

Increased CSF levels of IL-1 β , IL-6, and ACE in SARS-CoV-2–associated encephalitis

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A national outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan, China, rapidly evolving to the coronavirus disease 2019 (COVID-19) pandemic. Neurologic complications of COVID-19 include headache, confusion, hyposmia, and dysgeusia,¹ with encephalitis being rarely reported. Coronaviruses can potentially invade the CNS through trans-synaptic propagation via nasal entry, likely causing hyposmia. Alternatively, CNS dysfunction may result from the systemic hyperinflammatory response to the virus. We report 2 patients supporting this hypothesis.

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Patient 1

A 25-year-old healthy man presented with 1-day history of headache, left-sided paresthesias, and ipsilateral paresis progressing within 12 hours to confusion and agitation. His axillary temperature was 38.2°C. Brain CT and MRI scans were normal. CSF showed lymphocytic pleocytosis and increased proteins. He was started on IV acyclovir, ampicillin, and ceftriaxone, which were discontinued when CSF cultures and PCR ruled bacterial or viral etiologies. PCR for SARS-CoV-2 was negative in CSF but positive in the nasopharyngeal swab. On day 2, he fully recovered except for amnesia of the previous 2 days.

Patient 2

A healthy 49-year-old man presented with fever, myalgias, and dry cough lasting 1 week. A few hours after admission, he developed difficulty naming objects, temporospatial disorientation, confusion, and agitation. A thoracic CT scan showed bilateral peripheral opacities suggestive of COVID-19 pneumonia. Brain CT and MRI scans obtained 2 days later were unremarkable. CSF showed lymphocytic pleocytosis and increased proteins. The patient was empirically started on acyclovir, ampicillin, and ceftriaxone, which were discontinued once CSF cultures and PCR returned negative. PCR for SARS-CoV-2 was positive in the nasopharyngeal swab, but negative in CSF. Three days later, he was back to normal except for amnesia of the previous days.

None of the patients developed severe respiratory problems or required intensive care support.

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“Hospital Clínic Infecto-COVID-19” group and “Hospital Clínic Neuro-COVID-19” group coinvestigators are listed in appendix 2 at the end of the article.

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Table Basic demographic and clinical data of both cases

	Case 1	Case 2
Age	25	49
Sex	Male	Male
Comorbidities ^a	No	No
Respiratory symptoms	No	Yes
Rash	Yes	No
Anosmia and ageusia	No	No
Headache	Yes	No
Neck stiffness	No	No
C-reactive protein (CRP) [<1 mg/dL]	<0.40	1.70
Ferritin (20–400 ng/mL)	151	428
Procalcitonin (<0.50 ng/mL)	—	<0.03
LDH (<234 U/L)	190	254
Dimer D (<500 ng/mL)	600	600
Leukocyte count ($4\text{--}11 \times 10^9/\text{dL}$)	9	5.74
Lymphocyte count ($0.9\text{--}4.5 \times 10^9/\text{dL}$) (17–55%)	1.9 (21%)	0.8 (13.1%)
Platelets ($130\text{--}400 \times 10^9/\text{dL}$)	147	113
CSF proteins (150–450 mg/L)	1,055	1,155
CSF glucose (40–80 mg/dL) (2.8–4.2 mmol/L)	80 (3.6)	54 (2.99)
CSF nucleated cells/mm ³	95 neutrophils 0% Lymphocytes 98% Macrophages 2%	90 neutrophils 0% Lymphocytes 99% Monocytes 1%
CSF erythrocytes/mm ³	0	260
CSF IL-1 β (pg/mL)	14.8	<2.56
CSF IL-6 (pg/mL)	190	25
CSF IFN α (pg/mL)	<0.58	<0.58
CSF IFN β (pg/mL)	<8.78	<8.78
CSF ACE (U/L)	15.5	10.9

Abbreviations: ACE = angiotensin-converting enzyme; IL = interleukin.

^a Hypertension, respiratory chronic disease, cardiovascular disease, diabetes, cancer, chronic hepatopathy, or immunosuppression. CSF IL-1 β and IL-6 were considered increased when greater than 2.56 pg/mL and 7 pg/mL, respectively. As for ACE, the normal range was 0–2.5 U/L.

Clinical features, serum, and CSF characteristics including cytokines and angiotensin-converting enzyme (ACE) profile from both cases are shown in the table.

Discussion

These patients suggest that encephalitis may be the first or dominant manifestation of COVID-19. For patient 1, the focal neurologic deficits were the first symptom manifestation; his young age, absence of risk factors, and comprehensive studies ruling out other etiologies suggest a link between the neurologic symptoms and systemic SARS-CoV-2 infection. By contrast, patient 2 presented with typical COVID-19 symptoms,

but confusion, disorientation, and aphasia rapidly dominated the clinical picture.

Three previous case reports of CNS involvement in COVID-19 suggest different pathogenic mechanisms: direct CNS infection demonstrated by detection of SARS-CoV-2 RNA in CSF,² recrudescence of symptoms related to previous lesions (e.g., brain infarction) in the context of systemic infection,³ and inflammatory-mediated mechanisms resulting in acute hemorrhagic necrotizing encephalopathy. This is a rare complication of viral infections, usually influenza, considered to result from severe systemic inflammation associated with elevated cytokine levels, such as interleukin

(IL)-6 and tumor necrosis factor- α .⁴ No information on serum or CSF cytokine levels was provided for any of these 3 patients.

In our 2 patients, we cannot completely rule out a direct infectious mechanism, despite the negative CSF testing of SARS-CoV-2, but the rapid recovery in less than 3 days makes it unlikely. Alternatively, and in keeping with the abovementioned cytokine-mediated systemic inflammation, there is evidence that patients with coronaviruses can develop a cytokine storm syndrome with increased IL-1 and IL-6 among other inflammatory mediators. Hence, in a study of children with acute encephalitis-like syndrome, serum anti-human coronavirus-OC43 immunoglobulin M antibodies were present in 12% of patients and levels of IL-6, IL-8, monocyte chemoattractant protein-1, and Granulocyte Macrophage Colony-Stimulating Factor were increased in their CSF.⁵ The elevated CSF levels of IL-6 in our 2 patients, and IL-1 β in 1 of them, are in line with those studies. Biological anti-IL treatments targeting IL-1 (anakinra) or IL-6 (tocilizumab and siltuximab) are useful to treat symptoms of CNS involvement related to the cytokine storm triggered by chimeric antigen receptor T-cell therapy.⁶ Our patients improved spontaneously, but these treatments could be considered in more severe cases of COVID-19-associated encephalitis with increased CSF levels of ILs. Finally, our 2 patients also had increased CSF levels of ACE. It has been postulated that SARS-CoV-2 enters the cell using the ACE2 receptor.⁷ Although it is difficult to interpret the meaning of increased CSF levels of ACE in these 2 patients, they could be linked to the postulated alteration in the ACE pathway in COVID-19.

The main implication of these 2 patients is that physicians should be aware of COVID-19 infections presenting or predominantly manifesting as encephalitis, likely resulting from activation of inflammatory pathways with increased ILs and ACE in CSF.

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