

CSF Biomarkers in Patients With COVID-19 and Neurologic Symptoms

A Case Series

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Abstract

Objective

To explore whether hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and neurologic symptoms have evidence of CNS infection, inflammation, and injury using CSF biomarker measurements.

Methods

We assessed CSF SARS-CoV-2 RNA along with CSF biomarkers of intrathecal inflammation (CSF white blood cell count, neopterin, β_2 -microglobulin, and immunoglobulin G index), blood-brain barrier integrity (albumin ratio), and axonal injury (CSF neurofilament light chain protein [NfL]) in 6 patients with moderate to severe coronavirus disease 2019 (COVID-19) and neurologic symptoms who had undergone a diagnostic lumbar puncture. Neurologic symptoms and signs included features of encephalopathies (4 of 6), suspected meningitis (1 of 6), and dysgeusia (1 of 6). SARS-CoV-2 infection was confirmed by real-time PCR analysis of nasopharyngeal swabs.

Results

SARS-CoV-2 RNA was detected in the plasma of 2 patients (cycle threshold [Ct] value 35.0–37.0) and in CSF at low levels (Ct 37.2, 38.0, 39.0) in 3 patients in 1 but not in a second real-time PCR assay. CSF neopterin (median 43.0 nmol/L) and β_2 -microglobulin (median 3.1 mg/L) were increased in all. Median immunoglobulin G index (0.39), albumin ratio (5.35), and CSF white blood cell count (<3 cells/ μ L) were normal in all, while CSF NfL was elevated in 2 patients.

Conclusion

Our results in patients with COVID-19 and neurologic symptoms suggest an unusual pattern of marked CSF inflammation in which soluble markers were increased but white cell response and other immunologic features typical of CNS viral infections were absent. While our initial hypothesis centered on CNS SARS-CoV-2 invasion, we could not convincingly detect SARS-CoV-2 as the underlying driver of CNS inflammation. These features distinguish COVID-19 CSF from other viral CNS infections and raise fundamental questions about the CNS pathobiology of SARS-CoV-2 infection.

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Glossary

BBB = blood-brain barrier; $\beta_2\text{M}$ = β_2 -microglobulin; **COVID-19** = coronavirus disease 2019; **Ct** = cycle threshold; **IgG** = immunoglobulin G; **LP** = lumbar puncture; **NfL** = neurofilament light protein; **RdRP** = RNA-dependent RNA polymerase; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **WBC** = white blood cell.

Neurologic manifestations are common features of coronavirus disease 2019 (COVID-19), but questions remain regarding the underlying mechanisms of CNS pathology.¹ We have recently reported neuronal injury and glial activation in patients with COVID-19 using plasma markers of axonal and astrocytic damage.² A variety of CNS disorders, including strokes, seizures, and other encephalopathies, have been reported, particularly in severe COVID-19.³⁻⁷ In contrast, hyposmia and dysgeusia are relatively common in milder infection, possibly indicating viral invasion of the olfactory bulb.⁸

CSF biomarkers are useful in characterizing CNS responses to infection both by direct detection of invading pathogens and by host inflammatory responses. Indeed, CSF white blood cell (WBC) count is often used as the *sine qua non* indicator of meningitis or encephalitis. Likewise, soluble inflammatory markers can serve as useful measures of the character and consequences of CNS infections. Neopterin (a marker of cellular activation, including macrophage/microglia and astrocytes) and β_2 -microglobulin ($\beta_2\text{M}$) (a component of the major histocompatibility complex class I molecule) have proved to be robust and frequently altered in neuroinflammatory diseases.^{9,10} Similarly, CNS injury can be sensitively detected with CSF neurofilament light chain protein (NfL), a structural component of myelinated axons.^{9,11} In addition, the immunoglobulin G (IgG) index assesses intrathecal antibody responses, and the ratio of CSF albumin to blood concentration (albumin ratio) provides a measure of blood-brain barrier (BBB) disruption.¹² Together, these biomarkers aid in characterizing the magnitude, character, and effect of viral CNS infections.

Here, we present an analysis of these well-established CSF biomarkers in 6 patients with COVID-19 and neurologic symptoms.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study has been approved by the Swedish Ethical Review Authority (2020-01771). All participants provided informed written consent.

Study Population

We included patients with confirmed COVID-19 infection and neurologic abnormalities who had undergone a diagnostic lumbar puncture (LP). All patients were admitted to

Sahlgrenska University Hospital in Gothenburg, Sweden, between March 1 and April 4, 2020.

Viral Diagnostics

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed with real-time PCR analysis of nasopharyngeal swab specimens. Additional swab specimens and cell-free CSF and plasma samples were analyzed with the same protocols. Nucleic acid from 200 μL nasal swab medium, plasma, or CSF was extracted by a MagNA Pure LC instrument (Roche Diagnostics, Mannheim, Germany) with the Total Nucleic Acid isolation kit. The nucleic acids were eluted in 100 μL volume, and 5 μL of this was used for real-time PCR. Real-time PCR of a target in the RNA-dependent RNA polymerase (RdRP) region (modified from reference 13) was performed in a QS6 instrument (Applied Biosystems, Foster City, CA) in 20 μL reactions containing oligonucleotides and Taqman Fast Virus 1-step Mastermix (Applied Biosystems). The sequence of the primers was as follows: RdRP_Fi, GTCATGTGTGGCGGTTCACT; RdRP_Ri, CAACACTATTAGCATAAGCAGTTGT, and RdRP_probe, CAGGTGGAACCTCATCAGGAGATGC. After a reverse transcription step at 46°C for 30 minutes followed by 10 minutes of denaturation at 95°C, 45 cycles of 2-step PCR was performed (15 seconds at 95°C, 60 seconds at 56°C).¹³ Plasma and CSF samples with detectable SARS-CoV-2 were reanalyzed from stored specimens using the Xpert-Xpress SARS-CoV-2 test (Cepheid, Sunnyvale, CA) according to the manufacturer's instructions. Cycle threshold (Ct) values were used to estimate sample viral load using formula $(47 - \text{Ct}) / 3.4 = \log_{10}$ copies/sample. Ct values <37 were regarded as positive, values >40 as negative, and values between 37 and 40 as indeterminate.

Biomarker Analyses

CSF WBC count was performed using routine methods with a limit of detection of 3 cells/ μL . CSF and serum $\beta_2\text{M}$ concentrations were measured with the N Latex $\beta_2\text{M}$ kit on the Atellica NEPH 630 System (Siemens Healthcare GmbH, Erlangen, Germany). CSF and serum neopterin concentrations were measured with a commercially available immunoassay (BRAHMS, Berlin, Germany).⁹ CSF NfL was measured with a previously described in-house sandwich ELISA.¹⁴ Because NfL increases with normal aging, NfL concentrations were age adjusted to the median age (65 years) of the study group.¹¹ IgG and albumin concentrations were measured by immunoturbidimetry on a Cobas instrument (Roche Diagnostics, Penzberg, Germany). IgG index and albumin ratio were calculated as previously described.¹²

Data Availability

Researchers can apply for access to anonymized data from the present study for well-defined research questions that are in line with the overall research agenda for the cohort. Please contact the corresponding author.

Results

Study Population

During the study period, a total of 112 patients with COVID-19 were admitted to the clinic. Six patients who had undergone a diagnostic LP on clinical indications were identified and included in the study. All had respiratory symptoms with hypoxemia requiring hospitalization. Patient characteristics at baseline are shown in the table, and an overview of disease courses and timing of LP for each patient is shown in figure 1. Two patients were previously healthy; 1 had schizophrenia. Of 3 patients with hypertension, 2 had diabetes mellitus, 1 of whom also had ischemic heart disease. Two patients (patients 2 and 4) required intubation and intensive care; patient 5 had an elevated D-dimer 3 days after LP and was subsequently diagnosed with pulmonary emboli. Neurologic signs and symptoms are summarized in the table. The most common neurologic symptoms were various features of encephalopathy, found in patients 1 through 3 and 6. CT neuroimaging was performed in 4 patients.

Specifically, patient 1 presented with disorientation and lack of spatial awareness. CT scan showed evidence of small vessel disease and global cortical atrophy. Patient 2 was disoriented to time and place, exhibited poor memory and difficulty with fluent speech, performed poorly on simple tasks such as holding a fork or visiting the restroom independently, complained of extreme fatigue, and later developed multiple seizures. He underwent brain CT and CT angiography after the

seizures and EEG 2 days later that showed no epileptic activity but generalized background slowing while under deep sedation. The CT was normal while CT angiography showed atherosclerotic changes consonant with the patient's underlying risk profile and comorbid conditions. Patient 3 had cognitive slowing, expressive verbal difficulties, and altered personality according to relatives. He had a normal CT scan apart from discrete white matter changes. Patient 4 presented with somnolence, moderate neck stiffness, and photophobia suggesting meningitis and leading to the LP; a CT scan was normal. Patient 5 had dysgeusia and extreme fatigue and described an altered sense of reality. Patient 6 was disoriented to time, person, and situation at admission; was unable to perform simple tasks; and had severely limited verbal communication. None had clear focal motor or sensory neurologic signs by bedside examination. Due to restrictions imposed at the time to prevent transmission to hospital workers and other patients, no MRI scans or additional EEG examinations were performed.

CSF Viral Detection and Biomarkers

SARS-CoV-2 RNA was detectable in plasma in patients 1 and 2 (Ct values 37.0 and 35.0) and in CSF of patients 3, 4, and 5 (Ct values 39.0, 38.0, and 37.2, respectively). Due to these low levels of viral detection, all plasma and CSF samples with detectable viral RNA were reanalyzed with the Xpert assay. Both reruns in plasma confirmed SARS-CoV-2 RNA detection, while SARS-CoV-2 RNA was undetectable in all 3 CSF samples.

CSF biomarker analyses are shown in figure 2, A–D. None of the patients had CSF pleocytosis (WBC ≤ 3 cells/ μ L) (figure 2A). The albumin ratio reflecting BBB integrity and IgG index reflecting intrathecal IgG synthesis were within the normal range in all (figure 2B). The median (range) albumin ratio was

Table Patient Characteristics

Patient	Sex	Age, y	Comorbid conditions	Neurologic signs and symptoms	At time of LP				
					POX, % (O ₂ L/min)	CRP, mg/L	B-lymph, $\times 10^9$ cells/L	Creatinine, μ mol/L (GFR, mL/min/1.73 m ²)	ALT, μ kat/L
1	F	80s	DM, HT	Encephalopathy	91 (4.5)	160	0.8	76 (55)	0.67
2	M	60s	CHD, DM, HT, obesity	Encephalopathy, extreme fatigue, memory loss	90 (7)	109	0.6	71 (80)	0.5
3	M	60s	None	Encephalopathy, personality changes	95 (2)	190	1.1	96 (68)	0.5
4	M	60s	Schizophrenia	Moderate neck stiffness, photophobia, somnolence	95 (15)	120	1.3	242 (22)	2.3
5	M	40s	None	Extreme fatigue, dysgeusia, disorientation	96 (2.5)	120	0.7	78 (92)	1.1
6	M	70s	HT	Encephalopathy	94 (1)	110	0.7	67 (79)	2.4

Abbreviations: ALT = alanine aminotransferase; B-lymph = total blood lymphocyte count; CHD = coronary heart disease; CRP = C-reactive protein; DM = diabetes mellitus; GFR = glomerular filtration rate; HT = hypertension; LP = lumbar puncture; O₂ = oxygen; POX = pulse oximeter oxygen saturation.

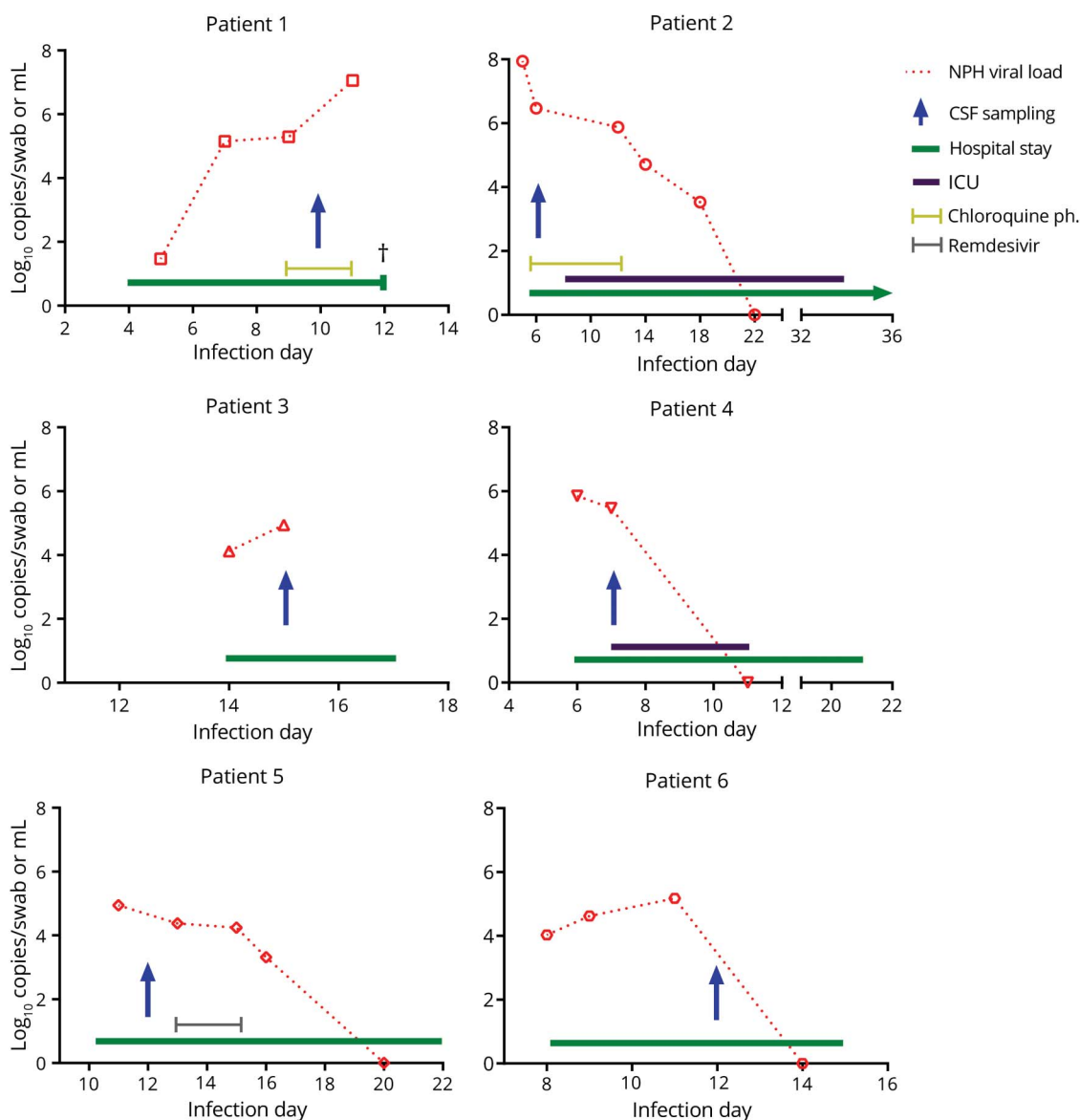
5.35 (4.3–9.7) with a reference value of <10.2, and the median (range) IgG index was 0.39 (0.32–0.43) with a reference value of <0.63. CSF and serum neopterin concentrations were elevated in all patients with median (range) neopterin concentrations of 43.0 (26.7–50.0) nmol/L in CSF and 41.9 (38.6–44.4) nmol/L in serum with upper normal reference values of 5.8 (CSF) and 8.8 (serum) nmol/L. CSF β_2 M was elevated in 5 of 5 measured CSF samples and in 6 of 6 serum samples. Median (range) β_2 M concentration was 3.1 (1.6–7.2) mg/L in CSF and 3.75 (2.8–6.0) mg/L in serum, with upper normal reference values of 1.8 mg/L (CSF) and 2.1 mg/L (serum). CSF neopterin and β_2 M concentrations were increased in all tested cases (figure 2C). Age-adjusted

CSF NfL was increased in patients 3 and 6 (figure 2D). The median (range) age-adjusted CSF NfL (65 years) was 974 (669–1998) ng/L with an upper normal reference value of 1,577 ng/L.

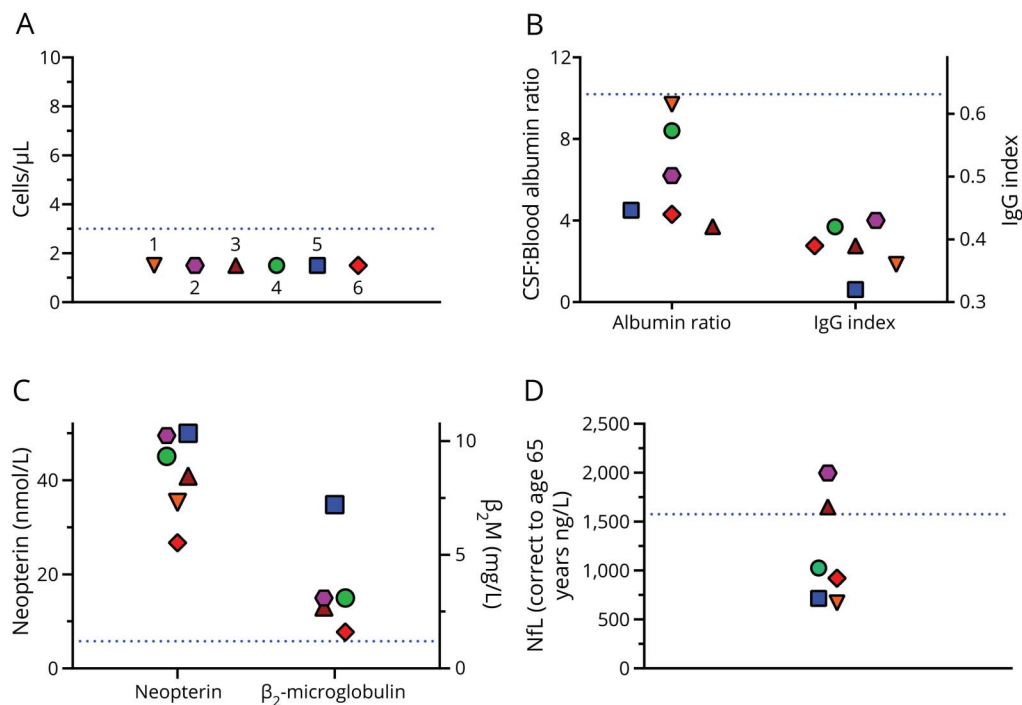
Discussion

In this case series study of CSF biomarkers in 6 patients with COVID-19 and neurologic symptoms, we found marked elevations of the 2 soluble inflammatory biomarkers in all and abnormal CSF NfL in 2 patients, while CSF WBC count, albumin ratio, and IgG index were normal in all participants.

Figure 1 Disease Course in the 6 Patients



Details of the disease courses in individual patients, including viral load in nasopharyngeal swabs as index. Vertical arrow indicates time of lumbar puncture. Geometric symbols on dashed line are individual as also seen in figure 2. Patient 1 died during the study period. Patient 2 was still admitted at the time of manuscript submission. Patients 3 through 6 were discharged. Patients 1 and 2 were treated with chloroquine phosphate; patient 5 was treated with remdesivir. ICU = intensive care unit; NPH = nasopharynx.



(A) CSF white blood cell was < 3 cells/ μ L in all patients; symbol shape and colors apply to the patient number and are used in all panels. (B) Albumin ratios and immunoglobulin G (IgG) index values were all in the normal range. The median (range) albumin ratio was 5.35 (4.3–9.7) with a reference value of < 10.2 , and median (range) IgG index was 0.39 (0.32–0.43) with a reference value of < 0.63 . (C) CSF neopterin concentrations were elevated in all patients. Median (range) CSF neopterin concentrations were 43.0 (26.7–50.0) nmol/L with an upper normal reference value of 5.8 nmol/L (CSF). CSF β_2 -microglobulin (β_2 M) was elevated in 5 of 5 measured CSF samples. Median (range) CSF β_2 M concentration was 3.1 (1.6–7.2) mg/L with an upper normal reference value of 1.8 mg/L. Both normal reference values are indicated by dashed lines. (D) CSF neurofilament light chain protein (NFL) was increased in 2 patients. The median (range) age-adjusted CSF NFL (65 years of age) was 974 (669–1998) ng/L with an upper normal reference value of 1,577 ng/L.

Two patients had low-level plasma viremia, while SARS-CoV-2 RNA was detected at indeterminate levels in only 1 of 2 PCR assays in the CSF of 3 patients. These findings outline an unusual pattern in patients with neurologic signs during a viral infection with marked elevation of soluble inflammatory biomarkers in the absence of CSF pleocytosis, BBB disruption, or intrathecal IgG synthesis.

It remains unclear whether SARS-CoV-2 RNA can reach the CNS compartment, although given previous experience in other coronavirus infections, CNS manifestations in COVID-19 are not unexpected and provided rationale for this initial study.^{15,16} Animal models of other coronavirus infections also suggest that viral invasion into the CNS can occur.¹⁷ The taxonomic similarities between SARS-CoV and SARS-CoV-2 have led many to believe that the route of entry to the brain is enabled by the membrane-bound angiotensin-converting enzyme 2.¹⁸ Angiotensin-converting enzyme 2 has been demonstrated to be expressed in neurons and endothelial and arterial smooth muscle cells in the brain, potentially facilitating SARS-CoV-2 entry across the BBB to subsequently affect the CNS.¹⁹ However, in these 6 patients with COVID-19 and clinically apparent neurologic symptoms, the lack of a cellular CSF response or signs of intrathecal IgG production usually seen in viral meningitis is interesting and implies that

the profound CNS immunoactivation reflected by the high CSF neopterin and β_2 M levels was not driven by direct neuroinvasion of SARS-CoV-2. CSF viral RNA detection has been challenging and has so far been described in 2 singular case reports.^{20,21} This discrepancy between the lack of CSF viral detection and consistent neurologic abnormalities in different stages of COVID-19 infection suggests an alternative pathophysiology in which the intense systemic inflammatory response induced by SARS-CoV-2 infection may be a driving factor. Neuropathogenesis in COVID-19 is likely multifactorial; hypoxemia, hypercoagulability, and systemic inflammation may all contribute to specific stroke syndromes and to the more general or diffuse encephalopathies seen in a majority of our included patients. Underlying comorbid conditions seen in 3 of 6 patients may also play a role in the severity of SARS-CoV-2 infection. The metabolic syndrome has been shown to promote a proinflammatory phenotype in macrophages and other immune cells, which may contribute to the hyperinflammatory response seen in individuals with such underlying conditions and COVID-19 infection²² and may increase the risk of vascular complications.

The pathophysiologic bases of the markedly elevated CSF concentrations of the immune activation indicators neopterin and β_2 M remain uncertain. Although the elevated CSF

neopterin and β_2M suggest CNS monocytic activation, their dissociation from viral detection, pleocytosis, or BBB disruption suggests mechanisms other than direct viral invasion and CNS infection. Because this was a common finding across all 6 patients, it may be a hallmark of more severe SARS-CoV-2 infection and provide a clue to the neurobiology of CNS disturbance and the “indirect” effects of systemic infection and immune activation on the CNS. Further studies across a broader spectrum of infection are needed to explore this further.

CSF NfL was elevated in 2 individuals, indicating axonal injury. We suspect that this may have been caused by an episode of hypoxia or other event but cannot clearly trace the cause. If more directly caused by viral infection or by vigorous CNS inflammation, this cannot be clearly defined in this small dataset.

There are a number of clear limitations in this study. Foremost are the small sample size and the inclusion of only individuals with moderate or severe systemic disease with neurologic presentations. These relate to the demands of patient care, including their life-threatening aspects and caregiver protections. Specifically, the study did not include a control group of patients with COVID-19 of comparable severity but without neurologic manifestations. Nonetheless, the findings are indeed highly provocative and call for further study. Viral RNA was detectable in CSF at low levels in only 1 of 2 assays. Although retesting of low-viral-load samples after freezing and thawing often fails, failure to reproduce viral detection on different platforms definitely adds a high degree of uncertainty to this finding. In addition, the timing of LP varied between 6 and 15 days from estimated disease onset, which may have affected the results.

We found an unusual pattern of marked CSF inflammation measured by the biomarkers neopterin and β_2M but without the typical responses of CSF pleocytosis, BBB disruption, or intrathecal IgG production seen in many other CNS infections. Although SARS-CoV-2 RNA was found in the plasma of 2 patients, viral detection in CSF was uncertain, and together, our data do not indicate direct neuroinvasion by SARS-CoV-2 as the underlying mechanism behind the profound CNS immunoactivation seen in this case series.

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Disclosure

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