SHORT REPORT

Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke

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ABSTRACT

Background Emergence of the novel corona virus (severe acute respiratory syndrome (SARS)-CoV-2) in December 2019 has led to the COVID-19 pandemic. The extent of COVID-19 involvement in the central nervous system is not well established, and the presence or the absence of SARS-CoV-2 particles in the cerebrospinal fluid (CSF) is a topic of debate.

Case description We present two patients with COVID-19 and concurrent neurological symptoms.

Conclusion Our report shows that patients’ CSF may be devoid of viral particles even when they test positive for COVID-19 on a nasal swab. Whether SARS-CoV-2 is present in CSF may depend on the systemic disease severity and the degree of the virus’ nervous tissue tropism and should be examined in future studies.

INTRODUCTION

The emergence of the novel corona virus (severe acute respiratory syndrome (SARS)-CoV-2) in December 2019 in Wuhan, China, has led to a global pandemic with almost unprecedented global health and economic consequences. In infected patients, the virus primarily causes severe respiratory symptoms that are collectively coined as COVID-19. These symptoms can culminate in a cytokine storm resulting in acute respiratory distress syndrome (ARDS).1 However, multiple reports have raised concerns about the virus’ tendency to invade the central nervous system (CNS).2 3 The spectrum of CNS involvement ranges from menigitis or encephalitis to ischaemic stroke believed to be caused by thrombophilia.4 The presence or the absence of SARS-CoV-2 in cerebrospinal fluid (CSF) is not established when a patient with a positive nasal swab has concurrent neurological symptoms.

In this report, we present two patients with COVID-19 and concurrent neurological symptoms who repeatedly tested negative for SARS-CoV-2 RNA in their CSF. Our first patient had a Hunt and Hess (H&H) grade 3 aneurysmal subarachnoid haemorrhage (SAH), and our second patient had an ischaemic stroke with massive haemorrhagic conversion.

CASE DESCRIPTION

Patient 1

The patient is a 31-year-old man who had flu-like symptoms due to COVID-19 and later developed an acute-onset severe headache and loss of consciousness and was diagnosed with a Hunt and Hess grade 3 subarachnoid haemorrhage from a ruptured aneurysm. Our second patient is a 62-year-old woman who had an ischaemic stroke with massive haemorrhagic conversion requiring a decompressive hemicraniectomy. Both patients’ CSF was repeatedly negative on real-time PCR analysis despite concurrent neurological disease.

Conclusion Our report shows that patients’ CSF may be devoid of viral particles even when they test positive for COVID-19 on a nasal swab. Whether SARS-CoV-2 is present in CSF may depend on the systemic disease severity and the degree of the virus’ nervous tissue tropism and should be examined in future studies.
intracranial haemorrhage—including the first reported case of 
aneurysmal SAH—both of whom tested positive for COVID-19.

It has been reported in the literature that SARS-CoV may invade 
the CNS, and due to the high similarity between SARS-COV and 
SARS-CoV-2, it is possible that the latter possesses the same 
potential. The initial report of the COVID-19 outbreak by 
Zhou et al corroborated previous reports and confirmed that 
SARS-CoV-2 uses the same receptor for cell entry as SARS-CoV, 
namely, membrane-bound ACE II (ACE2). ACE2 has been 
demonstrated to be expressed in neurons, as well as endothelial 
and arterial smooth muscle cells in the brain, potentially 
allowing SARS-CoV-2 to cross the blood–brain barrier and affect 
the CNS. This may allow the virus to cause viral meningitis or, in 
the case of our patients, could lead to intracranial or aneurysmal 
haemorrhage. Additionally, autopsy reports have revealed brain 
tissue oedema and neuronal degeneration in deceased patients,
and experimental animal studies using SARS-CoV or Middle 
East respiratory syndrome-CoV have shown that virus particles 
can be detected in specific brain areas, such as the thalamus 
and the brainstem. In a case study with 214 patients with 
confirmed COVID-19 infections, 36.4% showed neurological 
symptoms such as dizziness, headache and confusion, with 5.7% of 
these patients having cerebrovascular disease, including ischaemic 
stroke and intracerebral haemorrhage.

Perhaps the most striking evidence suggesting nervous tissue 
tropism comes as a by-product of two case reports from Japan 
and China, in which patients with COVID-19 showed signs of 
meningitis. In both patients, PCR analysis of the CSF samples 
turned positive for COVID-19, showing that the virus has the 
potential to cross the blood–brain barrier.

In our first patient, who had no risk factors for cerebral aneurysms, 
his sentinel event was preceded by days of fatigue, dry cough and general malaise. He then had sudden-onset loss of 
consciousness and was diagnosed at a nearby hospital with H&H grade 3 SAH and presented to our institution with lethargy and 
hydrocephalus, and later tested positive for COVID-19.

Our second patient was found to have COVID-19 as part of the 
preoperative work-up for tracheostomy placement. This 
illustrates the challenge of treating neurosurgical patients with 
this virus, as many patients are unable to describe symptoms 
prior to presentations.

In published reports on SARS-CoV-2, a cytokine storm has 
been postulated, which could result in cerebrovascular disease. 
Furthermore, severe cases of COVID-19 have shown elevated 
D-dimer levels and thrombocytopenia, rendering 
patients prone to cerebrovascular events, both thrombotic and 
haemorrhagic. Whether or not our first patient’s aneurysm 
rupture was directly related to his infection is difficult to 
ascertain. However, it is possible that in a patient without any 
significant risk factors, the cytokine storm, coupled with the 
sympathetic drive in an attempt to combat the infection, may 
have had a role in the aneurysm formation and rupture.

Furthermore, since our second patient was an asymptomatic 
carrier, it is unclear when her first exposure occurred. However, 
due to the proximity of her neurological events, it is likely that 
she carried the virus during the initial stroke event and her subseq-
uent haemorrhage. Therefore, it is conceivable that the thrombo-
etic event—in the absence of other risk factors—is secondary 
to derangements in the coagulation cascade related to COVID-
19, and the following haemorrhagic event may be related to the 
 aforementioned cytokine storm.

While it is nearly impossible to link COVID-19 to intra-
 cranial pathology, CSF analysis can be used as an objective 
marker for CNS involvement. In both of our patients who had
ventriculostomies placed, CSF samples were sent to evaluate for viral CNS involvement. Specific SARS-CoV-2 RNA was not detected in both patients’ CSF on two separate real-time PCR runs. This is in direct contradiction to a case report by Moriguchi et al., which showed no SARS-CoV-2 in the nasal swab but only in the CSF.²

Both of our patients had relatively mild respiratory symptoms without progression to ARDS. Our first patient was able to be extubated on POD 1 and did not require any extensive ventilator support. Our second patient was able to be weaned from ventilator support and never required ARDS treatment. We suspect that, in light of a non-fulminant course of the disease, there was no disruption of the blood–brain barrier that would allow for SARS-CoV-2 to cross into the CSF space.

CONCLUSION
We report the absence of SARS-CoV-2 in the CSF of two patients with concurrent severe neurological symptoms but a non-fulminant respiratory disease course. In such cases, an underlying inflammatory and hypercoagulable state may incite cerebrovascular disease without disruption of the blood–brain barrier. We encourage further CSF analysis in patients with confirmed COVID-19 as this will give us a better understanding of the virus’s tissue tropism.

REFERENCES

Contributors FAS and RG: conceptualisation and methodology; SP, ZW, NW, RM, AL, MBA, RFS, TT, NM, LP, FR, SIT, PJ and RHR: data curation and formal analysis; RG: study supervision; FAS and LP: visualisation; FAS: original draft preparation; All authors: writing, review and editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

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