CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

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

Marta Bodro, MD, PhD,* Yaroslau Compta, MD, PhD,* Laura Llansó, MD, Diana Esteller, MD, Antonio Doncel-Moriano, MD, Alex Mesa, MD, Alejandro Rodríguez, MD, Jordi Sarto, MD, Eugenia Martínez-Hernandez, MD, PhD, Alexandru Vlagea, MD, PhD, Natalia Egri, MD, Xavier Filella, MD, PhD, Manuel Morales-Ruiz, MD, PhD, Jordi Yagüe, MD, PhD, Álex Soriano, MD, PhD, Francesc Graus, MD, PhD, and Felipe García, MD, PhD, on behalf of the "Hospital Clínic Infecto-COVID-19" and "Hospital Clínic Neuro-COVID-19" groups

Correspondence
Dr. Bodro
mbodro@clinic.cat
or Dr. Compta
ycompta@clinic.cat

Neurol Neuroimmunol Neuroinflamm 2020;7:e821. doi:10.1212/NXI.0000000000000821

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.

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 of 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.

*Both these authors contributed equally to this work.

From the Infectious Diseases Service (M.B., Á.S., F. García), Hospital Clínic de Barcelona, Catalonia; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) (M.B., Y.C., X.F., M.M.-R., J.Y., Á.S., F. Graus, F. García), Barcelona, Catalonia; Department of Medicine (M.B., Y.C., Á.S., F. García), Universitat de Barcelona, Catalonia; Neurology Service (Y.C., L.L., D.E., A.D.-M., A.R., J.S.), Hospital Clínic de Barcelona, Catalonia; Institut de Neurociències (Y.C.), Maria de Maeztu excellence center, Universitat de Barcelona, Catalonia; Endocrinology and Nutricion Service (A.M.), Hospital Clínic de Barcelona, Catalonia; Immunology Service (A.V., N.E., J.Y.), Centre de Diagnòstic Biomèdic (CDB), Hospital Clínic de Barcelona, Functional Unit of Clinical Immunology, Hospital Sant Joan de Déu & Hospital Clínic, Barcelona, Catalonia; CDB (X.F., M.M.-R.), Hospital Clínic de Barcelona, Barcelona, Catalonia; and Department of Biomedicine (M.M.-R.), Universitat de Barcelona; CIBERehd; Catalonia, Spain.

Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

"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.

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 (4–11 × 109/dL)	9	5.74
Lymphocyte count (0.9–4.5 × 109/dL) (17–55%)	1.9 (21%)	0.8 (13.1%)
Platelets (130–400 × 109/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/mm3	95 neutrophils 0% Lymphocytes 98% Macrophages 2%	90 neutrophils 0% Lymphocytes 99% Monocytes 1%
CSF erythrocytes/mm3	0	260
CSF IL-1β (pg/mL)	14.8	<2.56
CSF IL-6 (pg/mL)	190	25
CSF IFNα (pg/mL)	<0.58	<0.58
CSF IFNβ (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-1β 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 chemotactic 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-1β 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.

Acknowledgment

The authors acknowledge the patients for their generosity and to all other people suffering the COVID-19 pandemics, as well as to all the health professionals and other staff crucially involved in their care and the handling of this unprecedented global crisis.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

Publication history

Received by *Neurology: Neuroimmunology & Neuroinflammation* May 1, 2020. Accepted in final form May 19, 2020.

Appendix 1 Authors

Name	Location	Contribution
Marta Bodro	Hospital Clínic de Barcelona, Barcelona, Spain	Designed and conceptualized the study; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content
Yaroslau Compta	Hospital Clínic de Barcelona, Barcelona, Spain	Designed and conceptualized the study; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content
Laura Llansó	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Diana Esteller	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Antonio Doncel-Moriano	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Alex Mesa	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Alejandro Rodríguez	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Jordi Sarto	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Eugenia Martínez-Hernández	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Alexandru Vlagea	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Natalia Egri	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Xavier Filella	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Manuel Morales-Ruiz	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Jordi Yagüe	Hospital Clínic de Barcelona, Barcelona, Spain	Acquisition of data and revised the manuscript for intellectual content
Alex Soriano	Hospital Clínic de Barcelona, Barcelona, Spain	Interpreted the data and revised the manuscript for intellectual content
Francesc Graus	Hospital Clínic de Barcelona, Barcelona, Spain	Interpreted the data and revised the manuscript for intellectual content
Felipe García	Hospital Clínic de Barcelona, Barcelona, Spain	Interpreted the data and revised the manuscript for intellectual content

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Laura Morata	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Juan Ambrosioni	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Estela Moreno-García	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Veronica Rico	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Berta Torres	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Alexy Inciarte	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Laia Albiac	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Daiana Agüero	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Lorna Leal	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Mariana Chumbita	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Celia Cardozo	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Montserrat Laguno	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Laura Linares	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Irene Macaya	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Fernanda Meira	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Ana Gonzalez-Cordón	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Marta Hernandez	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Jhon Rojas	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Lorena de la Mora	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Nicole García	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Pedro Puerta	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
David Nicolás	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Montserrat Solá	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Antonio Moreno	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Manuel Torres	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Jose Antonio Martínez	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Jose Mensa	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Carolina García-Vidal	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Aida Alejandre	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Sergio Amaro	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Sergi Borrego-Ecija	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Jordi Casanova	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Maria Centeno	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Estefania Conde	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Jose Miguel Contador	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Andrea García-Ortega	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Alicia Garrido	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Mar Guasp	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Sara Llufriu	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Laura Molina-Porcel	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Carmen Montejo	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Amaia Muñoz	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Judith Navarro-Otano	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Celia Painous	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
David Reyes	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Almudena Sánchez	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Raquel Sánchez	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
María Sepúlveda	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Ana Isabel Tercero	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Dolors Rambla	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Xenia Barcons	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Maria Dolores Sag	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Imma Zardoya	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Carlos Castillo	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Carmen Perez	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Soledad Barreiro	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Olga Bertran	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Ana Camara	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Guadalupe Fernandez	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
Idoia Zaro	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data
María Teresa Blazquez	Hospital Clinic de Barcelona, Barcelona, Spain	Site investigator	Collecting data

References

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–513.
2. Moriguchi T, Harii N, Goto J, et al. A first Case of Meningitis/Encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020;94:55–58.
3. Poyiadji N, shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorragic necrotizing encephalopathy: CT and MRI features. Radiology Epub 2020 Mar 31.
4. Filatov A, Sharma P, Hindi Fawzi, Espinosa PS. Neurological complications of coronavirus disease (COVID-19): encephalopathy. Cureus 2020;12:e7352.
5. Li Y, Li H, Fan R, et al. Coronavirus infections in the central nervous system and respiratory tract show distinct features in hospitalized children. Intervirology 2017;59:163–169.
6. Hays P, Costello C, Asudani D. Clinical care of chimeric antigen receptor T-cell patients and managing immune-related adverse effects in the ambulatory and hospitalized setting: a review. Future Oncol 2019;15:4235–4246.
7. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. JAMA Epub 2020 Mar 24.