Acute longitudinal extensive transverse myelitis secondary to asymptomatic SARS-CoV-2 infection

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SUMMARY
A 35-year-old woman, 6 months post partum, presented with acute onset back pain at the T8 level progressing to bilateral lower limb weakness and sensory loss with urinary retention and constipation. This patient had a pre-existing inflammatory disease, having recently developed ulcerative colitis antenatally. Five days prior to admission, she had tested positive asymptomatically on a SARS-CoV-2 reverse-transcriptase PCR nasopharyngeal swab. The positive swab result was confirmed on admission. Clinical examination revealed bilaterally exaggerated knee reflexes, lower limb weakness and positive Babinski’s sign. Sensation was impaired at L4 and L5 dermatomes and absent at S1 and S2. MRI findings suggested longitudinal extensive transverse myelitis, with multiple regions of patchy hyperintensity seen in the thoracic region of the spinal cord both centrally and peripherally. She was started on a course of intravenous corticosteroids and improvement was seen both clinically and on repeat imaging. This case demonstrates a rare complication to an asymptomatic COVID-19 infection and explores the potential neurotropic properties of COVID-19.

BACKGROUND
Novel SARS-CoV-2 has rapidly spread on a global scale since emerging from Wuhan City, Hubei Province, China at the end of 2019. Landmark features include fever, cough, dyspnoea, and altered sense of smell or taste. There is growing evidence demonstrating uncommon, but significant, neurological manifestations. This case report details one of the first cases of acute longitudinal extensive transverse myelitis (LETM) secondary to COVID-19 in the UK.

CASE PRESENTATION
A 35-year-old woman presented to Accident and Emergency with a 1-day history of gradual onset sharp right-sided back pain, lateral to the thoracic spine at T8. She had experienced progressive leg numbness and paresthesia bilaterally since the prior evening, impairing her ability to walk. In addition, she had developed urinary retention and constipation. Six months prior, she had delivered her first child vaginally with no complications. Notably, during her pregnancy, she developed ulcerative colitis while in the first trimester which was confirmed on flexible sigmoidoscopy and is well controlled on mesalazine enemas. Five days prior to admission, she had tested positive asymptomatically on a SARS-CoV-2 reverse-transcriptase PCR (RT-PCR) nasopharyngeal swab done prior to a routine hospital appointment. On admission, she had an additional nasopharyngeal swab, producing a confirmatory positive result on RT-PCR (in-house SARS-CoV-2 assay, RdRp gene target) with a cycle threshold (Ct) value of 13. The likelihood of a false positive result is low with two consecutive positive PCR results and low Ct value.

On examination, she had bilaterally exaggerated knee reflexes and positive Babinski’s sign. Power was decreased to grade 2 (active movements with gravity eliminated) on ankle dorsiflexion, great toe extension and ankle plantar flexion. Sensation was impaired at L4 and L5 and absent at S1 and S2 dermatomes.

INVESTIGATIONS
General lab results were unremarkable, with the haematogram and inflammatory markers within normal range. Thyroid, liver and renal functional tests were similarly normal, with a negative urine dipstick at bedside. Additional blood tests for syphilis, HIV, anti-neuronal antibodies, vasculitic screen, voltage-gated potassium channel antibodies, N-methyl-D-aspartate receptor antibodies and glutamic acid decarboxylase (GAD) antibodies were negative. A chest X-ray performed was normal. Following an unremarkable initial CT of the spine at admission, a lumbar puncture and MRI of the spine were performed within the first 24 hours of admission, following preliminary imaging and results.

The lumbar puncture cerebral spinal fluid (CSF) analysis for aquaporin-4 antibodies, anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies, protein, glucose, oligoclonal bands, microscopy, cultures and sensitivities, and viral PCR (including human T-cell leukaemia virus type 1 and SARS-CoV-2) all returned negative. CSF protein was 0.4 g, white cell count <0.001×10⁹/L, red cell count 0.0002×10¹²/L with no organisms.

MRI of the spine with gadolinium enhancement showed T2-weighted lesions in the dorsal region of the spinal cord. The spinal cord showed multiple regions of patchy hyperintensity, seen in the thoracic region of the spinal cord both centrally and peripherally (figure 1). The subarachnoid space was normal and the lumbosacral region was normal, ruling out cauda equina. An MRI of the brain was largely unremarkable, though a few tiny frontal parietal high signals were noted.

DIFFERENTIAL DIAGNOSIS
On initial presentation, cauda equina was ruled out as a priority via a normal lumbosacral region on MRI. Given the patient’s young age, lack of vascular risk factors and progressive onset of
Admission showing 2 Lee G. methylprednisolone 1 g intravenously once daily for 3 days, before being stepped down to prednisolone 60 mg orally once daily, with omeprazole 20 mg two times per day for gastroprotection.

Throughout her admission, she was seen by the physiotherapy team and improved to mobilising short distances independently. She was discharged with a weaning regimen of prednisolone and co-trimoxazole 960 mg orally once daily for pneumocystis pneumonia prophylaxis until weaned past 30 mg prednisolone.

OUTCOME AND FOLLOW-UP
During the course of steroids, she improved clinically and gradually regained full sensation in dermatomes L4, L5, S1 and S2 over her 2-week admission. She also regained motor function in her lower limbs, improving to walking short distances independently and climbing stairs with the aid of crutches. She fully regained bladder function.

A repeat MRI done on discharge showed interval reduction in the conspicuity of the previously seen long-segment myelopathy involving the mid-thoracic cord with no gadolinium enhancement identified, suggesting a resolving transverse myelitis. She is receiving ongoing physiotherapy as an outpatient, with neurology follow-up in a month.

DISCUSSION
The classical features of COVID-19 have been identified as fever, cough, dyspnoea, and altered sense of smell or taste.\(^1\) Lately, neurological complications following SARS-CoV-2 (COVID-19) infection have been reported in literature ranging from acute to weeks following infection with the SARS-CoV-2 virus. Neurological complications such as anosmia, hypogeusia, headache, myalgia and dizziness are common, with prevalence as high as 80% in hospitalised patients with COVID-19 being quoted in literature.\(^2\) A study of 214 patients hospitalised with COVID-19 in Wuhu, China showed a correlation between severity of infection and neurological complications.\(^3\) Motor and sensory deficits have been reported to be rare.\(^3\)

Transverse myelitis is rare in itself, with a reported incidence ranging from one to eight cases per million per year.\(^4\) There have only been a handful of reported of transverse myelitis cases following COVID-19 infection, with outcomes ranging from fatal to a full recovery.\(^5\)\(^6\) The neurotropic properties of COVID-19 have been theorised to be due to the presence of ACE 2 receptors (the primary target in the respiratory epithelium) in glial cells of the brain and spine neurons. Multiple mechanisms for neurological disease have been suggested, including hyperinflammation, hypercoagulable state, direct invasion of the nervous system and multiorgan failure in severe disease.\(^3\) The immunopathogenesis is not well understood and is theorised to be due to perivascular infiltration by monocytes and lymphocytes, with a mixed inflammatory response targeting a range of cells, including myelin, neurons, axons and oligodendrocytes.\(^5\) It is worth noting that in this case there was no SARS-CoV-2 detected in the CSF sample.

This rare case of transverse myelitis is particularly notable due to the presentation on a background of an atypical asymptomatic COVID-19 infection and preceding childbirth with development of ulcerative colitis antenatally. There have been associations noted between systemic inflammatory autoimmune disorders and transverse myelitis, such as Sjögren syndrome, sarcoidosis and systemic lupus erythematosus. While not a common autoimmune condition, there have been documented associations between neurological complications and inflammatory bowel disease in literature.\(^3\) However, in this case, the trigger of the patient’s transverse myelitis appeared to be the COVID-19

Figure 1 Axial image of gadolinium-enhanced MRI done on admission showing T2-weighted image hyperintensity lesions at the thoracic level involving the central and peripheral region of the spinal cord.

Symptoms made a vascular event less likely but was ruled out on head imaging regardless. The patient denied any trauma, and lab investigations did not suggest any systemic infections, including syphilis and HIV. Anti-neuronal antibodies returned negative for paraneoplastic syndrome. Vasculitis of the spinal cord was considered, but systematic vasculitis screen and CSF analysis were normal. Workup for neurological autoimmune disorders included voltage-gated potassium channels, NMDA receptor antibodies and GAD antibodies. These antibodies typically target the peripheral nerves or brain rather than the spine, and present with seizures, dyskinesias or psychiatric symptoms so were less in keeping with the presentation and returned negative as expected.

Given her recent positive COVID-19 test, post-viral acute LETM was considered the most likely diagnosis. Acute inflammatory demyelinating polyneuropathy was considered though was less likely given the upper motor neuron lesion presentation. Imaging ruled out any epidural space-occupying lesion. Noting the hyperintensity lesions on imaging, a lumbar puncture was done to investigate any localised infection including tuberculosis and human T-cell leukaemia virus type 1. Other differentials included multiple sclerosis and neuromyelitis optica spectrum disorder (NMOSD), given the pathology on MRI and clinical presentation, and also in the dominant presenting group as a white woman between 20 and 40 years. The spinal cord inflammation would be more suggestive of NMOSD, but the history and clinical presentation (lacking eye involvement) was more suggestive of LETM, and CSF analysis for aquaporin-4 antibodies, anti-MOG antibodies, protein, glucose and oligoclonal bands returned negative.
infection, though having an immune system prone to immunomodulation, as evidenced by the development of inflammatory bowel disease during pregnancy, and being a young woman are likely risk factors.

We have been fortunate to have a successful outcome here, with the case in India presented by Chakraborty et al dying from respiratory complications. Similar to other cases in literature, our patient had improvement of neurological symptoms on commencement of steroids, with physiotherapy as an adjunct. Immunosuppression is the mainstay of treatment, with steroids recommended first line, followed by consideration of plasma exchange, and mycophenolate or rituximab in recurrent disease.10

Learning points

► SARS-CoV-2 is a variable disease, and is important to consider in neurological presentations lacking the classic respiratory signs.
► While COVID-19 is a novel infection, the principles of clinical practice remain the same: ruling out the most critical differentials as a priority while organising further diagnostic investigations.
► Corticosteroid treatment with physiotherapy can improve symptoms in longitudinal extensive transverse myelitis.
► If a cerebral spinal fluid sample can be obtained, consider running PCR for SARS-CoV-2 in the lab given the theorised neurotropic mechanisms.
► CT of the spine is appropriate to do initially for speed and availability, but some pathology may not be visible and requires gadolinium-enhanced MRI for full visualisation.

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