

A young man presenting with encephalopathy and seizures secondary to SARS-CoV-2

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SUMMARY

COVID-19 has now emerged from a respiratory illness to a systemic viral illness with multisystem involvement. There is still a lot to learn about this illness as new disease associations with COVID-19 emerge consistently. We present a unique case of a neurological manifestation of a patient with structural brain disease who was COVID-19 positive and developed mental status changes, new-onset seizures and findings suggestive of viral meningitis on lumbar puncture. We also review the literature and discuss our case in the context of the other cases reported. We highlight the value of considering seizures and encephalopathy as one of the presenting features of COVID-19 disease.

BACKGROUND

COVID-19 is caused by the SARS-CoV-2 that typically manifests as an upper or lower respiratory tract infection. However, there is emerging evidence that it is a systemic viral illness affecting many organ systems. Neurological manifestations of COVID-19 have been reported and are divided into the central nervous system (CNS), peripheral nervous system and musculoskeletal.¹ Mao *et al* specifically investigated neurological manifestation of COVID-19 in Wuhan, China and found that 25% of the patients with COVID-19 had neurological manifestations.² We report a unique presentation of mental status changes and new-onset seizures in a young patient with COVID-19 infection, with abnormalities on cerebrospinal fluid (CSF) analysis.

CASE PRESENTATION

A 29-year-old man with a history of a partially resected choroidal fissure arachnoid cyst at age 19 months developed an insidious onset of bizarre behaviour including visual and auditory hallucinations, intermittent confusion and confabulation. He had a subjective fever for the preceding 3 days and recently had multiple family members test positive for COVID-19. He developed a decreased level of consciousness that prompted presentation to the emergency room.

He was hypoxic to 89% on room air, requiring 2 L of supplemental oxygen via nasal cannula, haemodynamically stable and mildly tachypneic on presentation with a respiratory rate between 28 and 36 per minute. He was awake but had slurred speech and was intermittently confused, taking off cardiac monitor leads and blood pressure cuff repeatedly. A linear, left parietal paramedian incision from his childhood surgery was visible. Bilateral fine crackles

were heard on lung auscultation. The rest of the physical examination was unremarkable.

INVESTIGATIONS

The patient tested positive for SARS-CoV-2 by real-time (RT) PCR via a nasopharyngeal swab in the emergency room. His chest radiograph (CXR) showed multifocal parenchymal hazy opacities. A CT angiogram of the chest was unremarkable for a pulmonary embolism; however, it did show extensive multifocal ground-glass opacities consistent with COVID-19 viral pneumonia (figure 1A,B). A head CT scan showed a 2.5×2.4 cm choroid fissure cyst with dilatation of the left temporal horn of the lateral ventricle, without midline shift or extra-axial fluid collections (figure 2). A urine drug screen was negative, and the blood alcohol level was undetectable. Laboratory data have been summarised in table 1. A lumbar puncture (LP) was performed on day 2 of hospitalisation with an opening pressure of 26 cm H₂O; spinal fluid was clear in appearance, and CSF analysis labs are summarised in table 2.

DIFFERENTIAL DIAGNOSIS

The patient presented with confusion, bizarre behaviour and new-onset seizures 12 hours after presentation to the intensive care unit (ICU). Considerations for his illness include recreational drug use, alcohol intoxication or withdrawal, drug overdose, meningoencephalitis and intracranial haemorrhage. Our patient was not diabetic, so hypoglycaemia is essentially ruled out as a cause of seizures. This patient also had a structural brain lesion, and complications such as enlargement of the choroidal fissure arachnoid cyst would also be a differential however patient never had any prior seizures and his first seizure episode after being infected with SARS-CoV-2 favours the seizures secondary to SARS-CoV-2 infection. The choroidal fissural cyst is a congenital cyst and likely not of any clinical concern as it has not changed in size. The characteristic CSF findings and absence of commonly known causes of the viral encephalitis make SARS-CoV-2 the most likely cause of encephalitis and resultant seizures.

TREATMENT

He was admitted to the ICU for close monitoring of his neurologic dysfunction, placed in airborne isolation, started on remdesivir and administered a unit of convalescent plasma. He had a witnessed generalised tonic-clonic seizure 12 hours after admission to ICU and required intubation for airway protection during his postictal state. He



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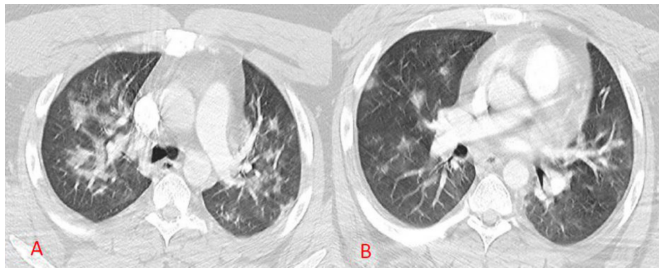


Figure 1 (A, B) CT chest showing bilateral ground glass opacities in craniocaudal distribution.

denied a prior history of seizures in his life and had never been on antiepileptic medications. He was sedated with a continuous infusion of propofol and started on intravenous levetiracetam. Phenytoin was added as a second antiepileptic agent after the patient had two subsequent seizures a few hours after the loading dose of levetiracetam. Due to high clinical suspicion for encephalitis, he was started on empiric treatment with acyclovir, ceftriaxone and vancomycin. An MRI brain was performed that showed a 2.3 cm left choroidal fissural cyst with associated ventriculomegaly of the temporal horn of the left lateral ventricle (figure 3).

A continuous electroencephalogram (EEG) after intubation showed generalised slowing without any electrographic seizures visualised. He improved with antiviral treatments and supportive care in the next 3 days and was successfully liberated from mechanical ventilation and discharged home on antiepileptic medications after a 5-day hospital stay.

OUTCOME AND FOLLOW-UP

A repeat CXR 6 weeks after the initial CXR showed a complete resolution of the bilateral pulmonary opacities. The patient did not report any further seizures after discharge from the hospital.



Figure 2 CT scan showing a 2.5x2.4 cm choroid fissure cyst with dilatation of the left temporal horn of the lateral ventricle.

Table 1 Summary of laboratory data

Test	Result	Reference range
Leucocytes	14.8	4.5–11.0 K/ μ L
Haemoglobin	15.8	13.5–18.0 g/dL
Haematocrit	47.1	40.0%–52.0%
Platelet count	184	140–440 K/ μ L
Segmented neutrophils	76	%
Lymphocytes	17	%
Eosinophils	0	%
Glucose	114	70–99 mg/dL
Sodium	133	136–145 meq/L
Potassium	4.3	3.5–5.1 meq/L
Chloride	101	98–107 meq/L
Carbon dioxide	25	21–32 meq/L
Urea	11	7–18 mg/dL
Creatinine	0.9	0.70–1.30 mg/dL
Calcium	8.3	8.5–10.1 mg/dL
Albumin	3.6	3.4–5.0 g/dL
Globulin	4.6	2.4–3.5 g/dL
Bilirubin, total	0.6	0.2–1.0 mg/dL
Alkaline phosphatase	42	45–117 U/L
Sgot (AST)	44	15–37 U/L
Sgpt (ALT)	48	16–61 U/L
Procalcitonin	0.13	ng/mL
LDH	416	85–227 U/L
Ferritin	778	26–388 ng/mL
TSH	2.07	0.36–3.74 uIU/mL

ALT, Alanine transaminase; AST, Aspartate transaminase; LDH, Lactate Dehydrogenase; TSH, Thyroid Stimulating Hormone.

DISCUSSION

A majority of cases of COVID-19 present with fever and upper respiratory tract symptoms.³ While COVID-19 can cause a lethal respiratory illness, we are continually learning about other organ systems involved in patients infected with SARS-CoV-2. A variety of viral infections can cause lethal damage to the nervous system's structure and function, such as human respiratory syncytial virus, influenza virus, human metapneumovirus and coronavirus.⁴ Coronaviruses help recruit inflammatory cytokines, mainly interleukin-8 and monocyte chemoattractant protein-1 (MCP1). MCP1 is present on other CNS cells and helps in degradation of the blood-brain barrier and recruit more inflammatory markers causing a cytokine storm in the brain resulting in cortical irritation and seizures.^{5–7}

Coronaviruses have been linked to neurological involvement in patients with respiratory tract infections, and in particular, the neurotropic and neuroinvasive potential of the coronavirus has been described after nasal infection in humans. The virus enters the CNS through the olfactory bulb and can reach the brain and CSF in less than 7 days.⁴ In one study, most neurological manifestations developed early in the illness (median time 1–2 days into hospital admission). Critically ill patients appear to have higher rates of neurological complications than patients with less severe disease.² The exact mechanism by which the SARS-CoV-2 causes encephalitis is unclear, but certain hypotheses have been suggested, including retrograde travel of the virus from cranial nerves into the CNS and haematogenous spread of virus particles via lymphocytes. In addition, the host immune response leading to a cytokine syndrome can damage the blood-brain barrier and cause viral encephalitis.⁶

Neurological findings have been described in 49 out of 58 critically ill COVID-19 patients in one report.⁸ In this series, the MRI findings showed leptomeningeal enhancement, EEG findings

Table 2 Analysis of cerebrospinal fluid, including PCR testing for viral and bacterial organisms and cultures

CSF test	Result (reference range)
Protein	84 (15–45 mg/dL)
Glucose	90 (40–70 mg/dL)
RCC	1 (/μL)
WCC	12 (0–5/μL)
Segmented neutrophils	1 (0%–6 %)
Lymphocytes	70 (40%–90 %)
Monocytes	29 (15%–45%)
Gram stain	No organisms seen
Bacterial culture	No growth
AFB Culture	No AFB isolated
Fungal culture	No yeast or fungus isolated
VDRL	Non-reactive
Cytomegalovirus	Not detected
Enterovirus	Not detected
Herpes simplex virus 1	Not detected
Herpes simplex virus 2	Not detected
Human herpes virus 6	Not detected
Human parechovirus	Not detected
Varicella zoster virus	Not detected
West Nile virus	Not detected
SARS-CoV-2	Not detected
<i>Escherichia coli</i> K1	Not detected
<i>Haemophilus influenzae</i>	Not detected
<i>Listeria monocytogenes</i>	Not detected
<i>Neisseria meningitidis</i>	Not detected
<i>Streptococcus agalactiae</i>	Not detected
<i>Streptococcus pneumoniae</i>	Not detected
<i>Cryptococcus neoformans</i>	Not detected
<i>Cryptococcus gattii</i>	Not detected

AFB, Acid Fats Bacilli; CSF, cerebrospinal fluid; RCC, red cell count; VDRL, Venereal Disease Research Lab; WCC, white cell count.

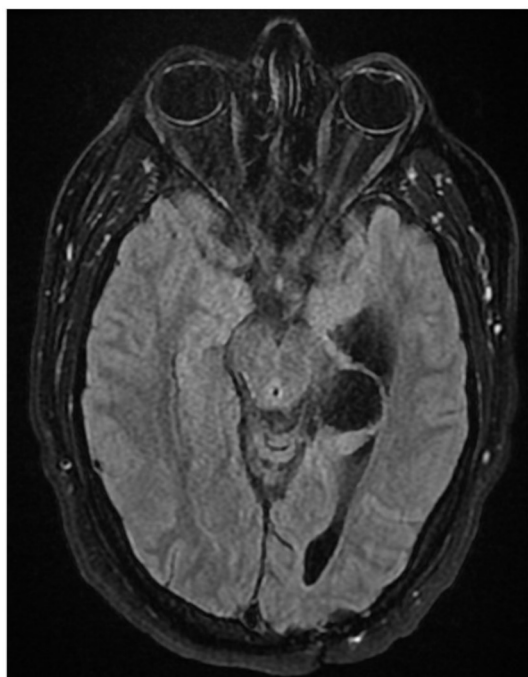


Figure 3 MRI brain was performed that showed a 2.3 cm left choroidal fissural cyst with associated ventriculomegaly of the temporal horn of the left lateral ventricle.

were non-specific, and all seven patients who underwent CSF analysis had negative RT PCR for SARS-CoV-2. Seizures have been reported in case series as well as isolated case reports in COVID-19. The first case of meningitis/encephalitis associated with SARS-CoV-2 reported seizures in a 24-year-old man who had a negative nasal RT PCR but positive RT-PCR from CSF with elevated white cell count in CSF.⁷ MRI findings showed right lateral ventriculitis and encephalitis on the right mesial lobe and hippocampus. In other reports, a 72-year-old man without a history of seizures developed seizures on day 3 of admission to the ICU while on mechanical ventilation, his CT head was unremarkable for any acute pathology and LP was not performed.⁶ Another report is of a 78-year-old woman with COVID-19 who had a history of hypertension and post-herpetic encephalitis, who developed seizures and tested positive for SARS-CoV-2 on a nasal PCR test but did not have an LP performed.⁹ A very recent case report also considers SARS-CoV-2 as a possible aetiology of seizures in a 57-year-old woman; her CT head showed age-related changes, and MRI of the brain was reported normal although LP was not performed.¹⁰

There are a growing number of reports of seizures in patients with COVID-19, which could be related to metabolic abnormalities, hypoxia or even encephalitis.¹¹ Seizures can also be a presenting symptom of COVID-19, as reported in another case series.⁵ With the ever-rising numbers of COVID-19, there is a need for vigilance for neurological symptoms and appropriate testing including CT and MRI imaging, EEG and CSF sampling should be considered.

Learning points

- ▶ Our case report highlights a neurological presentation of COVID-19 with encephalopathy and seizures.
- ▶ Early initiation of a neurological workup helps make critical clinical decisions, especially the initiation of antiepileptic medications and antimicrobials.
- ▶ For COVID-19 patients with neurological symptoms, a multidisciplinary care team approach should be considered to enhance the care of these patients.

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