A case of limbic encephalitis associated with asymptomatic COVID-19 infection

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), millions have been diagnosed with COVID-19. The major clinical manifestations of SARS-CoV-2 infection are pulmonary, however reports of COVID-19-associated central nervous system complications emerged.\(^1\)\(^2\) We report a case of encephalitis in a pulmonologically asymptomatic patient with COVID-19.

A 66-year-old female presented in mid-March 2020, with a few hours history of confusion. She was completely well until the day of admission. There was no medical, infectious or behavioural prodrome. There was no alcohol or nutritional history. She was lymphopaenic at 0.4×10\(^9\)/L (0.8–3.7). Other observations were normal. She had travelled to Spain, the USA and Mexico in the 3 months prior, but had been home for 19 days. She suddenly complained that her head 'felt funny'. She carried on normal tasks but, within an hour, became confused, amnestic and was unaware of why social interactions emerged.\(^1\)\(^2\) We report a case of limbic encephalitis in a pulmonologically asymptomatic patient with COVID-19.

On admission, her temperature was 37.9°C. Other observations were normal. She was lymphopaenic at 0.4×10\(^9\)/L (0.8–3.1). Full blood count was otherwise normal. C-reactive protein (CRP) was 14.5 mg/L (0–5). Routine blood tests, including renal function, liver function and clotting, were normal. A brain CT was unremarkable. Six hours after admission, she had a single, spontaneously resolving, generalised tonic-clonic seizure. Her postictal Glasgow Coma Score (GCS) was 6/15 (E4/V4/M6). This remained unchanged for 48 hours. Postictal neurological examination showed equal, reactive pupils, no response to visual menace, no vestibulo-ocular reflex, normal tone bilaterally, symmetrical brisk reflexes and extensor plantars. She remained febrile (37.9°C) for 48 hours. Oxygen saturation dropped to 93% on air only once during her 4-week admission. She never developed breathlessness, cough or tachyypnoea.

An MRI of the brain on day 2 showed non-enhancing, symmetrical T2 and FLAIR (fluid-attenuated inversion recovery) hyperintensities in mesial temporal lobes and medial thalami and to a lesser extent upper pons, as well as scattered subcortical white matter hyperintensities (figure 1). There were no microhaemorrhages on T2* imaging. Diffusion scans showed punctate bright signal on the B1000 map in the medial temporal lobes, thalami and fornices. The images were consistent with limbic encephalitis.

Cerebrospinal fluid (CSF) examination showed white cell count 3/mm\(^3\), red blood cells 11/mm\(^3\), protein 1.0 g/L (0.15–0.45) and glucose 3.5 mmol/L (2.2–3.9). CSF PCR was negative for streptococci, meningococcus, haemophilus, listeria, Escherichia coli, herpes simplex virus (HSV) 1 and 2, human herpesvirus 6 (HHV6), enteroviruses, parechovirus, cytomegalovirus (CMV), Varicella zoster virus (VZV) and Cryptococcus. Oligoclonal bands were negative in CSF and serum. CSF IgG index was normal (0.48).

Neuroimmunological tests were negative in serum and CSF for LGi1 and Caspr 2, NMDA receptor antibodies, anti-Hu, anti-Yo, anti-Ri, anti-Ma-1, anti-Ma-2, anti-CV2 (CRMP-5), anti-Amphiphysin, anti-Zic-4, anti-Sox 1, anti-Tr, anti-GAD, anti-Aquaporin 4, anti-MOG and anti-DPPX. ANA and ANCA were negative. HIV and treponemal serology testing was negative.

A CT of chest, abdomen and pelvis showed multiple small peripheral foci of ground-glass opacification in the lungs, suggestive of bilateral atypical pulmonary infection with COVID-19. SARS-CoV-2 PCR was positive in a nasopharyngeal swab. SARS-CoV-2 IgG was negative.\(^3\) CSF was subsequently tested for SARS-CoV-2 at National Reference Laboratory in Colindale, where the RNA-dependent RNA-polymerase (RdRp) gene is the target, and at University College London Hospitals (UCLH), where the Nucleocapsid gene is the target. Both were negative.

She was treated with ceftriaxone, aciclovir and levetiracetam. After the MRI and CSF results, ceftriaxone and aciclovir were stopped, pabrinex and pulsed intra-venous methylprednisolone (1g/day for 3 days) were started. After steroid treatment, GCS improved rapidly from 6/15 to 14/15 (E4/V4/M6). She was disorientated to time and place and amnestic. She had mild word-finding difficulties. Cranial nerve examination was normal. There was no limb weakness, ataxia, pyramidal or extra-pyramidal signs or gait abnormalities. Plantars were flexor. She also received a course of intravenous immunoglobulin and made a steady improvement. Addenbrooke’s Cognitive Examination (ACE III) scores were 61/100 at baseline with subscores of

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**Figure 1** MRI brain. Corresponding Axial T2 (top row), Axial Diffusion weighted (middle row) and Axial FLAIR (bottom row) images demonstrate T2 hyperintense signal abnormalities in the limbic lobes, bilateral medial thalami and frontal white matter. The limbic and thalamic lesions show punctate and small, discrete foci of high signal on DWI, without demonstrable restriction on ADC maps (not shown). Similar lesions were also present in the pons but less conspicuous in signal and number (not shown). There were no microhaemorrhages or abnormal lesional or meningeal enhancement.

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13/18 for attention, 12/26 for memory, 3/14 for fluency, 21/26 for language and 12/16 for visuospatial skills. Ten weeks after symptom onset, ACE III score was 88/100 with only memory (22/26) and verbal fluency (7/14) incompletely recovered. She remains on 20mg prednisolone.

**DISCUSSION**

Neurological manifestations of COVID-19 appear more common in patients with severe respiratory disease. However, our patient had minimal respiratory involvement. No common COVID-19 symptoms developed, despite immunosuppressive treatment. This case illustrates the fact that neurological manifestations associated with COVID-19 infection are not a reflection of critical illness, and makes a case for actively looking for evidence of COVID-19 infection in patients presenting with neurological illness.

The brain imaging appearances here are strikingly similar to those described by Poyiadji et al in the location of the signal abnormality, but there was no haemorrhagic change. Acute necrotising encephalopathy was considered in the differential, given the thalamic and subcortical pontine changes. There was no previous or family history of similar episodes to suggest infection-induced acute encephalopathy. We felt that the patient’s age, the lack of infectious prodrome, the cognitive neurological deficit without motor features and the predominant medial temporal lobe signal changes made limbic encephalitis most likely. There were no risk factors for Wernicke’s encephalopathy, but the patient was treated for this.

We did not isolate SARS-CoV-2 in the CSF, consistent with current literature, where all but two reported cases had negative CSF reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2. CSF samples were tested for SARS-CoV-2 in two laboratories. The National Reference laboratory at Public Health England (PHE) tests for a 100 base-pair conserved region of the RdRp gene. More recently, PHE laboratories changed the RT-PCR target gene to Orf1 a/b and repeat testing on the same CSF sample was negative. UCLH Virology Laboratory used an in-house RT-PCR for a conserved region of the nucleocapsid gene. Neither assay is validated for detection of SARS-CoV-2 in CSF.

In the absence of evidence of viral RNA in CSF, a diagnosis of viral encephalitis is not possible. It may be that the presence of the virus in CSF is transitory, or that the pathogenesis is a SARS-CoV-2-induced immune response. IgG antibodies to SARS-CoV-2 were negative, suggesting that the COVID-19 infection was likely concomitant with the CNS presentation and that the CNS presentation was para-infectious, not postinfectious. The presence of intrathecal antibodies could give support to the hypothesis of direct invasion of the CNS. We were not able to test for intrathecal antibodies in the CSF, as the assay had not been validated at the time of our patient’s admission; however, we hypothesise that the intrathecal antibodies would have been negative because the CSF was collected 48 hours after symptom onset. Larger case series would help clarify whether the neurological associations reported to date are simply coincidental given the prevalence of COVID-19 infection, or whether there are particular phenotypes and correlations specific to SARS-CoV-2. Our case suggests that neurological manifestations can be the initial symptom of COVID-19 and that COVID-19 infection should be considered in patients presenting with limbic encephalitis.

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**REFERENCES**