

MRI-negative myelitis associated with cerebral venous thrombosis after COVID-19 infection

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SUMMARY

Transverse myelitis and cerebral venous thrombosis represent some of the described neurological complications of coronavirus disease. A woman in her early 30s presented with headache, left-sided sensory symptoms and voiding difficulty. The patient also reported dry cough, fever, nasal congestion, anosmia and ageusia 2 weeks before presentation. The clinical examination showed sensory disturbances on the left side of the body, starting from the lower abdomen and extending to the left leg, which was consistent with transverse myelitis. The laboratory assessment confirmed a previous infection with coronavirus disease and excluded autoimmune entities. Radiological investigations revealed left transverse sinus thrombosis with no spinal cord abnormalities. The treatment was started with therapeutic anticoagulation and intravenous high-dose steroids. The patient showed significant improvement, and the neurological deficits resolved after 3 months. This is the first documented case of imaging-negative myelitis associated with cerebral venous thrombosis after coronavirus disease.

BACKGROUND

COVID-19 is characterised by severe acute respiratory syndrome in association with respiratory tract infection. Different types of systemic complications after the initial infection were identified.¹ As the virus can affect both the central and peripheral nervous systems, neurological sequelae are some of the most prominent systemic involvements.^{2,3}

Transverse myelitis is one of the documented neurological complications of the disease.⁴ This type of myelopathy is usually associated with radiological changes in MRI. However, some cases are not associated with MRI abnormalities. This is known as MRI-negative myelitis, and it was previously reported in the context of myelin oligodendrocyte glycoprotein-IgG-associated myelitis and recently after COVID-19 infection.⁵

Vascular manifestations belong to the common complications of COVID-19 infection, and they were widely studied in the literature. The most frequent presentation is thrombotic events in both the arterial and venous systems.⁶ In this report, we present the first documented case of MRI-negative myelitis in association with cerebral venous thrombosis, which presented about 2 weeks after COVID-19 infection and showed a good response to treatment.

CASE PRESENTATION

A woman in her early 30s presented to our clinic complaining of headache and disturbed sensation on the left side of the body. The symptoms started about 1 week before presentation with a new-onset severe headache, bilateral tinnitus and blurry vision. The headache was also associated with nausea and anorexia. After nearly 48 hours, the patient noticed disturbed sensation on the left side of the lower body. Since then, she also complained of constipation and voiding difficulties.

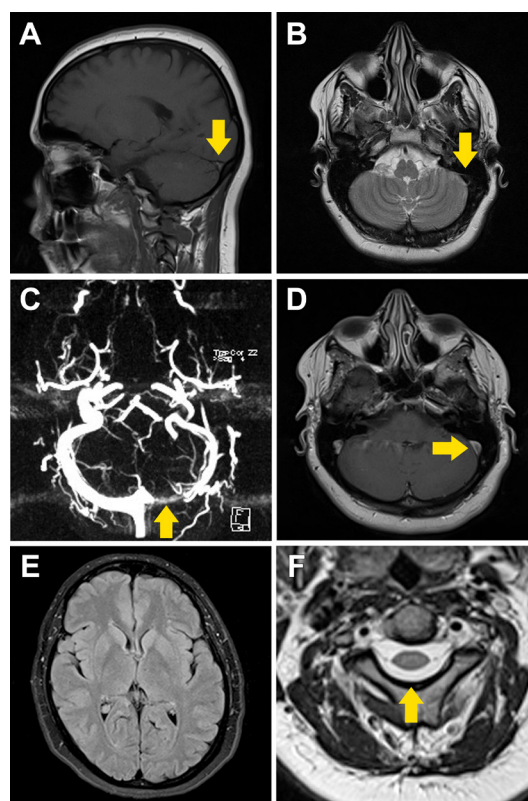


Figure 1 MRI of the brain and spinal cord with and without contrast (1.5 teslas) at presentation. (A) T1-weighted sagittal view without contrast showing hyperintense signal of the left transverse sinus (arrow). (B) T2-weighted axial view showing hypointense left transverse sinus (arrow). (C) Magnetic resonance venography in axial view showing partial left transverse sinus thrombosis (arrow). (D) The sinus shows a filling defect after contrast injection (arrow). (E) FLAIR axial view of the brain at the level of the thalamus and the corona radiata without visible lesions. (F) Magnified axial T2-weighted view of the cervical spinal cord (arrow) at the C3/C4 level showing no focal hyperintensities.



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Table 1 Laboratory results in serum

Laboratory assay	Patient's results	Reference range
Haemoglobin, g/dL	13.4	11.6–16.5
White blood count, $\times 10^9/L$	9.7	4.5–11.0
Platelet count, $\times 10^9/L$	332	150–450
CRP, mg/L	3.21	0–6
Glucose, mg/dL	112	75–120
Sodium, mmol/L	139	135–145
Potassium, mmol/L	4.2	3.5–5
Calcium, mg/dL	8.01	8.5–10.05
Magnesium, mmol/L	0.99	0.74–1.19
INR	1.44	1.0–1.06
D-Dimer, $\mu g/mL$	0.23	0–0.5
TSH, mU/L	0.57	0.4–4.4
Copper, $\mu g/dL$	112	80–155
Iron, $\mu g/dL$	68.5	37–145
Ferritin, ng/dl	12.5	5–148
Vitamin B12, pg/ml	308	174–878
COVID-19 IgM	1.39	Positive >1.0
COVID-19 IgG	2.21	Positive >1.0
HBs-Ag, IU/mL	0.13	Positive >1.0
Anti-HBc-Ag, U/mL	0.24	Positive >1.0
Rheumatoid factor, IU/mL	9.27	0–20
ANA	Negative	Negative
cANCA, U/mL	7.63	< 10
pANCA, U/mL	4.86	< 10
Anti-cardiolipin IgG, U/mL	7.21	≤ 10
Anti-cardiolipin IgM, U/mL	6.89	≤ 10
Homocysteine, $\mu mol/L$	8.36	5.9–15
Lupus anticoagulant	Negative	Negative
Anti-MOG antibodies	Negative	Negative

ANA, antinuclear antibodies; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibodies; CRP, C reactive protein; HBc-Ag, hepatitis B virus core antigen; HBsAg, hepatitis B virus surface antigen; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalised ratio; MOG, myelin oligodendrocyte glycoprotein; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; TSH, thyroid-stimulation hormone.

On further questioning, the patient described symptoms consistent with COVID-19 infection 2 weeks before the onset of the current complaints. At that time, she had nasal congestion, fever with chills and dry cough. She also developed anosmia and ageusia 2 days later. No nasopharyngeal swab was taken at that time. The patient showed gradual improvement under symptomatic therapy, oral antibiotics and dexamethasone 4 mg daily. This all happened 2 weeks before the onset of the neurological symptoms.

In her medical history, the patient has essential hypertension that is treated with bisoprolol. No significant surgical or travel history was described. She does not smoke or consume alcohol, and her familial history is non-significant.

On neurological examination, the patient showed normal muscular strength in the upper and lower extremities with diffusely brisk reflexes. A sensory deficit level was noted at T5–T6 with diminished pinprick and temperature sensation, loss of vibratory sensation and impaired proprioception on the left side of the body. Plantar responses were in extension bilaterally. The patient had a wide-based cautious gait with a positive Romberg sign. Her visual acuity, visual fields and optic fundus were all within normal limits.

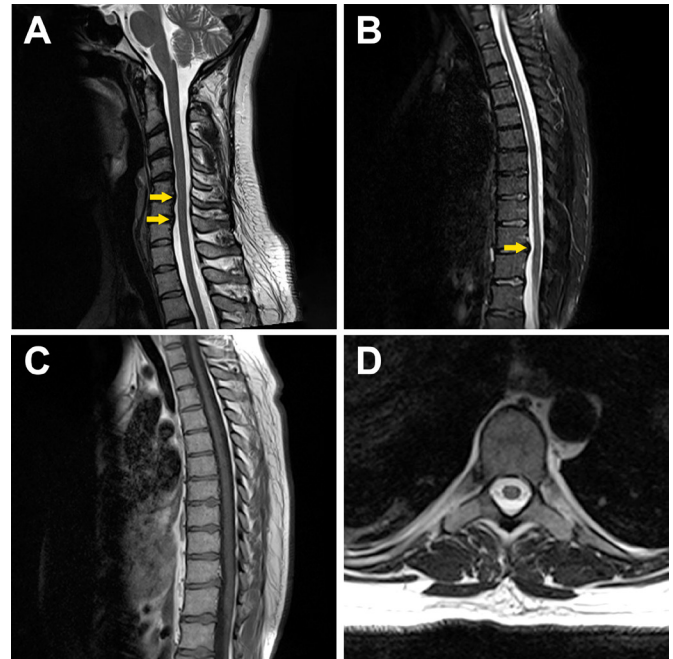


Figure 2 MRI of cervical and thoracic spine 1 week after initiation of therapy. The arrows show bulging in some intervertebral discs without compromising the spinal cord. Otherwise, the images show no spinal abnormalities. (A) T2-weighted sagittal view. (B) Short tau inversion recovery sequence with a sagittal plane view. (C) Gadolinium-enhanced T1-weighted sagittal view of the thoracic spine. (D) T2-weighted axial view of the thoracic spine at the T4/T5 level.

INVESTIGATIONS

We ordered an MRI of the brain, cervical and thoracic spine with and without contrast (figure 1). This revealed partial thrombosis in the left transverse sinus, along with small atypical bilateral frontal foci, most likely vascular in origin. There was no evidence of compressive myelopathy or signal abnormalities in the spinal cord.

As presented in table 1, the laboratory study showed normal thrombocytes, coagulation study and D-dimer level. Both IgM and IgG for COVID-19 were positive. Myeloneuropathy laboratory results such as copper and vitamin B12 were within the reference range. Autoimmune tests and hepatic viral study were also negative. We also investigated potential thrombophilia using homocysteine and antiphospholipid antibodies, which were all within the normal range. Cerebrospinal fluid analysis via lumbar puncture did not show abnormalities. Nerve conduction studies and electromyography of the upper and lower limbs were within normal limits. CT of the chest showed no abnormalities related to COVID-19 infection.

DIFFERENTIAL DIAGNOSIS

Many conditions can be considered within the differential diagnosis of transverse myelitis. For simplification, these could be divided into two main groups: acute/subacute myelopathy and chronic progressive myelopathy.⁷

The acute/subacute group may contain spinal cord infarctions, acute disseminated encephalomyelitis, paraneoplastic syndromes, radiation myelopathy, as well as postinfection and postvaccination myelopathy. Among the chronic causes, one may mention nutritional and toxic myelopathy, neoplastic causes, spinal dural arteriovenous fistula, motor neuron disease and genetic disorders. In light of the presentation of the patient as

Table 2 Reported cases of MRI-negative myelitis after COVID-19 infection

No.	Author	Age (year)	Gender	Latency period	Manifestations	CSF	NCS/EMG	Management	Improvement
1	Memon <i>et al</i> ¹⁷	65	F	9 weeks	Acute onset of paraparesis and urinary retention	Cell count 20/ μ L, lymphocytes predominant, protein 81 mg/dL	Normal	Methylprednisolone IV, Plasmapheresis	Partial
2	Abrams <i>et al</i> ⁴	69	M	NA	Subacute leg weakness, numbness, urinary retention and constipation	NA	Mild denervation at L3-4 myotomes	Methylprednisolone IV and immunoglobulin IV for 5 days	Absent
3	Abrams <i>et al</i> ⁴	64	M	4 months	Acute onset of bilateral paraesthesia in the lower extremities, progressive weakness	NA	NA	Methylprednisolone IV	Partial
4	Abrams <i>et al</i> ⁴	64	F	4 months	Left leg muscle cramps and endorsed weakness and numbness	NA	Mild denervation at L5-S1 myotomes, left more than right	NA	NA
5	Abrams <i>et al</i> ⁴	58	F	1 week	Acute onset of cramping pain in both legs followed by leg weakness and gait imbalance	NA	Normal	Methylprednisolone IV	Partial
6	Abrams <i>et al</i> ⁴	63	M	1 month	Subacute onset of gait disturbance and left leg ataxia	NA	Mild denervation at S1 myotome	NA	NA
7	Metya <i>et al</i> ¹⁵	54	F	12 days	Acute urinary retention with weakness in the lower limbs	Pleocytosis with mild protein elevation	Motor axonal polyradiculopathy in the lower limbs	Methylprednisolone IV and immunoglobulin IV for 5 days	Mild
8	Kallivoulos <i>et al</i> ²⁰	39	M	8 days	Lower body paraesthesia, gait disturbance and bladder dysfunction	lymphocytosis and type four oligoclonal bands	NA	Methylprednisolone IV	Partial
9	Masaad <i>et al</i>	32	F	2 weeks	Subacute onset of headache and left hemianesthesia	Cell count 5/ μ L, lymphocytes predominant, protein 45 mg/dL	Normal	Dexamethasone IV	Significant

*The mean time between COVID-19 infection and the development of neurological manifestations.

CSF, cerebrospinal fluid; F, female; IV, intravenous; M, male; NA, not available; NCS/EMG, nerve conduction study and electromyography.

well as the previously mentioned investigation results, postinfectious myelitis constitutes the most probable diagnosis in this case.

TREATMENT

The management targeted both entities: cerebral venous thrombosis and MRI-negative transverse myelitis. For thrombosis, we administered subcutaneous enoxaparin (60 mg twice daily) for 10 days followed by oral rivaroxaban (20 mg once daily). As for myelitis, the treatment included intravenous dexamethasone (16 mg daily) for 5 days.

Under this therapy, the patient reported significant improvement in both headache and myelopathic symptoms. One week after her first presentation, we performed a repeat MRI of the brain, cervical and thoracic spine with and without contrast. This showed the same radiological findings at the level of the brain, again with a normal spinal cord (figure 2). Further therapy included oral corticosteroids using prednisolone (1 mg/kg) with gradual tapering. Therapeutic anticoagulation was continued for 3 months.

The last follow-up visit was 3 months after the presentation. The patient expressed a significant improvement in symptoms with very mild residual numbness on the left lower extremity. The therapy with steroids and oral anticoagulants was concluded at this point.

DISCUSSION

Three years have passed since the emergence of COVID-19, which is one of the most devastating pandemics the world had ever encountered.⁸ Although respiratory syndrome is the most common presentation, the infection can be also associated with several types of manifestations in many organ systems. Concerning the nervous system, the most common neurological manifestations include headache, ataxia and seizures as well as peripheral involvement such as anosmia, ageusia and Guillain-Barré syndrome.⁹ Other reported manifestations include meningitis, encephalitis and encephalopathy in addition to transverse myelitis and vascular complications (ischaemic strokes, intracerebral haemorrhage and cerebral venous thrombosis).^{6,9}

Myelopathy is the term used to describe spinal cord dysfunction.⁷ Transverse myelitis is an inflammatory myelopathy that can be a part of an immune system disorder, such as multiple sclerosis and neuromyelitis optica, but it was also reported after several types of infections as well as vascular abnormalities.¹⁰ Some microorganisms tend to involve the spinal cord (the most common examples are enterovirus and flavivirus), while others exhibit more diverse neurological manifestations (such as herpesviridae). Fungal and parasitic infections were only rarely reported as a cause of myelopathy.¹¹

MRI is the most useful modality in detecting transverse myelitis and differentiating it from other lesions.¹² The most

common radiological feature of transverse myelitis on MRI is T2-weighted hyperintense signal alteration, which extends over more than two segments and involves more than two-thirds of the axial area of the spinal cord.^{12 13} In more severe instances, haemorrhage and necrosis can be also identified.¹⁴ The careful study of the transverse sections helps differentiate these lesions from other pathologies based on the magnitude of the involvement, the afflicted components and the pattern of interference.¹²

A MRI of the brain with and without contrast was performed in our case. The left transverse sinus showed a partial thrombosis that cannot justify the clinical picture. The same applies to the slight disc prolapse, which is not associated with compressive myelopathy. MRI shows pathological alterations in 90%–96% of patients with transverse myelitis, with the rest showing no manifestations and thus designated as having an MRI-negative disease.^{5 13} It is important to note that MRI-negative myelitis is a ‘diagnosis by exclusion’, which is based on the presence of the typical symptoms or signs and exclusion of other causes. Making the diagnosis of transverse myelitis in such cases may be particularly complex, especially when the findings of the cerebrospinal fluid analysis are not conclusive.

Several cases of MRI-negative myelitis after COVID-19 were described in the literature, with some of them being associated with radiculopathy.¹⁵ Table 2 shows all the nine documented cases of MRI-negative myelitis in association with COVID-19, five of them were reported in the series of Abrams *et al.*⁴ Notably, all cases showed partial or no improvement after management, whereas our patient demonstrated an almost complete resolution of symptoms. Interestingly, Cabral *et al.*¹⁶ reported recently a case of MRI-negative transverse myelitis induced by the

COVID-19 vaccine in a 33-year-old male; complete resolution of symptoms was described after 3 months.

It is unclear why our case showed considerable improvement compared with the other reported cases with post-COVID-19 myelitis. In the case reported by Memon *et al.*,¹⁷ aggressive treatment was delayed due to normal investigations. Therefore, the early initiation of therapy may be a contributing factor. However, Metya *et al.*¹⁵ described only mild improvement of the already severe symptoms at presentation. So, the severity of symptoms may be another factor that can determine the degree of improvement after treatment.

Several papers reported the occurrence of cerebral venous thrombosis (CVT) after a primary coronavirus infection. However, this article presents the first case that documents the association of MRI-negative myelitis with CVT. The proposed mechanism of thrombotic complications after COVID-19 infection includes cytokine storm, high levels of both prothrombotic and inflammatory markers and endothelial damage associated with binding of the virus to the ACE receptors-2, which all lead to a hypercoagulable state.¹⁸ In contrast to the predominance of isolated CVT in young females, COVID-19 related cases were more common among older males and were associated with a poorer prognosis and higher mortality rates.^{6 19}

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Contributors DM treated and followed the patient, gathered the data, researched the literature and wrote the first draft. SY selected the figures, wrote the figure captions and discussed the radiological aspects of the case. MFS organised the literature review and edited the discussion. MSA reviewed the article for scientific adequacy and improved the discussion. All authors reviewed and approved the final manuscript before submission.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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Patient's perspective

It was all like a nightmare. I was always healthy and then I suddenly started losing my power. My story began with a simple flu as I thought at that time. Then, I discovered that it was a COVID-19 infection. Everybody was talking about the virus and how some cases were extremely serious, but I have never thought that I could be one of the victims. Fortunately, I sought medical help at the right time and received the proper management that helped me overcome the disease. I was willing to share my experience through this article in order to tell people all around the world how this virus can invade your body and how much it is important to be aware of every single symptom that you may have and to seek help as soon as you feel abnormal.

Learning points

- ▶ The available knowledge about the neurological manifestations of COVID-19 is still growing.
- ▶ Neurological symptoms during or after COVID-19 should alert the physician to serious neurological sequelae and prompt generous investigations.
- ▶ Multiple manifestations can occur simultaneously. In this case, cerebral venous thrombosis was associated with transverse myelitis.
- ▶ Early recognition, prompt treatment and vigilant follow-up can improve the prognosis in imaging-negative transverse myelitis.

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