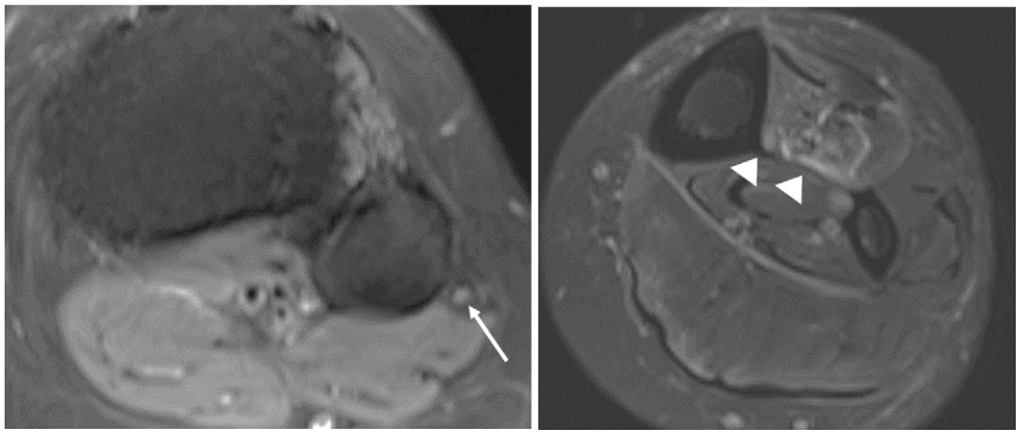
A B



C D

Figure 6: 66-year-old female with history of breast cancer who had a prolonged hospital course for COVID-19 respiratory failure requiring intubation and prone positioning. During her hospital course she developed moderate to severe right upper extremity weakness with clinical suspicion for prone positioning related peripheral nerve injury. The patient was unable to tolerate attempted MR neurography due to severe claustrophobia. *A,* Ultrasound of the median nerve (arrow, calipers) demonstrates moderate hypoechogenicity, thickening, and loss of fascicular architecture at the level of the wrist. *B,* Ultrasound of the posterior interosseous nerve (arrow, calipers) demonstrates thickening and hypoechogencity at the level of the elbow. The

adjacent superficial branch of the radial nerve (arrowhead, calipers) is normal. *C,* Ultrasound of the bilateral thenar musculature (calipers) demonstrates mild atrophy of the right thenar musculature compared to the left. *D,* Ultrasound of the bilateral supinator musculature (calipers) demonstrates moderate fatty atrophy of the right supinator muscle compared to the left. She was diagnosed with COVID-19 related polyneuropathy and referred to a peripheral nerve surgeon.



a. **b.**

Figure 7: 23 year old female with history of COVID-19 ARDS whose hospital course included intubation and prone positioning presenting with new-onset left extensor hallucis longus weakness. MR neurography of the left lower leg was performed. **(a)** Axial STIR image demonstrates subtle signal hyperintensity of the common peroneal nerve (arrow) at the level of the fibular head. **(b)** Axial STIR image demonstrates mild intra-muscular edema of the tibialis anterior and extensor muscles (arrowheads), suggestive of denervation.

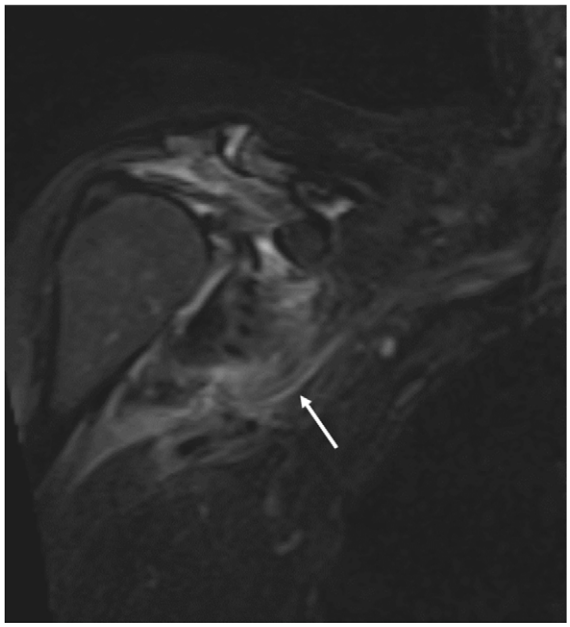
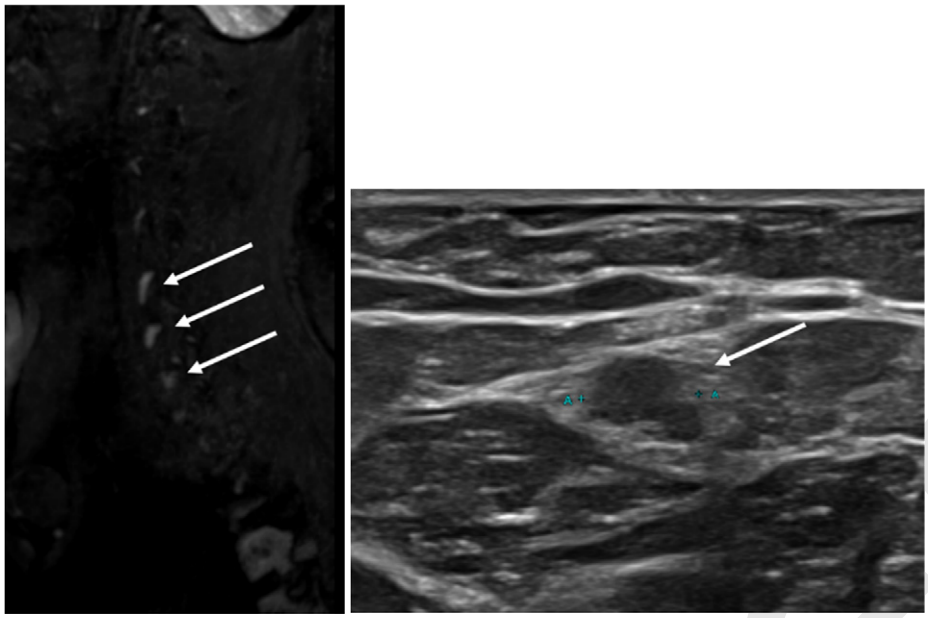
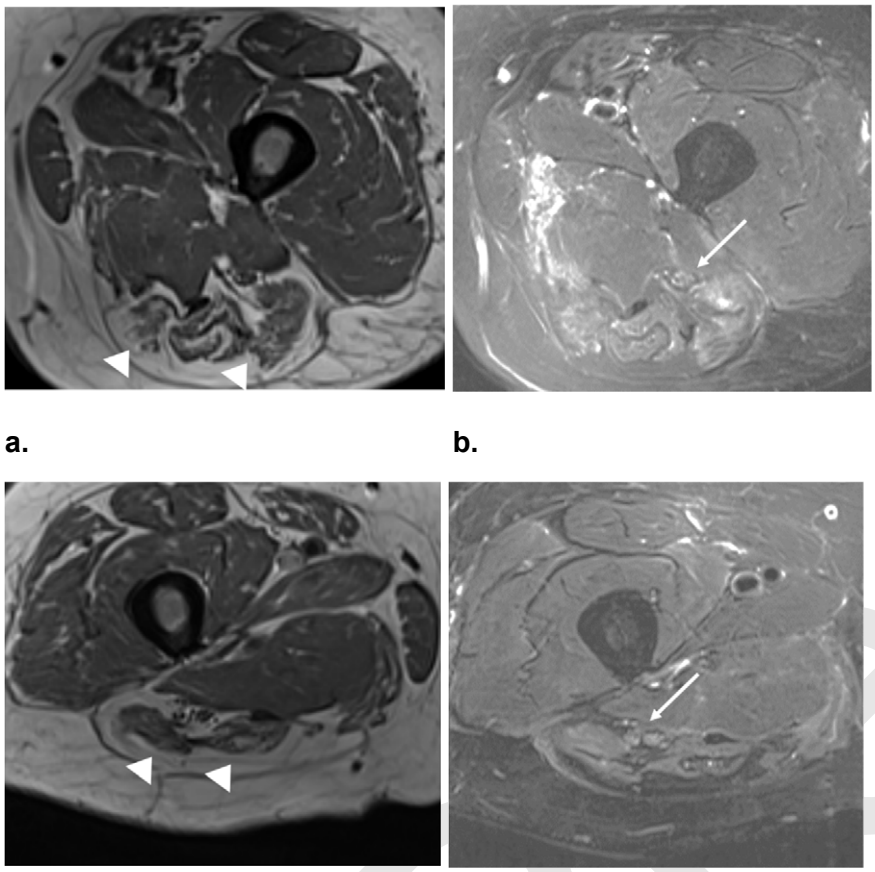


Figure 8: 44 year old female with history of COVID-19 requiring prone positioning presenting with difficulty abducting the right upper extremity. MR neurography of the brachial plexus was performed. Coronal STIR image demonstrates signal hyperintensity of the right axillary nerve (arrow) as it arises from the posterior cord of the brachial plexus and courses anterior to the right subscapularis. Nonspecific right axillary soft tissue edema and rotator cuff edema is noted.



a. **b.**

Figure 9: 46-year-old male with history of uncontrolled diabetes who presented to the emergency room for headache and foot pain and was found to be COVID-19+. The patient had pre-existing mixed polyneuropathy including features of distal symmetric polyneuropathy. Review of the medical record demonstrated prior pre-COVID-19 imaging of the left brachial plexus and right ulnar nerve. **(a)** Sagittal T2 SPACE STIR post-contrast for vascular suppression image demonstrates signal hyperintensity of the left C5-C7 nerve roots (arrows). **(b)** Short axis ultrasound demonstrates hypoechogencity and fascicular enlargement of the right ulnar nerve within the upper arm (arrow). His neuropathy symptoms were unchanged during the course of his SARS-CoV-2 infection.



a. **b.**

c. **d.**

Figure 10: 62 year old man with history of diabetes and obesity who was admitted to an in-patient rehabilitation facility following hospitalization for COVID-19. He reported bilateral foot drop and EMG localized peripheral nerve injury at the level of the sciatic nerves. MR neurography of the bilateral thighs was performed. **(a)** Axial T1 weighted and **(b)** axial T2 weighted fat saturated imaging of the right thigh demonstrate mild signal hyperintensity of the sciatic nerve (arrow) and moderate disproportionate atrophy of the posterior compartment musculature (arrowheads). **(c)** Axial T1 weighted and **(d)** axial T2 weighted fat saturated imaging of the left thigh demonstrate mild signal hyperintensity of the sciatic nerve (arrow) and moderate disproportionate atrophy of the posterior compartment musculature (arrowheads). Findings are compatible with distal symmetric polyneuropathy.

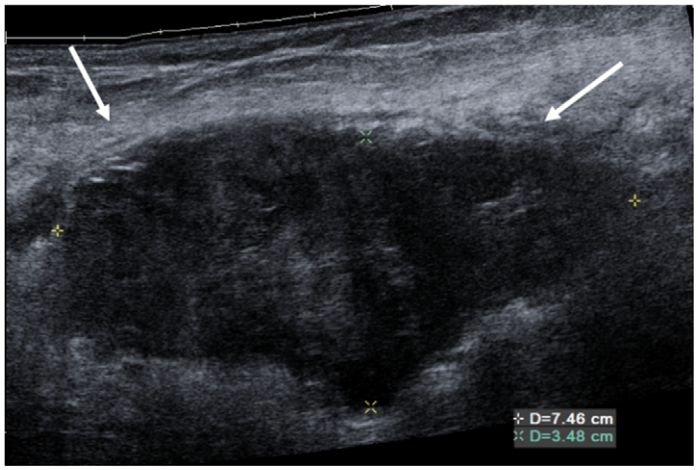
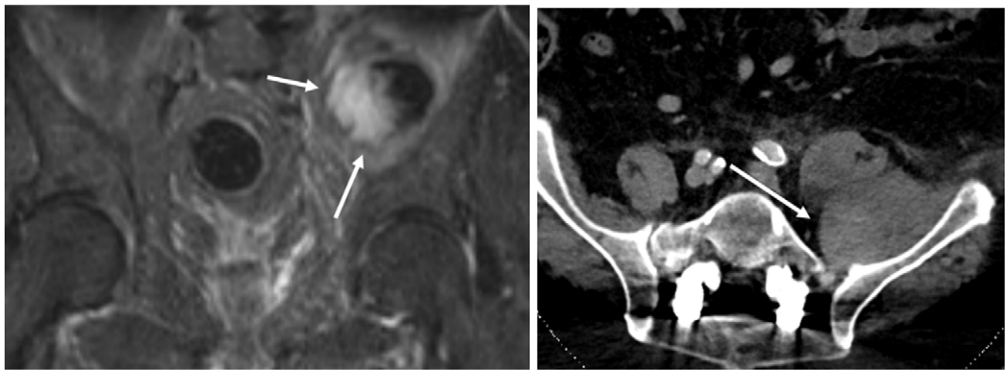
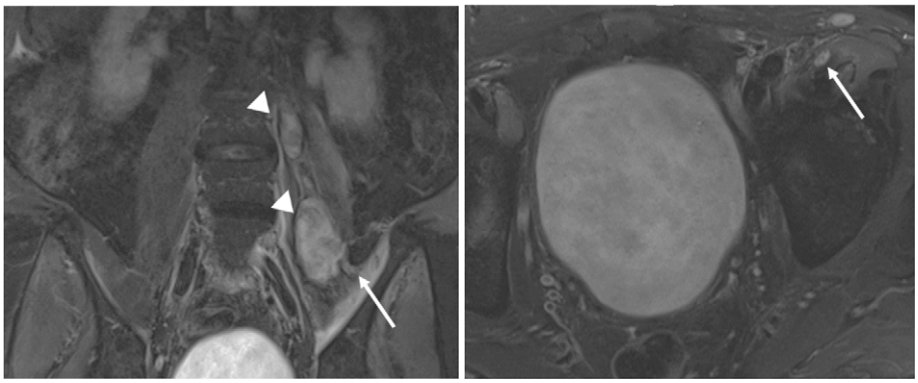


Figure 11: 66-year-old female with COVID-19 respiratory failure who developed right upper extremity weakness during her hospital course which had been complicated by deep venous thrombosis treated with anti-coagulation. Palpable mass-like swelling and ecchymosis of the posterior superior right upper extremity was noted. Ultrasound demonstrates a complex fluid collection, compatible with a hematoma (arrows).

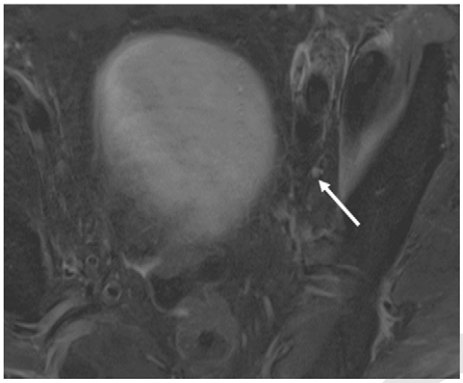


a. **b.**

Figure 12: 82-year-old male with recent history of hospitalization for COVID-19 pneumonia requiring intubation and anti-coagulation medication who presented to the Emergency Department with left lower extremity pain and sensory deficit of the anterior thigh. **(a)** Coronal STIR MR image of the hip demonstrates an intra-muscular hematoma within the left iliopsoas muscle (arrows). **(b)** Axial CT image demonstrates asymmetric enlargement and hyperdensity of the iliacus muscle (arrow). Imaging findings and clinical history are concerning for femoral nerve compression secondary to iliopsoas hematoma.



a. **b.**



c.

Figure 13: 60 year old male with history of diabetes and prior COVID-19 ARDS presenting from an in-patient rehabilitation center with left hip and thigh pain. Electrophysiologic study suggested lumbar plexitis with left femoral and obturator neuropathy and denervation. Working clinical diagnosis prior to imaging was diabetic amyotrophy in a COVID-19 survivor. MR neurography was performed. **(a)** Coronal STIR image demonstrates intra-muscular hematomas (arrowheads) in the left psoas muscle with mass effect on the adjacent femoral nerve (arrow). **(b)** Axial STIR image just distal to the inferior hematoma demonstrates signal hyperintensity of the left femoral nerve (arrow). **(c)** Axial STIR image demonstrates signal hyperintensity of the left obturator nerve (arrow). MR neurography findings are compatible with nerve entrapment in the setting of hematoma formation. The referring physician was notified and patient history of anticoagulation treatment during his COVID-19 hospitalization was confirmed.