Journal of
Neurology, Neurosurgery
& Psychiatry

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

Journal:	*Journal of Neurology, Neurosurgery, and Psychiatry*
Manuscript ID	jnnp-2020-323839.R1
Article Type:	Letter
Date Submitted by the Author:	n/a
Complete List of Authors:	Zambreanu, Laura; University College London Hospitals NHS Foundation Trust, MRC Centre for Neuromuscular Diseases Lightbody, Sophie; West Hertfordshire Hospitals NHS Trust, Stroke Unit Bhandari, Mohit; West Hertfordshire Hospitals NHS Trust, Stroke Unit Hoskote, Chandrashekar; National Hospital for Neurology & Neurosurgery, Lysholm Department of Neuroradiology Kandil, Hala; West Hertfordshire Hospitals NHS Trust, Microbiology Houlihan, Catherine ; University College London Hospitals NHS Foundation Trust, Department of Virology Lunn, Michael; University College London Hospitals NHS Foundation Trust National Hospital for Neurology and Neurosurgery, MRC Centre for Neuromuscular Disease and Department of Molecular Neuroscience; University College London Hospitals NHS Foundation Trust, NIHR Biomedical Research Centre
Keywords:	AUTOIMMUNE ENCEPHALITIS, LIMBIC SYSTEM, VIROLOGY
Specialty:	Neuro-inflammation

A CASE OF LIMBIC ENCEPHALITIS ASSOCIATED WITH ASYMPTOMATIC COVID-19 INFECTION.

Corresponding author:
Dr Laura Zambreanu
1. Neurology Department, Watford General Hospital, West Hertfordshire NHS Trust, Vicarage Road, Watford WD18 0HB, UK
Email: l.zambreanu@nhs.net
Tel: 01923217350
2. MRC Centre for Neuromuscular Disease, National Hospital for Neurology, University College London Hospitals NHS Foundation Trust, London, UK

Co-authors:
Dr Sophie Lightbody, Acute Stroke Unit, Watford General Hospital, West Hertfordshire NHS Trust, Watford, UK
Dr Mohit Bhandari, Acute Stroke Unit, Watford General Hospital, West Hertfordshire NHS Trust, Watford, UK
Dr Chandrashekar Hoskote, Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK.
Dr Hala Kandil, Microbiology Department, Watford General Hospital, West Hertfordshire NHS Trust, Watford, UK
Dr Catherine F Houlihan, Virology Department, University College London Hospitals NHS Foundation Trust, London, UK
Prof Michael P Lunn, MRC Centre for Neuromuscular Disease and Department of Molecular Neuroscience, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK

Keywords: encephalitis, limbic, SARS CoV-2

Word count: 1106
Number of references: 8

Since the emergence of the SARS-CoV-2 virus, 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 COVID-19 patient.

A 66-year-old lady presented 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 had travelled to Spain, the USA and Mexico in the three months prior, but had been home for nineteen 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 distancing measures were being observed.

On admission, her temperature was 37.9°C. Other observations were normal. She was lymphopaenic at $0.4x10^9$/L (0.8-3.1). Full blood count was otherwise normal. 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 post-ictal Glasgow Coma Scale (GCS) was 6/15 (E1/V1/M4). This remained unchanged for 48 hours. Post-ictal 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 pyrexial (37.9°C) for 48 hours. Oxygen saturation dropped to 93% on air only once during her four-week admission. She never developed breathlessness, cough or tachypnoea.

An MRI brain on Day 2 showed non-enhancing, symmetrical T2 and FLAIR 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), glucose 3.5 mmol/L (2.2-3.9). CSF polymerase chain reaction (PCR) was negative for streptococci, meningococcus, haemophilus, listeria, E. coli, HSV 1 and 2, HHV6, enteroviruses, parechovirus, CMV, VZV, Cryptococcus. Oligoclonal bands were negative in CSF and serum. CSF IgG index was normal (0.48).

Neuroimmunology 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 was negative.

A CT 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 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 intravenous methylprednisolone (1 gram/day for three days) were started. After steroid treatment, GCS improved rapidly from 6/15 to 14/15 (E4/V4/M6). She was disoriented 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 extrapyramidal 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 sub-scores of 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(2). 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(4) in the location of the signal abnormality, but there was no haemorrhagic change. Acute necrotizing encephalopathy was considered in the differential, given the thalamic and subtle 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(5,6) had negative CSF 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 RNA-dependent RNA-polymerase gene (RdRp)(7). 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(8). 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(3) were negative, suggesting that the COVID-19 infection was likely concomitant with the CNS presentation and that the CNS presentation was parainfectious, not post-infectious. 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 hypothesize 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.

References:

1. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med. 2020 Apr 15. doi: 10.1056/NEJMc2008597.

2. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020 Apr 10. doi: 10.1001/jamaneurol.2020.1127.

3. Evaluation of Roche Elecsys Anti-SARS-CoV-2 serology assay for the detection of anti-SARS-CoV-2 antibodies. https://www.gov.uk/government/publications/covid-19-laboratory-evaluations-of-serological-assays. 11 June 2020 (Last accessed 19th June 2020).

4. Poyiadji N, Shahin G, Noujaim D, et al. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology. 2020 Mar 31:201187. doi:10.1148/radiol.2020201187.

5. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARSCoronavirus-2. Int J Infect Dis. 2020 Apr 3;94:55-58. doi: 10.1016/j.ijid.2020.03.062.

6. Xiang P, Xu X.M., Gao L.L., et al. First case of 2019 novel coronavirus disease with Encephalitis. ChinaXiv. 2020;T202003:00015.

7. COVID-19 virus testing in NHS laboratories. Guidance and standard operating procedure https://www.england.nhs.uk/coronavirus/wpcontent/uploads/sites/52/2020/03/guidance-and-sop-covid-19-virus-testing-in-nhs-laboratoriesv1.pdf. 16 March 2020 (Last accessed 14th June 2020).

8. Grant PR, Turner MA, Shin GY, et al. Extraction-free COVID-19 (SARS-CoV-2) diagnosis by RT-PCR to increase capacity for national testing programmes during a pandemic. https://www.biorxiv.org/content/10.1101/2020.04.06.028316v2.full.pdf.