Neurotropism of SARS-CoV-2: COVID-19 presenting with an acute manic episode

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SUMMARY
A 41-year-old man with no significant medical history presented with acute behavioural disruption on the background of a 1-day history of severe headache and a 10-day history of dry cough and fever. He was sexually disinhibited with pressured speech and grandiose ideas. His behaviour worsened, necessitating heavy sedation and transfer to intensive care for mechanical ventilation despite no respiratory indication. Investigations confirmed that he was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Neuroimaging and a lumbar puncture were normal. Initial screening for SARS-CoV-2 in the cerebrospinal fluid was negative although no validated assay was available. The patient’s mental state remained abnormal following stepdown from intensive care. Psychiatric assessment found features consistent with acute mania, and he was detained under the Mental Health Act. This case indicates the need to consider COVID-19 in a wider series of clinical presentations and to develop a validated assay for SARS-CoV-2 in the cerebrospinal fluid.

BACKGROUND
COVID-19 is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus was identified as the cause of an outbreak of pneumonia in Hubei Province, China, in December 2019 and has spread globally, so far responsible for over 2 million cases and 150 000 deaths worldwide. SARS-CoV-2 is the seventh coronavirus known to infect humans and is a member of the orthocoronavirus subfamily. It appears to be principally transmitted via respiratory droplets and contact with surfaces conveying the pathogen. Entry into the host cells is reportedly via the ACE-2 receptor. The most common initial symptoms of COVID-19 are fever, dry cough, fatigue and myalgia. The primary complication is acute lung injury resulting in type 1 respiratory failure, with a significant proportion requiring intensive care unit admission. However, in addition to these respiratory features, the disease affects multiple organs including the cardiovascular system and gastrointestinal system. There have been few case reports of primarily neurological presentations of the disease.

This article outlines a case of COVID-19 presenting with an acute manic episode necessitating emergency intubation and discusses potential mechanisms for the development of neuropsychiatric disease.

CASE PRESENTATION
A 41-year-old man with no significant medical history other than congenital nystagmus presented to the emergency department in the early hours of the morning. He had woken at night restless, agitated and reported feeling like his ‘brain was racing’. He told his wife that he felt like he was ‘going to die’. He also confessed to numerous hitherto undisclosed homosexual encounters and other sexual behaviours described as uncharacteristic by his wife. This acute presentation was preceded by a 1-day history of severe occipito-parietal headache, described as the ‘worst headache ever’, and a 10-day history of a dry cough and fever. His wife also reported similar but milder symptoms. He did not report anosmia. He had no significant smoking or alcohol history and denied any illicit drug use. He did however report a severe transient mood reaction with some possible paranoid features to cannabis in 2004 with no further use since then. His sister had a previous episode of postpartum psychosis and was subsequently diagnosed with bipolar disorder.

Physical examination revealed fine bibasal inspiratory crepitations and a nystagmus in all directions. Neurological examination was otherwise normal. His mental state examination however was abnormal. He was loud and highly aroused with sexual disinhibition and overfamiliar behaviour, inappropriately questioning and touching members of staff. His speech was pressured, and his mood subjectively and objectively elevated. His thoughts were grandiose with persecutory elements, and he had persistent strong religious ideas, manifestations of which included attempts to anoint fellow patients with water. He also obsessively wrote down every personal interaction and bodily sensation. He said he found this experience ‘liberating’. He did not report visual or auditory hallucinations. This abnormal behaviour worsened while in the emergency department to the point where it was deemed necessary for him to be transferred to intensive care for sedation and mechanical ventilation despite no respiratory indication.

INVESTIGATIONS
A nose and throat swab taken on admission subsequently tested positive for the presence of SARS-CoV-2 viral RNA and chest X-ray showed features consistent with a COVID-19 pneumonitis. Bloods results during admission are shown in table 1. His CRP and neutrophils were raised initially but
settled shortly after admission, as did his mild lymphopaenia. Liver function tests were initially normal, but he developed a mild transaminitis soon after admission. Thyroid stimulating hormone, B12 and folate were normal. Serological screening was negative for HIV antigen and antibody, hepatitis B surface and core antigen, hepatitis C IgG antibodies and Treponema pallidum antibodies. No common autoantibodies were found in the serum, apart from mildly raised Hep2 antinuclear antibodies of uncertain significance. A coeliac screen was also negative, as were N-methyl-D-aspartate receptor (NMDA) and voltage-gated K+ channel autoantibodies. CT and MRI brain showed no acute intracranial pathology or evidence of encephalitis. A lumbar puncture with normal opening pressure demonstrated ginclear cerebrospinal fluid (CSF) and no erythrocytes, leucocytes or other organisms. Glucose level in the CSF has 4.8 mmol/L (plasma glucose 8.4 mmol/L) and protein level 0.19 g/L. The sample was also was negative for herpes simplex virus DNA, varicella zoster virus DNA, enterovirus RNA and parechovirus RNA not detected. Initial screening for SARS-CoV-2 in the CSF were also negative, although a validated assay was not yet available making interpretation difficult.

OUTCOME AND FOLLOW-UP

During this admission, he continued on regular antipsychotics and benzodiazepines for sedation. He required transfer to the emergency department while still an inpatient where he was investigated for severe left-sided chest pain. A CT pulmonary angiogram confirmed ongoing inflammatory changes consistent with COVID-19 pneumonitis but no other pathology.
His mania improved on return to the psychiatric unit, and he was discharged 12 days after instigation of the Section 2 order. His medications on discharge included olanzapine 10 mg daily with a plan to reduce this to 7.5 mg within the next week and 1 mg twice daily of clonazepam also to be weaned in the community. At follow-up 23 days from the original presentation, he was well at home, and he and his wife reported that he was now at his baseline level of function.

DISCUSSION
This report outlines a rare case of acute mania associated with SARS-CoV-2 infection. This was particularly severe, necessitating emergency intubation and subsequent inpatient psychiatric admission. Although this may represent a first episode of a primary psychiatric condition such as bipolar disorder, it is also important to consider other organic disease given the simultaneous diagnosis of COVID-19. Although it is not yet possible to confirm here due to the lack of a validated CSF-PCR assay, previous reports have implicated SARS-CoV-2 in the development of viral encephalitis, and this remains an important differential. In one of the initial reports on patient presentations and outcomes from Wuhan, confusion accounted for 9% of reported symptoms, although the nature of these episodes was not expanded on.7 In addition to this, there are further reports of COVID-19 causing acute haemorrhagic necrotising encephalopathy and acute inflammatory neuropathy in Guillain-Barre syndrome. An acute delirium was also considered, although the absence of a fluctuating course and inattention as key features made this less likely.

Neurotropism of SARS-CoV-2 has been tentatively reviewed in the literature. The entry of SARS-CoV-2 into human host cells is mediated mainly using ACE-2 as a receptor, and although the lungs and the gastrointestinal tract are the principle sites of expression of ACE-2 in the body, the protein is also expressed throughout endothelial cells in the brain providing a theoretical route of entry into the central nervous system. More specifically, the amygdala, which has key functions in emotional intelligence as well as those related to sexual arousal, has been demonstrated to express ACE-2 in animal models thus providing a focus to which the spike proteins of the virus may bind. It has also been hypothesised that the virus may enter via peripheral nerve terminals. Neurological invasion of the virus therefore may represent another potential aetiology for this acute illness in absence of any other biological, psychological or social precipitating factors.

This is, to the best of our knowledge, the first report of an acute episode of mania or psychosis as a result of SARS-CoV-2 infection. The pathophysiology of this is yet to be discerned, but given the temporal relation, we are led to assume that viral infection mediated this presentation. The ideal treatment modality for neuropsychiatric manifestations of COVID-19 and the long-term prognosis of such cases remain to be seen. This case indicates the need to consider testing for and diagnosis of COVID-19 in a wider series of clinical presentations including new onset psychiatric and neurological disorder. More research is required to look at the neurological manifestations of COVID-19, as well as a need to develop a validated assay for SARS-CoV-2 in the CSF in order to determine the neuroinvasive potential of the virus.

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REFERENCES

Learning points
► COVID-19 manifests in a number of ways affecting multiple systems including the central nervous system (CNS).
► The neuroinvasive potential of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (neuropotism) has been reported, but the pathophysiology remains unclear with uncertainty over its long-term consequences.
► There are multiple effects of SARS-CoV-2 virus on the CNS, and currently, there are no specific treatment options available particularly for the neurotropic sequelae.
► Further research is needed to develop a validated assay for SARS-CoV-2 in the cerebrospinal fluid.

New disease