Inflammatory peripheral neuropathy: A diagnostic dilemma

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Our patient

- 64 year old male with Hx of ADHD, gastric bypass, and low back pain and leg pain 2/2 severe lumbar stenosis L4-5 s/p right L4-5 microdiscectomy and decompression 2013
  - COVID vaccination dates 1/30/20, 2/20/20, and 4/15/22
- Initially presented in 3/2020 complaining of 1 month of **LBP and right leg pain** in an L3-4 distribution following an injury lifting boxes.
  - No neurologic deficits so treated with celebrex and told to follow up PRN
- Re-presented in 3/2022 complaining of left sided **LBP and left buttock and leg pain** in an L3 distribution
  - Sent for XR lumbosacral spine comprehensive, XR left hip, and MR lumbar spine with/without IV contrast:
    - XR Hip unremarkable, XR Lumbosacral spine showed diffuse DDD greatest L5-S1
    - MR Lumbar spine with/without IV contrast showed multilevel degenerative changes especially at **L2-L3 level with severe lateral recess and mod-severe central canal narrowing, mod-severe R and mild-mod L neural foraminal narrowing**
- Had LESI L2-3 on 4/2022. He reported 80% pain relief within 3 days

More background

- Next day he was lifting a box and experienced pain on the **left groin/thigh.**
- One week later he started to have pain in **right groin/ thigh** and calf
- 5/6 went to ER by ambulance because he was “screaming in pain”.
- Admitted & tx with hydromorphone, lyrica, valium, & dexamethasone
  - Repeat MRI showed moderate foraminal narrowing R>L L3-4, L4-5
- Discharged on a dexamethasone taper

More background

- Pain tolerable for 1 week then reported pain in **right groin/anterior thigh** at night severe enough to cause him to scream, as well as constant **numbness and tingling** since 5/6
- Had LESI L5-S1 on 5/17.
  - This **resolved his back pain and left sided** symptoms
  - **Continued to have right groin and thigh pain** down to his calf into top of foot and **numbness** in the anterior cal

XR R hip, femur, tibia, EMG and MR lumbosacral plexus with/without IV contrast:

- XR showed minimal R hip osteoarthritis, otherwise unremarkable hip, femur, tibia/fibula.
- EMG showed **e/o chronic right L4 or L5 radiculopathy** and **no e/o femoral neuropathy** or more generalized large fiber neuropathy

MR lumbosacral plexus showed mildly T2 hyperintense and hyperenhancement of the **right femoral nerve** vs left **from L5 level to the inguinal ligament** compatible with **right femoral neuropathy.** Unremarkable obturator, genitofemoral, ilioinguinal and lumbosacral roots L4-S3 otherwise

- Started on a dexamethasone taper

Back in clinic

- Complaining of **LBP with pain in right groin and thigh**
- Also had recent **COVID**, **lost 5-6 pounds** and **no appetite**, **night sweats** and had complaints of **blurred vision** and intermittent **hearing loss**
- Given 40 pack-year smoking hx we ordered:
  - ESR, CRP, Lyme, SPEP
  - CT chest/abdomen/pelvis
  - MRI auditory canal
  - Neurology referral

Neurology 7/14

Neurologist noted 2+ patellar reflex on L and none on R.

- ANTINUCLEAR ANTIBODIES (ANA)
- SJOG AB-SSA(RO)/SSB(LA)
- RHEUMATOID FACTOR (RF)
- GLIADIN PEPTIDE AB, IGA/IGG
- TISSUE TRANSGLUTAMINASE AB,IGA
- IMMUNOGLOBULIN QN PROFILE
- VITAMIN B12
- VITAMIN B6, PLASMA
- COPPER, SERUM/PLAS
- TSH (THYROID STIM HORMONE),3RD GENERATION
- HEMOGLOBIN A1C
- CBC PLATELET W/O DIFFERENTIAL
- COMPREHENSIVE METABOLIC PANEL, PLASMA
- PTT PERIPHERAL VEIN
- PROTHROMBIN TIME - INR
- CREATINE KINASE - CK (CPK)

- MR LUMBOSACRAL PLEXUS WITH + WITHOUT IV CONTRAST

- LUMBAR PUNCTURE;
- CSF CELL COUNT
- ANGIOTENSIN CONV ENZYME(ACE),CSF
- CYTOLOGY, NON-GYN
- GLUCOSE, CSF
- PROTEIN, TOTAL, CSF
- FLOW CYTOMETRY

The results

Low B-12

Everything else was normal

More imaging

PET-CT skull base to mid-thigh negative for malignancy

Repeat Lumbar spine MRI showing DDD, chronic superior endplate deformity at L3, L4-5 very **small disc protrusion minimally impinging right L4 nerve root** with mild extraforaminal edema & **mod/severe Left foraminal stenosis causing compression of L5 nerve root** with mild extraforaminal edema

Repeat MR Lumbar Plexus showed signal hyperintensity and enlargement of the **extraforaminal right L4 nerve root with signal intensity propagating into the right femoral and obturator nerves**

Back in clinic

Returned to clinic 8/24 with **left low back pain and groin pain** so we did

Left L3, L4, L5 LMBB to address his back pain

Back is better now but the etiology of his peripheral neuropathy is still unclear

64 year old male with hx lumbar DDD presenting with alternating and disabling leg pain with T2 hyperintensity and enhancement of the Right femoral and obturator nerves on plexus studies

Was this related to the COVID vaccination? Where is the link?

Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review

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Nerve imaging

Peripheral nerve injury can occur in patients with COVID-19 secondary to **post infectious inflammatory neuropathy, prone positioning–related stretch and/or compression injury, systemic neuropathy, or nerve entrapment from hematoma.**

Although mechanisms of COVID-19–related neuropathy are yet to be fully understood, the **receptor for severe acute respiratory syndrome coronavirus 2 infection (angiotensin-converting enzyme 2) has been found to be expressed in the nervous system**

Infectious peripheral neuropathy is **known to occur secondary to other viruses** such as hepatitis C, human immunodeficiency virus, and varicella zoster.

Similarly, **immune-mediated neuropathies** such as Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy are **known to occur in the setting of viral infection.**

Prolonged hospitalization can in itself lead to peripheral nerve abnormality due to critical illness polyneuropathy or secondary to prolonged patient positioning

MR neurography can help detect skeletal muscle changes earlier than electromyography—as soon as 4 days after injury

Pathogenesis

“SARS-CoV-2 has a **spike protein surface** unit 1 that has a high binding affinity to the human receptor **angiotensin-converting enzyme 2 (ACE2)**. The increased expression of ACE2 in the epithelial cells in the lower respiratory tract facilitates viral entry by fusion with the cell membrane. The expression of the ACE2 receptors likely explains the involvement of medullary structures by SARS-CoV-2, but is less likely to be an explanation for the involvement of the temporo-limbic structures by the virus. ACE2 is strongly expressed in the **ventrolateral medulla and the nucleus of the tractus solitarius**, two areas that are closely involved in the regulation of the respiratory cycle”

Pathogenesis

“A **neuronal dissemination model** of coronavirus invasion, in which the **virus infects a peripheral neuron** and relies on the machinery of **active transport, synaptic terminals and retrograde transport** to the neuronal cell body in remote areas of the brain, has been postulated. This trans-synaptic transfer mechanism is supported by studies involving the hemagglutinating encephalomyelitis virus strain 67 N (HEV-67 N), the first CoV strain that was found to invade the porcine brain.”

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

Etiology	Recommended Imaging	MRI Characteristics	US Characteristics	Pertinent Clinical Features
Inflammatory neuropathy (21,26)	MRI, 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)*	MRI (for better evaluation of muscle), US (for small nerves not well seen at MRI)	Signal hyperintensity, thickening, often of multiple plexus nerves; muscle edemalike signal	Hypoechogencity, thickening of affected nerve (ie, suprascapular, long thoracic nerve)	Sudden and rapid onset, following infection
Positioning-related peripheral nerve injury of extremities (11,16,17)	MRI (for better evaluation of muscle), US (for dynamic imaging, well tolerated)	Signal hyperintensity of affected nerve with or without muscle edemalike signal if acute, fatty atrophy if chronic	Hypoechogencity, thickening of affected nerve; with or without subluxation on dynamic maneuvers; with or without 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)	MRI, US (limited by clavicle)	Signal hyperintensity, thickening of upper or lower plexus with or without muscle edemalike signal if acute, fatty atrophy if chronic	Hypoechogencity, thickening of upper or lower plexus with or without 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 with or without multifocal muscle edemalike signal/fatty atrophy based on etiology and chronicity	Thickening of the affected nerve with or without multifocal muscle atrophy if chronic	Preexisting polyneuropathy plus comorbidity (ie, diabetes) versus acquired polyneuropathy and myopathy in critical illness
Nerve entrapment (16–18)	MRI or US	Signal hyperintensity of affected nerve, nerve compression, or altered course due to mass effect with or without adjacent hematoma	Hypoechogencity, thickening of affected nerve, nerve compression or altered course due to mass effect with or without adjacent hematoma	Weakness/sensory deficit acquired while undergoing anticoagulation therapy; with or without swelling/palpable mass

Note.—COVID-19 = coronavirus disease 2019.

* The diagnosis of Parsonage-Turner Syndrome is one of exclusion and the rarity thus far of reported immune-mediated cases after COVID-19 (aside from Guillain-Barré syndrome and its variants) should be considered. Source.—Reference 8.

SARS-CoV-2 vaccine-related neurological complications

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Case A

- 87 year old man with HTN, had COVID infection November 2020. 13 days after initial mild flu-like symptoms, he developed b/l disabling, progressive generalized, action-induced myoclonus.
  - Labs negative for metabolic cause and negative COVID PCR
  - MRI brain negative for structural lesions
  - CSF analysis showed no abnormalities
- Because of the subacute onset and unremarkable ancillary investigations, a **SARS-CoV-2 associated para-infectious myoclonus was diagnosed**
- Treatment with levetiracetam, clonazepam, and pulse methylprednisone was initiated
- Two months after primary infection, he was **vaccinated with Pfizer COVID vaccine** and had **progression of myoclonus**, however had improvement within days.
- Three months after initial presentation only a mild action-induced myoclonus persisted

Case B

- 62 year old woman with ocular melanoma experienced a **thunderclap headache** without any other complaints, after Pfizer COVID vaccine.
- Headache spontaneously improved after 1 day
- **10 days after vaccination** she had a **second thunderclap headache** and a sudden brief **loss of consciousness** without head trauma
- Neuro exam showed a bradyphrenic woman with motoric dysphasia and mild dysmetria in all extremities, otherwise normal
- Labs, brain CT and MRI, EEG, and CSF analysis were all unremarkable
- Symptoms recovered, then had the **second vaccination** and experienced **another thunderclap headache** without any other neurological deficits

Case C

- 21 year old women with unremarkable past medical history developed generalized malaise and subfebrile temperature **two hours after her first COVID vaccination**
- 6 hours later experienced a **thunderclap headache with nausea and vomiting with tachycardia, HTN and restlessness**
- Neurological examination, blood analysis, and brain CT and CTA were all normal
- She was treated with paracetamol, NSAIDs, IV morphine, and oxygen therapy and symptoms diminished over 24h

Long-Segment Nonfocal Peripheral Neuropathies After COVID-19 Infection: A Case Report of Magnetic Resonance Neurography Findings

Darryl
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Patient 1

50-year-old man with diabetes, hypertension, and asthma, was hospitalized with acute respiratory failure 5 days after developing a cough and fever. He tested positive for COVID on PCR, developed severe ARDS and was intubated for 3 weeks in the supine position.

He awoke with the **inability to plantarflex or dorsiflex his left foot or toes.** He also had **severe neuropathic pain** and hyperesthesia in the **sciatic distribution.**

He was discharged 1 week later to inpatient rehabilitation.

1.5 months postdischarge, he had significant recovery in the tibial division of his sciatic nerve by examination; however, he reported **persistent pain and had severe deficits in the peroneal nerve distribution**. He also had **diminished sensation to light touch distal to the knee**.

EDX at that time confirmed a severe, proximal sciatic neuropathy.

MR neurography of the left pelvis and thigh 3 months post-onset revealed diffuse, long- segment, T_2-weighted signal **hyperintensity of the sciatic nerve throughout the thigh**, with otherwise maintained nerve fascicular architecture and size. Prominent T_2-signal hyperintensity of all hamstring musculature was compatible with **active denervation.**

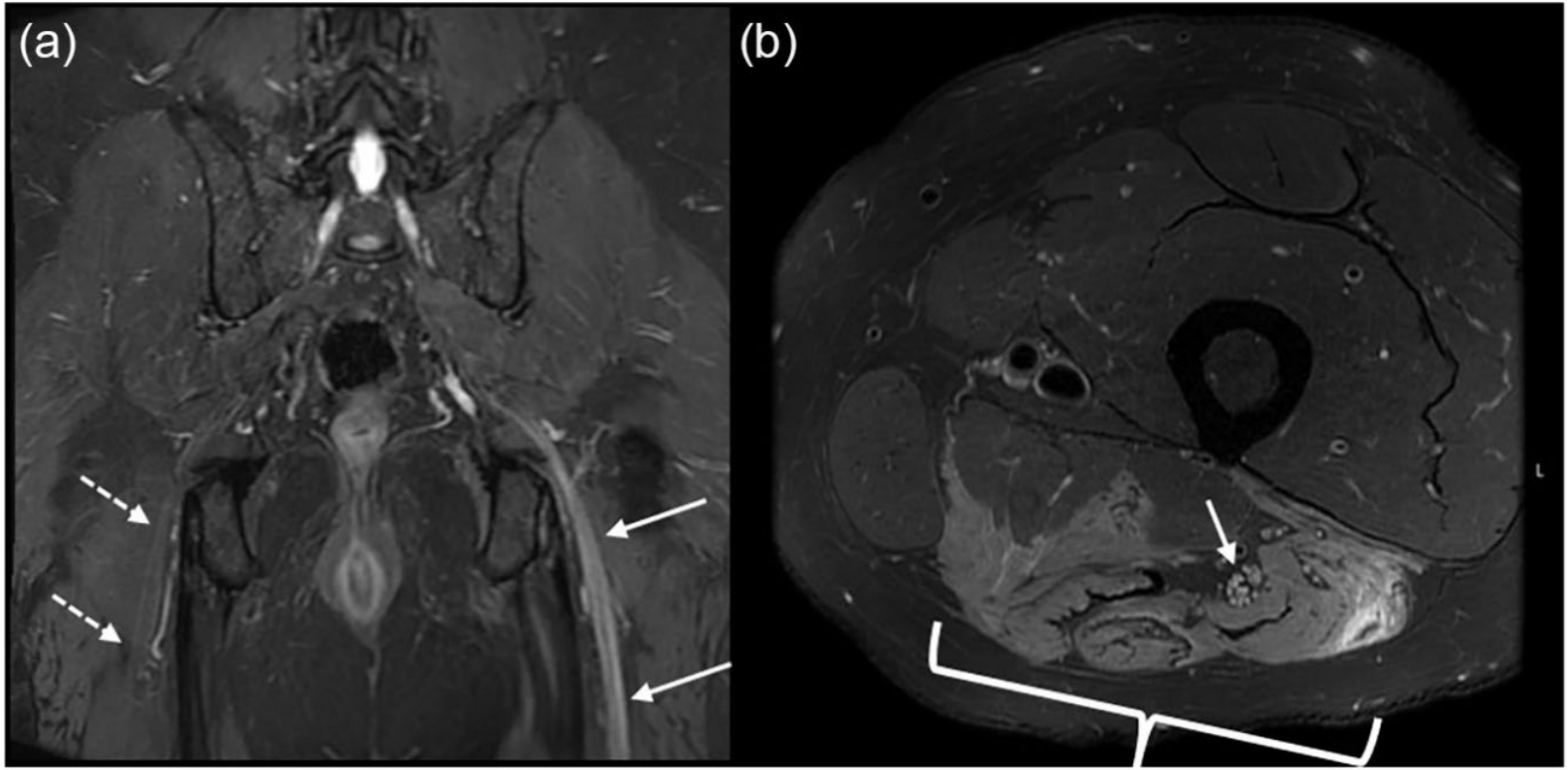

Fig. 1. Magnetic resonance neurography of the pelvis and left thigh in patient 1 (50-year-old man). Coronal (a) and axial (b) T_2-weighted Dixon water images through the pelvis (a) and left thigh (b) demonstrate long-segment signal hyperintensity of the left sciatic nerve (solid arrows) and denervation edema pattern of the hamstring musculature (bracket, b). Compare with the normal signal intensity of the right sciatic nerve (dashed arrows, a).

Patient 2

55-year-old man with a history of paroxysmal A. fib. was admitted with acute respiratory failure and diagnosed with COVID-19 by PCR. He was intubated for 7 weeks in the supine position.

After extubation, **severe, patchy, left upper extremity weakness, numbness, and pain** were noted.

EDX 5 days later suggested a **left brachial plexopathy with complete muscle denervation** in the distribution of the **musculocutaneous, median, and ulnar nerves and partial radial nerve denervation.**

He was treated with gabapentin 1800 mg daily, with some improvement in pain and numbness but persistent weakness.

Repeat EDX 7 weeks later revealed **marked sensorimotor abnormalities** in the left median and ulnar nerve distributions and, to a lesser degree, the radial, axillary, musculocutaneous, and suprascapular nerve distributions. Neurologic examination revealed patchy weakness throughout the left upper extremity, with most severe involvement (no movement observed) of the abductor pollicis brevis and interosseous muscles of the hand.

MR neurography of the left brachial plexus and arm 3 months post-onset demonstrated diffuse, T_2-weighted signal **hyperintensity of the plexus**. Within the arm, the **ulnar, median, and musculocutaneous nerves** were all hyperintense. Findings of active muscle denervation in the distribution of multiple nerves within the arm and forearm were noted.

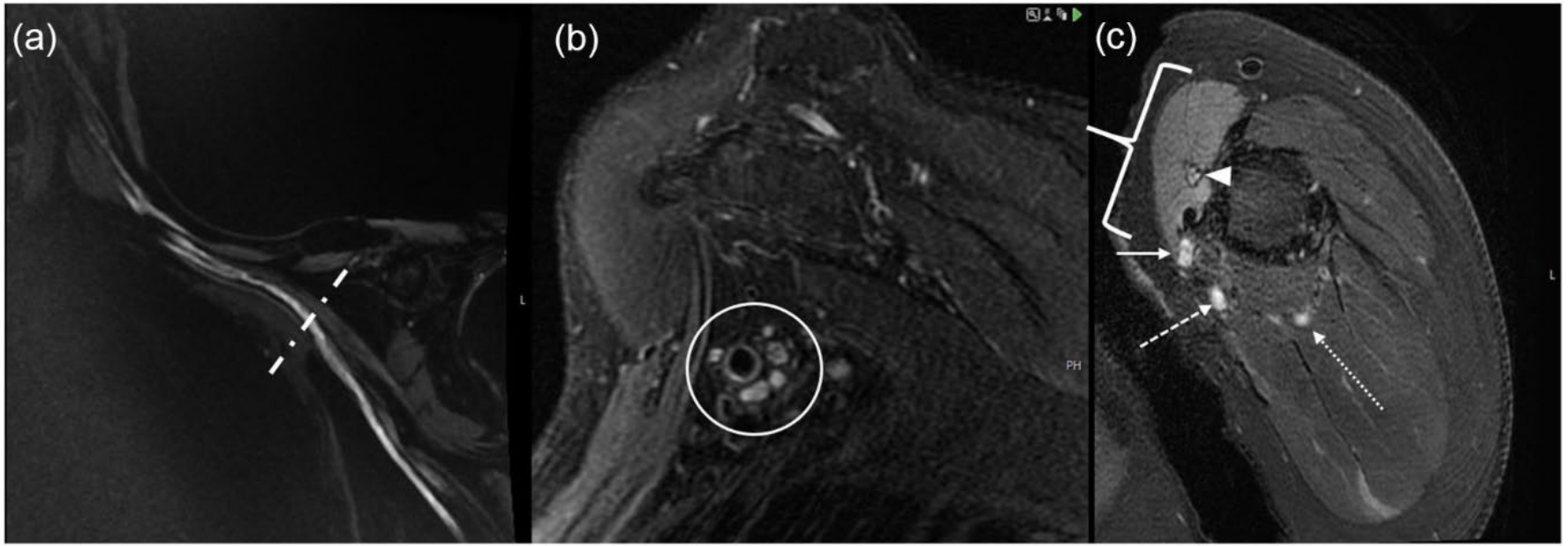

Fig. 2. Magnetic resonance neurography of the left brachial plexus in patient 2 (55-year-old man). Coronal T_2-weighted, post-gadolinium inversion recovery image (a) demonstrates prominent signal hyperintensity of nerves throughout the left brachial plexus. Oblique sagittal T_2-weighted Dixon water image (b), orthogonal to the infraclavicular plexus, as delineated by the dashed line in A, confirms signal hyperintensity of the terminal branches in short axis. Axial T_2-weighted Dixon water image (c) through the proximal arm demonstrates denervation edema pattern of the biceps muscle (bracket) and signal hyperintensity of the median (solid arrow), ulnar (dashed arrow), musculocutaneous (arrowhead), and radial (dotted arrow) nerves.