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COVID-19-Associated Myelitis Involving the Dorsal and Lateral White Matter Tracts: A Case Series and Review of the Literature

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ABSTRACT

SUMMARY: Coronavirus disease 2019 (COVID-19) myelitis is a rare condition, most commonly presenting with nonenhancing central expansile cord T2 signal changes. A single case report has also described longitudinal involvement of the dorsal columns. We present 5 cases of COVID-19-associated myelitis with tract-specific involvement of the dorsal and lateral columns and discuss potential pathophysiologic pathways for this unique pattern.

ABBREVIATION: COVID-19 = coronavirus disease 2019

Coronavirus disease 2019 (COVID-19) is primarily known as a respiratory illness; however, neurologic responses to this infection have been increasingly described, including infectious encephalopathy, meningoencephalitis, Guillain-Barre syndrome, and stroke.[1] Myelitis has been reported multiple times as a post-infectious inflammatory reaction from COVID-19 infection. Previously documented cases have predominantly described central longitudinal T2 changes without corresponding enhancement,[2-12] with 2 cases of autoimmune myelitis (antimyelin oligodendrocyte glycoprotein-spectrum disorder and aquaporin-4 neuromyelitis optica) also found to be associated with COVID-19 infection.[13,14] At the more extreme ends of the spectrum, 1 report described T2-bright and centrally necrotic enhancing lesions,[15] with another case presenting with clinical symptoms of transverse myelitis with paraplegia below the T10 level but with a normal appearance of the spinal cord on clinical MR imaging.[16] A few cases have noted more tract-specific disease, with 1 case demonstrating ventral horn–predominant T2 hyperintensity and acute flaccid myelitis[17] and 1 interesting case demonstrating dorsal column–predominant T2 signal abnormality with progressive numbness in the feet and hands.[18]

Although most reports of COVID-19-associated myelitis have noted central-predominant T2 signal change, we describe 5 cases demonstrating lateral and dorsal column–specific disease. All patients were seen at our single academic institution, and were the only 5 cases of COVID-19-associated myelitis diagnosed and treated since the beginning of the pandemic in March 2020.

Case 1

Presentation. A 62-year-old woman without prior neurologic disease presented 10 days after a COVID-19 diagnosis with a 1-day history of rapidly ascending numbness with gait impairment and fecal incontinence. She previously experienced mild COVID-19 symptoms, including anosmia and cough, which had resolved several days before her hospitalization. Her examination findings were notable for diffuse hyperreflexia and reduced vibratory and pinprick sensations distally with sensory ataxia.

Laboratory Findings. Serum laboratory evaluation demonstrated elevated inflammatory markers including erythrocyte sedimentation rate and C-reactive protein, a ganglioside panel positive for ganglioside-monosialic acid antibodies, and CSF with elevated lymphocytes. CSF protein and glucose levels were normal. Further laboratory studies were unremarkable, including vitamins B3, B6, B12, copper, methylmalonic acid, vitamin E, and viral panels (Online Supplemental Data).

Imaging Findings. Thoracic spine MR imaging showed patchy areas of T2 hyperintensity as well as patchy areas of enhancement throughout the thoracic cord, predominantly involving the lateral cord and dorsal columns (Fig 1). There was also ventral and

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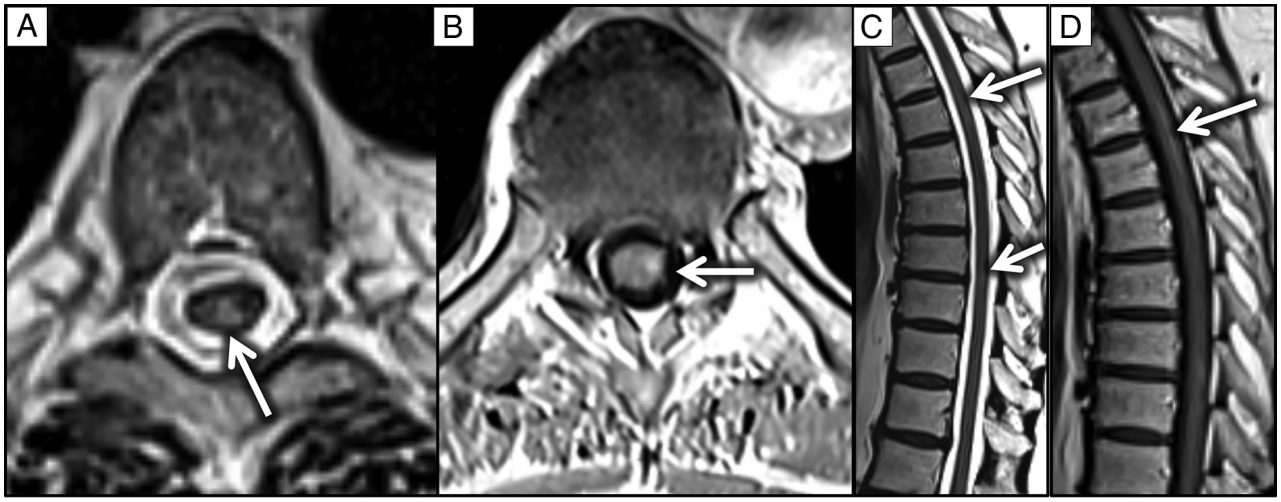

FIG 1. Axial T2 (*A*), and T1 postcontrast (*B*) images demonstrate T2 hyperintensity involving the posterior columns and patchy enhancement predominantly in the posterior and lateral columns (*arrow* pointing to posterior column in *A*, and *arrow* to lateral column in *B*). Sagittal T2 (*C*) and postcontrast T1 (*D*) images demonstrate corresponding signal changes (*arrows*).

dorsal nerve root enhancement along the cauda equina. MR imaging findings of the brain were unremarkable, with no enhancing lesions or other pathology. Electromyography and nerve conduction studies were obtained 12 days after the onset of symptoms, which did not show electrodiagnostic evidence of a peripheral polyneuropathy.

Management. Treatment with plasma exchange and oral prednisone was initiated with improvement in her clinical symptoms. She was discharged with a month-long oral prednisone taper. At the 4-month follow-up visit, her previous clinical symptoms had largely resolved.

Case 2

Presentation. A 79-year-old man with a history of hypertension, hyperlipidemia, prior back surgery, and chronic low back pain requiring a walker for ambulation at baseline presented with a 2-month history of worsening lower extremity weakness and fecal incontinence. He had been diagnosed with COVID-19 infection approximately 2 weeks before symptom onset. His examination was notable for paraparesis with minimal right-ankle dorsiflexion and plantar flexion, areflexia, and increased tone in his lower extremities, as well as reduced vibration and proprioception in a length-dependent pattern.

Laboratory Findings. Serum laboratory evaluation demonstrated elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), but CSF studies showed a normal white blood cell count and protein and glucose levels. Further laboratory studies showed normal vitamins B1, B12, vitamin E, folate, copper, monoclonal protein, and methylmalonic acid levels. He was found to be heterozygous for the methylenetetrahydrofolate reductase (*MTHFR*) genes (C665T and A1286C) (Online Supplemental Data).

Imaging Findings. MR imaging demonstrated ventral medullary and left-lateral/dorsal-lateral cord signal abnormality from C2 through C3 along with patchy lateral and dorsal column involvement of the mid and lower cervical cord and thoracic cord with associated diffusion restriction (Fig 2). There was no associated enhancement. Electromyography and nerve conduction studies showed signs of active denervation in the proximal-greater-than-distal lower extremities.

Management. He was treated with 5 days of intravenous immunoglobulin and 5 sessions of plasma exchange, unfortunately without notable improvement in symptoms. He was then discharged to inpatient rehabilitation with a rehabilitation course complicated by urinary tract infection and aspiration pneumonitis. After extensive inpatient rehabilitation, he demonstrated improvement in his functional status and was discharged home.

Case 3

Presentation. A 40-year-old woman with a medical history including kidney transplant secondary to focal segmental glomerulosclerosis on chronic immunosuppression, latent tuberculosis, and diabetes mellitus type 2 presented with new and rapid onset of low back pain, lower extremity weakness, and sensory changes. She developed these symptoms within a few days of testing positive for COVID-19. Her examination findings were notable for hyperreflexia in the lower extremities and decreased strength in the proximal-greater-than-distal lower extremities with preserved sensation.

Laboratory Findings. Serum laboratory evaluation demonstrated an elevated inflammatory marker (erythrocyte sedimentation rate with normal C-reactive protein levels). CSF studies showed a normal white blood cell count and protein and glucose levels, but 11 unique oligoclonal bands. Findings for evaluation of serum antibodies including myelin oligodendrocyte glycoprotein aquaporin-4 antibody immunoglobulin G for demyelinating disease were negative. Other laboratory studies included normal vitamin B12, B1, B6, D, copper, and folate levels (Online Supplemental Data). In the setting of her immunosuppressive

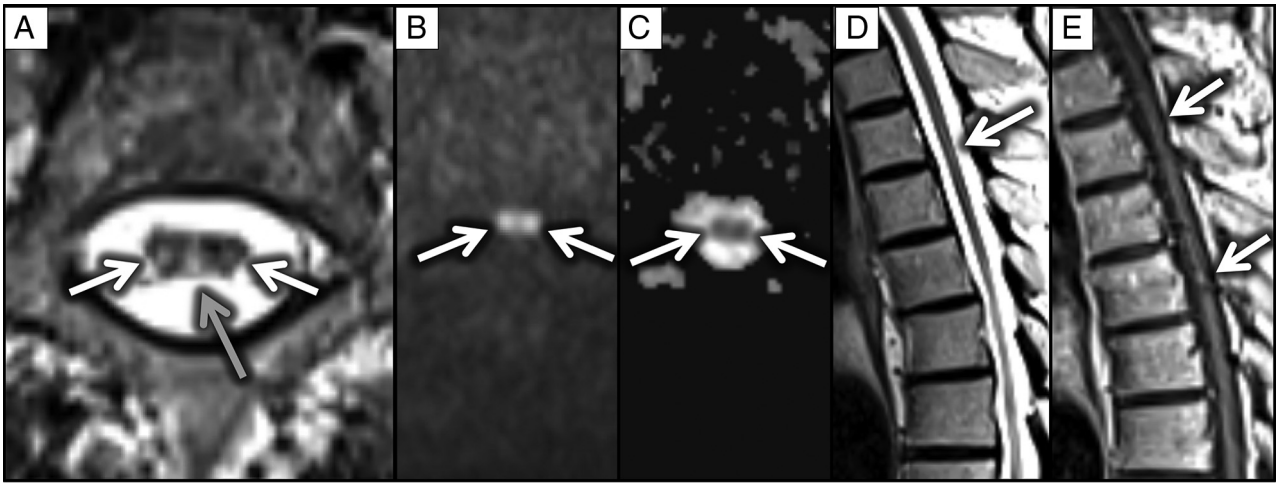

FIG 2. Axial T2 (*A*) and diffusion-weighted (*B*) images demonstrate T2 hyperintensity involving the posterior (*gray arrow*) and lateral columns (*white arrows*) with corresponding DWI hyperintensity and ADC hypointensity (*C*) confirming restriction (*white arrows*). Findings were less conspicuous on sagittal T2 (*D*) and postcontrast T1 (*E*) images, with only faint signal changes present (*white arrows*).

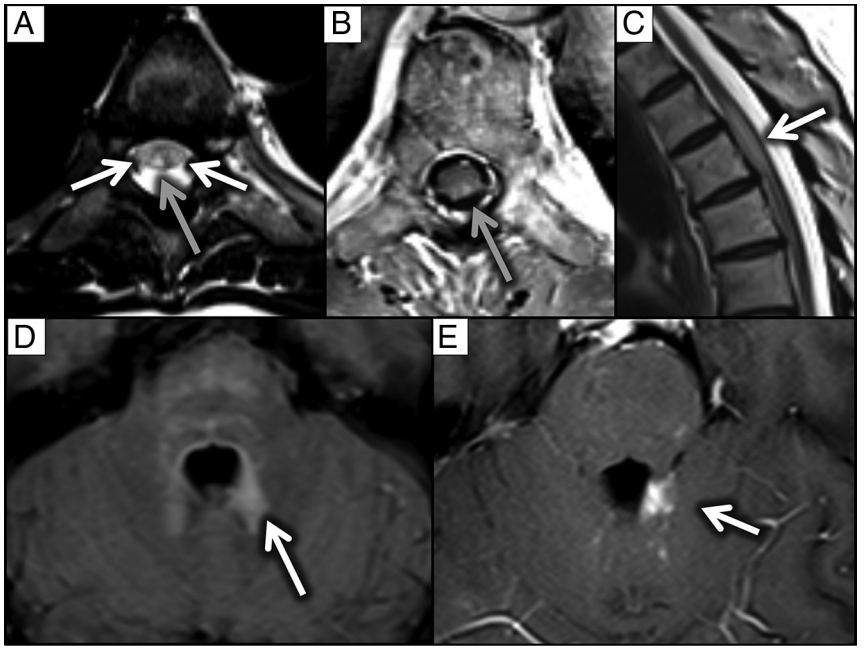

FIG 3. Axial T2 (*A*) and T1 postcontrast (*B*) images demonstrate T2 hyperintensity involving the posterior columns (*gray arrow*), with faint involvement of the lateral columns (*white arrows*, *A*). There was corresponding scattered patchy enhancement in these regions (*gray arrow*, *B*). T2 hyperintensity and expansion of the upper thoracic cord was well-demonstrated on sagittal views (*white arrow, C*). Brain MR imaging shows T2/FLAIR hyperintensity and corresponding enhancement surrounding the fourth ventricle (*white arrows*, *D* and *E*).

state, extensive infectious work-up was performed, which did not show evidence of active infection. Electromyography and nerve conduction studies showed no evidence of neuropathy or myopathy.

Imaging Findings. MR imaging of the brain showed T2 and FLAIR hyperintensities with enhancement in the midbrain, pons, and medulla. MR imaging of the spine showed multifocal T2/STIR hyperintensities and enhancement predominantly involving the dorsal and lateral columns within the cervical and thoracic spinal cord (Fig 3). Intracranial MR vessel wall imaging showed no arterial narrowing or abnormal enhancement along the vessel walls.

Management. She was given a 3-day course of high-dose intravenous methylprednisolone with subjective improvement in her symptoms. She was discharged home with an increased dose of oral prednisone along with her other immunosuppressive medications. Unfortunately, during the course of several months, she developed worsening symptoms, including increased weakness, gait instability, severe constipation, and sensory changes. Repeat MR imaging demonstrated worsened T2-hyperintense enhancing lesions at the level of T3–T4 as well as new enhancing brain lesions with enhancement most pronounced in the basal ganglia, pons, and cerebellum. Further investigation regarding other etiologies of her encephalomyelitis, including unremarkable brain biopsy findings, have been unrevealing thus far, and her working diagnosis remains COVID-19-associated encephalomyelitis.

Case 4

Presentation. A 62-year-old man with a history of end-stage renal disease on hemodialysis, diabetes mellitus type 2, hypertension, and hyperlipidemia presented with back pain, fever, cough,

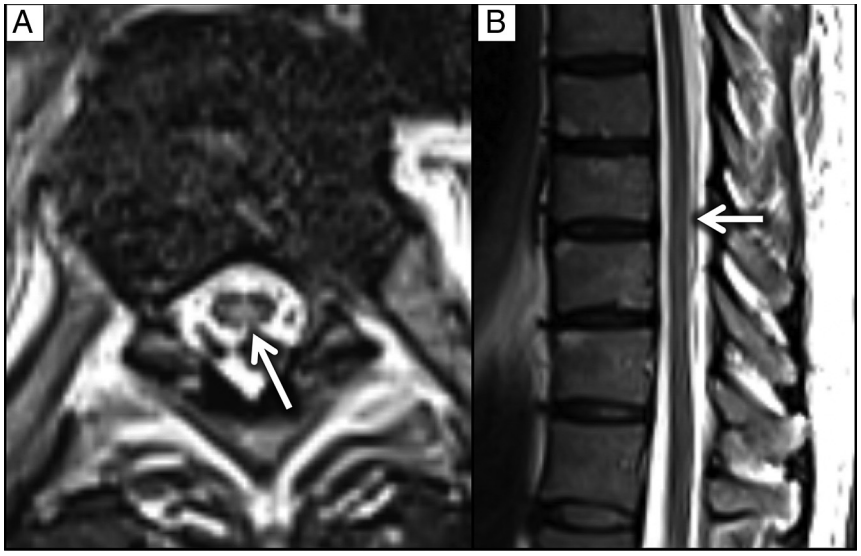

FIG 4. Axial T2 image through the thoracic cord demonstrates T2 hyperintensity involving the posterior columns (*white arrow*). Subtle hyperintensity could be seen in this region on sagittal T2 images (*white arrow*).

and chills. Symptoms started 2 days after receiving the COVID-19 vaccine, and he subsequently tested positive for COVID-19 infection. His examination was notable for mildly decreased strength in the bilateral upper extremities with intact strength in the lower extremities without noted sensory deficits.

Laboratory Findings. Serum evaluation demonstrated elevated inflammatory markers including erythrocyte sedimentation rate and C-reactive protein. Vitamin B12 and folate levels were normal (Online Supplemental Data).

Imaging Findings. MR imaging of the spine showed intramedullary T2 hyperintensities throughout the cervical and thoracic cord, predominantly involving the lateral and dorsal columns (Fig 4).

Management. He was discharged with medications for pain management, but no immunomodulating therapies were prescribed.

Case 5

Presentation. A 64-year-old man with no prior neurologic history on zinc supplementation during the COVID-19 pandemic, presented with a 3-month history of lower extremity paresthesia and gait imbalance, which had a rapid onset 2 days after diagnosis of COVID-19 infection. Physical examination findings were notable for lower extremity hyperreflexia and reduced vibratory and proprioceptive sensations in a length-dependent pattern with sensory ataxia and preservation of strength.

Laboratory Findings. Serum laboratory evaluation demonstrated an elevated zinc level and an undetectable copper level (Online Supplemental Data).

Imaging Findings. Findings of MR imaging of the brain were unremarkable, with no enhancing lesions or other pathology. MR imaging of the spine showed diffuse T2-hyperintense signal abnormality predominantly involving the dorsal columns throughout the length of the spinal cord (Fig 5). Electromyography and nerve conduction studies demonstrated mild axonal neuropathy.

Management. He underwent oral copper supplementation. On repeat evaluation 3 months later, he reported no subjective improvement in his symptoms. Testing for serum copper levels was repeated at that time with findings within normal limits.

DISCUSSION

Hypothesized mechanisms for neurologic sequelae of COVID-19 have been ascribed to a systemic inflammatory response or sequela of critical illness.[19] While multiple reports have described associated nonspecific central cord edema, few have demonstrated tract-specific disease in the setting of this virus.[18]

Lateral and dorsal column involvement is relatively atypical in viral myelitis, which usually demonstrates a propensity for central gray matter regions of the cord.[20] While infectious posterior column involvement has been seen in HIV,[21] and posterior and lateral column involvement in human T-cell lymphotropic virus type 1-associated myelopathy,[22] involvement of these regions is more commonly seen in the noninfectious setting of subacute combined degeneration.[20] Subacute combined degeneration is caused by a disturbance in the methylation pathway,[23] which can stem from metabolic causes such as vitamin B12[24] and copper deficiency, vitamin E deficiency,[25,26] and toxic causes such as excess nitrous oxide (secondarily causes qualitative B12 deficiency),[27] and intrathecal methotrexate.[28] Metabolic and nutritional factors have been found to have key roles in supporting the immune system, specifically in the setting of COVID-19,[29] with some evidence supporting vitamin B12 supplementation in the fight against this pathogen.[30]

It can only be speculated that COVID-19 may affect the methylation cycle, which, in turn, may expose deficiencies in the immune system that are supported by this pathway. This finding may be supported by dorsal and sometimes lateral column involvement in these cases as well as in the 2 cases that demonstrated an underlying propensity for methylation cycle abnormalities. In case 2, the patient was heterozygous for mutation of the *MTHFR* gene, which has been found to strongly predispose to subacute combined degeneration.[31] Most interesting, the *MTHFR* C677T polymorphism has also previously been found to predispose to a more severe course of COVID-19, with vitamin supplementation recommended in individuals with this mutation.[32] In case 5, the patient had an underlying copper deficiency, likely resulting from zinc toxicity from supplementation. Although this may be considered a confounder for the patient's myelitis findings, clinical symptoms of rapid onset are in line

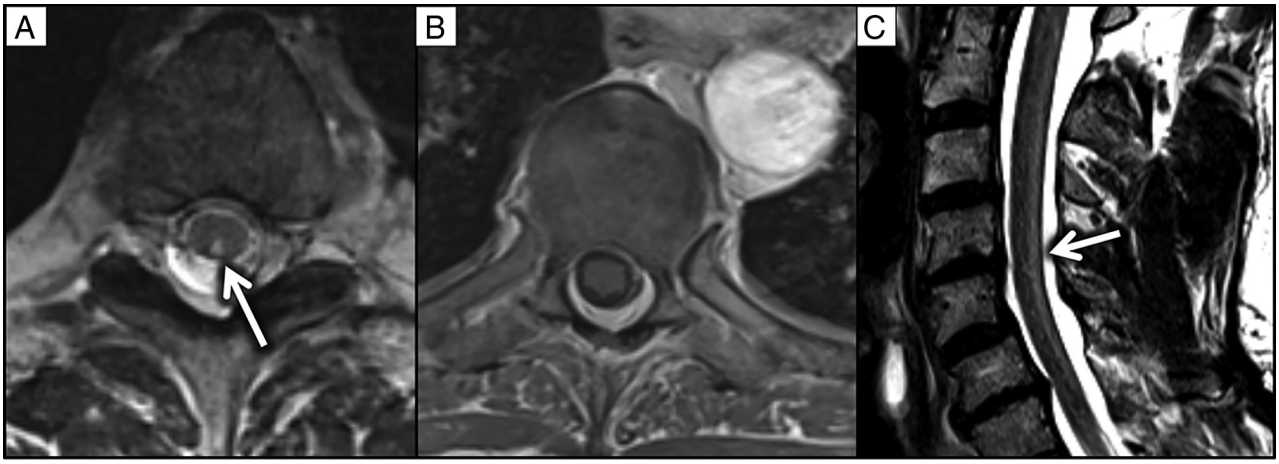

FIG 5. Axial T2 (*A*) and T1 postcontrast (*B*) images through the thoracic cord demonstrate T2 hyperintensity involving the posterior columns (*white arrow*), with no corresponding enhancement. A sagittal T2 image in the cervical spine (*C*) demonstrates hyperintensity along the dorsal aspect of the cord (*white arrow*).

with the other reported COVID-19-associated cases, and these symptoms did not improve with reversal of the copper deficiency.

Most interesting, none of the 5 COVID-19-associated cases of myelitis diagnosed and treated at our institution demonstrated the predominantly central expansile T2-signal hyperintensity reported most commonly throughout the literature.[2-12] This finding may be related to regional differences in viral strains or environmental factors. Additionally, it may be that this tract-specific appearance, only rarely described in the literature, is not always clinically attributed to the patient's COVID-19 status.

Work-up and management of these 5 patients varied widely. These differences can be attributed to inpatient-versus-outpatient evaluation as well as different primary services overseeing their care. Ideally, further investigation regarding the mechanism and etiology of COVID-19 myelitis would provide a more comprehensive and consistent evaluation of these patients.

CONCLUSIONS

Imaging features of dorsal and lateral white matter tract viral/postviral involvement further support a vitamin deficiency/nutritional component to the severity of COVID-19 symptoms. A link between the pathophysiology of COVID-19 and the methylation pathway is possible.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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