Neuromyelitis optica spectrum disorder secondary to COVID-19

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Introduction

Neurological symptoms associated with severe acute respiratory syndrome coronavirus (SARS-CoV) infection is a growing area of interest. It has long been accepted that human coronaviruses can infect neural cell cultures (Arbour et al, 2000). The coronavirus SARS-CoV-2 with coronavirus disease 2019 (COVID-19) responsible for the current pandemic has so far yielded limited clinical evidence of such manifestations. The most common

Case report

A septuagenarian man was admitted to the emergency department following a fall with loss of consciousness, shortness of breath and bradycardia. The patient had a background of hypertension, atrial fibrillation and gastro-oesophageal reflux disease. Regular medications included lansoprazole, bisoprolol and losartan. He lived alone, walked unaided and kept himself fit and active through weekly golfing. He was on no other medication, had no known allergies, drank an average of one unit of alcohol a week and was an ex-smoker.

His COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test on admission was negative for severe acute respiratory syndrome coronavirus (SARS-CoV-2). Computed tomography of the chest, abdomen and pelvis demonstrated the characteristic bilateral patchy ground-glass opacification, raising suspicion of a false-negative RT-PCR result.

On day 9 of his admission, the patient developed visual blurring in the superior nasal aspect of his left eye with mild ptosis. A magnetic resonance imaging scan of the head showed no obvious abnormalities. Over the following days he also developed bilateral lower limb weakness and urinary incontinence. Spinal magnetic resonance imaging showed patchy multifocal areas of enhancement from T5 to T11, thought to be in keeping with transverse myelitis (**Figure 1**). On examination he had significant weakness in his lower limbs (2/5 power score on the left and 3/5 on the right on the Medical Research Council power scale), but had normal sensation, tone and reflexes in these limbs. He subsequently developed fasciculations of his left lower limb. Upon these findings, discussion with neurology teams led to the differential diagnoses that included transverse myelitis and neuromyelitis optica. Lumbar puncture and analysis CSF for COVID-19 and antibody profile were recommended.

The patient was retested for SARS-CoV-2 (day 9 post admission), this time yielding a positive result. During the next few days, he developed a fever and an increased oxygen demand despite treatment with intravenous antibiotics, fluids and electrolyte replacement. A chest X-ray showed progressive changes in keeping with worsening COVID-19 pneumonitis. Given these progressive signs of infection, intravenous steroids to treat the suspected neuromyelitis optica were not recommended.

Days 18 to 23 of his admission saw a steady deterioration into type one respiratory failure, with worsening inflammatory markers (C-reactive protein 2 mg/litre (day 0) rising to 282 mg/litre (day 22)), requiring high flow oxygen. This progressive decline culminated in intensive care unit admission where he was given non-invasive ventilation. Imaging ruled out pulmonary embolism, but showed extensive ground-glass, patchy peripheral consolidation and reactive lymphadenopathy. CSF analysis was clear, colourless and sterile with a normal cell count, glucose and protein level as well as culture (and negative for RT-PCR SARS-CoV-2). He was intubated on day 25 because of his increased respiratory effort. By day 26 his white cell count had risen to 25.76 $x10^9$/litre and he required high levels of vasopressors. The patient deteriorated through multi-organ failure despite intensive care through both circulatory and ventilatory support and haemofiltration. The decision to withdraw care was made following discussion with the family. The patient died on day 26 as a result of multiorgan failure and sepsis secondary to COVID-19 infection. Test results for aquaporin-4 (AQP-4) antibodies subsequently returned positive.

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Figure 1. Sagittal magnetic resonance imaging of the spine (T1 left, T2 right) demonstrating changes associated with transverse myelitis (arrows).

Table 1. Diagnostic criteria for neuromyelitis optica

Absolute criteria	1. Optic neuritis 2. Acute myelitis
Supportive criteria	1. Negative brain magnetic resonance imaging at disease onset 2. Spinal cord magnetic resonance imaging with contiguous T2-weighted signal abnormality extending over three or more vertebral segments 3. Neuromyelitis optica-IgG seropositive status

Adapted from Bizzoco et al (2009)

neurological manifestations (in severely affected patients) are acute cerebrovascular disease and altered consciousness (Lau et al, 2004; Paterson et al, 2020; Robinson and Busl, 2020; Zhao et al, 2020).

This article presents a case of neuromyelitis optica spectrum disorder associated with systemic COVID-19 infection.

Discussion

Neuromyelitis optica spectrum disorder is an inflammatory disease characterised by recurrent attacks of optic neuritis and longitudinally extensive transverse myelitis, and often involves antibodies against aquaporin-4 (Table 1). Symptoms often progress in relapsing episodes and include ocular pain, visual field changes, and neurological dysfunction syndromic of longitudinal transverse myelitis: ascending paraesthesia, a pyramidal weakness pattern and incontinence (Bizzoco et al, 2009).

Risk factors for developing neuromyelitis optica spectrum disorder include being female, having an existing autoimmune condition (in particular, Sjögren's syndrome), a history of malignancy, or a recent history of a systemic infection (Akaishi et al, 2020). In the absence of any other risk factors, this case may be the first documented case of neuromyelitis optica spectrum disorder caused by a systemic coronavirus infection.

In recent pandemics, virus-associated neurological manifestations have been incredibly diverse. Transverse myelitis has been more commonly seen in patients with infections caused

Learning points

- This patient developed neuromyelitis optica spectrum disorder secondary to severe acute respiratory syndrome coronavirus infection and represents the first documented case of neuromyelitis optica associated with COVID-19.
- Albeit rare, systemic infection is a known risk factor for neuromyelitis optica spectrum disorder and thus should be considered in any patient with systemic illness secondary to infection, including COVID-19.

by influenza viruses (such as H1N1) rather than coronaviridae (Robinson and Busl, 2020). There are currently only sporadic case reports of patients with demonstrated neuroinvasion of severe acute respiratory syndrome coronaviridae and detectable levels of viral RNA within the CSF (Lau et al, 2004). A case report from Zhao et al (2020) reported a patient who developed a similar bilateral flaccid paralysis following SARS-CoV-2 infection, but no CSF or magnetic resonance imaging results were available. Possible mechanisms of neuroinvasion are postulated by Zubair et al (2020).

There are currently no published cases of autoimmune disease associated with CNS SARS-CoV-2 infection. However, Marques et al (2011) demonstrated a neurotropic coronavirus-induced encephalomyelitis,and antibody-producing cells were shown to migrate from the periphery to the CNS in a CXCR3-dependent manner. Furthermore, persistent viral infection caused sustained expression of CXCR3 ligands and consequently an increase in antibody-producing cells within the CNS. While this would normally have a protective role in persistent infection, in the context of autoimmune disease this could precipitate a flare-up. Interestingly, Chihara et al (2013) demonstrated this mechanism in the pathogenesis of neuromyelitis optica. It is therefore feasible that the patient's SARS-CoV-2 infection caused a worsening of his neuromyelitis optica spectrum disorder in this case.

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