Autoimmune Encephalitis After SARS-CoV-2 Infection
Case Frequency, Findings, and Outcomes

Cristina Valencia Sanchez, MD, PhD, Elitza Theel, PhD, Matthew Birnicker, PhD, Michel Toledano, MD, and Andrew McKeon, MD

Neurology® 2021;97:e2262-e2268. doi:10.1212/WNL.0000000000012931

Abstract

Background and Objectives
Autoimmune encephalitis (AE) cases after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported, but the frequency is unknown. We aimed to determine the frequency and diagnostic features of coronavirus disease 2019 (COVID-19)–related AE.

Methods
Residual sera from 556 consecutive Mayo Clinic Rochester patients (laboratory cohort) who underwent autoimmune encephalopathy neural immunoglobulin G (IgG) evaluation were tested for total antibodies against the SARS-CoV-2 spike glycoprotein using a Food and Drug Administration–authorized chemiluminescence assay (October 2019–December 2020). Clinical records from patients with a positive SARS-CoV-2 antibody result and available research consent were reviewed. This laboratory cohort was cross-referenced with the Department of Neurology’s COVID-19–related consultative experience (encephalopathy cohort, n = 31).

Results
Eighteen of the laboratory cohort (3%) were SARS-CoV-2 antibody positive (April–December 2020). Diagnoses were as follows: AE, 2; postacute sequelae of SARS CoV-2 infection (PASC), 3; toxic-metabolic encephalopathy during COVID-19 pneumonia, 2; diverse non–COVID-19 relatable neurologic diagnoses, 9; unavailable, 2. Five of the encephalopathy cohort had AE (16%, including the 2 laboratory cohort cases that overlapped), representing 0.05% of 10,384 patients diagnosed and cared for with any COVID-19 illness at Mayo Clinic Rochester in 2020. The 5 patients met definite (n = 1), probable (n = 1), or possible (n = 3) AE diagnostic criteria; median symptom onset age was 61 years (range, 46–63); 3 were women. All 5 were neural IgG negative and 4 tested were SARS-CoV-2 PCR/IgG index negative in CSF. Phenotypes (and accompanying MRI and EEG findings) were diverse (delirium [n = 5], seizures [n = 2], rhombencephalitis [n = 1], aphasia [n = 1], and ataxia [n = 1]). No acute disseminated encephalomyelitis cases were encountered. The 3 patients with possible AE had spontaneously resolving syndromes. One with definite limbic encephalitis was immune therapy responsive but had residual mood and memory problems. One patient with probable autoimmune rhombencephalitis died despite immune therapy. The remaining 26 encephalopathy cohort patients had toxic-metabolic diagnoses.

Discussion
We encountered occasional cases of AE in our 2020 COVID-19 experience. Consistent with sporadic reports and small case series during the COVID-19 pandemic, and prior experience of postinfectious AE, our cases had diverse clinical presentations and were neural IgG and CSF
viral particle negative. Application of diagnostic criteria assists in differentiation of AE from toxic-metabolic causes arising in the setting of systemic infection.

Various neurologic disorders associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported during the coronavirus disease 2019 (COVID-19) pandemic. However, the frequency of autoimmune encephalitis (AE) associated with SARS-CoV-2 is unknown. In this study, we aimed to evaluate the frequency of SARS-CoV-2 antibodies in sera of patients who underwent neural antibody testing as part of the diagnostic evaluation for AE at Mayo Clinic in Rochester, Minnesota, during 2020, and report AE cases occurring after COVID-19. In addition, we cross-referenced our institution’s COVID-19 encephalopathy cohort for cases meeting AE diagnostic criteria.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This retrospective study was approved by the Mayo Clinic Institutional Review Board. Medical records of patients who consented to research review were included.

Laboratory Cohort

The laboratory cohort consisted of 556 patients with available residual serum samples (from 642 submitted during the epoch from November 1, 2019, to December 31, 2020) who had been tested for AE-pertinent neural autoantibodies (e.g., NMDA receptor antibody; eAppendix 1, links.lww.com/WNL/B608). Residual sera were tested for total antibodies against the SARS-CoV-2 spike glycoprotein using the Roche Diagnostics Elecsys Anti-SARS-CoV-2 S electrochemiluminescence immunoassay, which has received emergency use authorization from the US Food and Drug Administration, and was clinically validated prior to implementation. Clinical records from patients with a positive SARS-CoV-2 antibody result and signed research waiver were reviewed.

Encephalopathy Cohort

In 2020, a total of 10,384 patients with any COVID-19 illness were cared for at Mayo Clinic, Rochester, Minnesota, 614 of whom underwent neurologic evaluation in the inpatient or outpatient setting in the context of contemporary or prior SARS-CoV-2 infection (January 1–December 31, 2020). Thirty-one patients had objective clinical evidence of encephalopathy. Their clinical and test findings were recorded in a database. Diagnostic criteria were applied to ascertain cases of AE and assign a level of diagnostic certainty (possible, probable, definite; eAppendix 1, links.lww.com/WNL/B608).

Data Availability

Anonymized data used for this study are available upon request.

Results

A total of 5 patients met diagnostic criteria for AE (Figure 1 and Table), representing 0.05% of all patients with COVID-19 illnesses evaluated at our institution. All 5 were identified in the encephalopathy cohort, 2 of whom (and no others) were also identified in the laboratory cohort. The 3 AE cases detected in the encephalopathy cohort, but not the laboratory cohort, had SARS-CoV-2 antibody negativity (serum was drawn early during simultaneous acute respiratory and neurologic presentations, n = 1; AE antibody testing ordered in CSF only, thus no serum was referred for laboratory testing, n = 2).

Laboratory Cohort

Of 556 patients tested for SARS-CoV-2 antibody, the median serum draw age was 59 years (range, 1–91). Eighteen (3.2%) tested positive. None had received SARS-CoV-2 vaccination prior to the serum draw. All SARS-CoV-2 antibody positive cases were detected between April 27, 2020, and December 30, 2020 (Figure 2).

Clinical records of 16 patients with research consent available were reviewed. The 2 AE cases aside (clinically described herein with the encephalopathy cohort, and in the Table), the remaining 14 patients had postacute sequelae of SARS-CoV-2 infection (PASC), 3; toxic-metabolic encephalopathy in the setting of severe COVID-19 pneumonia, 2; and diverse non–COVID-19 relatable neurologic diagnoses, 9. These 9 patients had neurologic symptoms prior to the COVID-19 pandemic (n = 6) or neurologic disorders that evolved over the course of 2020, but without known temporal relationship to COVID-19 (1 each of functional movement disorder, optic neuritis, and limbic encephalitis). The 3 patients with PASC had one or more of fatigue, cognitive complaints, headache, and dizziness, with unremarkable neurologic examinations, neuroimaging, EEG, and CSF analyses.

Glossary

ADEM = acute disseminated encephalomyelitis; AE = autoimmune encephalitis; COVID-19 = coronavirus disease 2019; IgG = immunoglobulin G; PASC = postacute sequela of SARS-CoV-2 infection; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
periventricular white matter, posterior internal capsule, and di
cron signs on examination, and brain MRI demonstrating
worsening encephalopathy, quadriparesis, upper motor neu-
monia, but developed a rhombencephalitis characterized by
toxic-metabolic disorder in the setting of COVID-19 pneu-
presented with delirium, and was initially considered to have a
toxic-metabolic cause, but her evolved clinical course, MRI, and CSF findings proved
consistent with a diagnosis of probable AE.

**Discussion**

Overall, the number of post–COVID-19 AE cases encoun-
tered in our large clinical experience was low, representing
0.05% of patients with COVID-19–related diagnoses at our
institution in 2020. None of the 5 patients was resident in the
immediate vicinity of Mayo Clinic (Olmsted County, which
had an overall AE incidence rate of 0.8/100,000 person-years
in 1995–2016).6 Consistent with our findings, the literature to
date has been confined to case reports or small case series, and
respiratory symptoms were absent in some.7 Prior reports
include mostly seronegative AE and occasional reports of anti-
NMDAR and myelin oligodendrocyte glycoprotein
antibody–associated encephalitides.8–19 We did not encounter
cases of ADEM, although cases have been reported in the
literature.20 One other patient previously reported from our
institution, who died from systemic complications of SARS-
CoV-2, had ADEM-like neuropathologic features, but also
diffuse microscopic infarcts.2 The low frequency of possible
post–COVID-19 immune-mediated encephalitides we en-
countered is consistent with similarly low numbers reported
for Guillain-Barré syndrome in 2020.21

Clinical presentations and test findings in our patients with
AE were diverse, and neural IgG testing was universally
negative. Three of our 5 cases had a “possible” AE diagnosis
only and had spontaneous resolution of symptoms. Differen-
tiation from toxic-metabolic encephalopathy in systemi-

cally unwell patients proved challenging, but we erred on
the side of specificity in that regard, utilizing established di-
agnostic criteria with graded levels of diagnostic certainty.5 All
5 patients reported herein had subacute onset encephalopa-
thy, and 4 had no confounding reasons for encephalopathy
such as COVID-19 pneumonia. The one patient with pneu-
monia was initially considered to have a toxic-metabolic cause,
but her evolved clinical course, MRI, and CSF findings proved
consistent with a diagnosis of probable AE.

**Encephalopathy Cohort**

Of 31 encephalopathy cases encountered, 5 met criteria for
AE (16%), and the remainder were diagnosed with toxic-
metabolic encephalopathy. Clinical features and paraclinical
test results of the 5 patients with AE (define, n = 1; probable,
n = 1; and possible, n = 3) were diverse; all were neural
immunoglobulin G (IgG) negative in serum and CSF. None
had acute disseminated encephalomyelitis (ADEM). All were
hospitalized. Median symptom onset age of the 5 AE cases
was 61 years (range, 46–63); 3 were women. All were resident
within the regional referral area of Mayo Clinic (Minnesota,
n = 3; Iowa, n = 2), but none resided in the immediate vicinity
(Olmsted County). At the time of neurologic presentation, 4
of 5 were SARS-CoV-2 PCR positive by nasal swab, and 1 was
recorded as SARS-CoV-2 IgG seropositive at presentation, 8
weeks into her clinical course. All patients were encephalitis-
pertinent neuronal and glial IgG negative (serum, 4; CSF, 5).
In CSF, SARS-CoV-2 PCR and IgG index (relative to serum)
were negative in 4 patients tested.

Two patients presented with respiratory symptoms, and 3
presented acutely with fever and subacute encephalopathy.
Patient 1 had encephalopathy, seizures, and mood distur-
bance. She had mesial temporal T2 signal change without T1
postgadolinium enhancement (Figure 3), CSF lymphocytic
pleocytosis, and electroencephalographic seizures. Patient 2
presented with delirium, and was initially considered to have a
toxic-metabolic disorder in the setting of COVID-19 pneu-
monia, but developed a rhombencephalitis characterized by
worsening encephalopathy, quadriaparesis, upper motor neu-
ron signs on examination, and brain MRI demonstrating
diffuse T2 hyperintensities of the medulla, bilateral dentate,
periventricular white matter, posterior internal capsule, and
subcortical white matter regions, without gadolinium en-
hancement (Figure 3). Myelin oligodendrocyte glycoprotein–
IgG serum testing was negative, but CSF-restricted oligoclonal
bands were detected. Patient 3 presented with subacute onset
encephalopathy and seizures 3 weeks after hospitalization
with COVID-19 pneumonia. He had epileptiform discharges
on EEG, but normal brain MRI and CSF. Patient 4 had
delirium and mild gait ataxia on examination and T2 hyper-
intensities in the bilateral cerebellar peduncles extending to
the pons, without contrast enhancement (Figure 3), and
diffuse slowing on EEG. Patient 5 had delirium, normal MRI,
and generalized slowing with intermittent rhythmic delta over
bilateral frontal head regions (FIRDA) and triphasic waves
on EEG.

All 3 patients with possible AE had spontaneous resolution of
symptoms and signs. Of 2 treated with immune therapy, 1 im-
proved (definite limbic encephalitis) and 1 died (probable AE).
<table>
<thead>
<tr>
<th>Patient/age, y/sex</th>
<th>COVID-19 respiratory (other) symptoms, testing data at evaluation</th>
<th>Days from respiratory symptoms to neurologic symptoms</th>
<th>Neurologic presentation</th>
<th>MRI</th>
<th>CSF</th>
<th>EEG</th>
<th>Immune therapy</th>
<th>Outcome</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/61/F</td>
<td>Yes, PCR--; COVID-19 IgG Ab+</td>
<td>13</td>
<td>Delirium and seizures</td>
<td>T2 hyperintensities, mesial temporal lobes</td>
<td>WBCs 30 (92% lymphocytes)</td>
<td>Bitemporal seizures</td>
<td>Corticosteroids, plasma exchange</td>
<td>Improved; seizure-free; residual mild amnestic cognitive impairment and mood disturbance</td>
<td>Definite limbic encephalitis*</td>
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<tr>
<td>2/53/F</td>
<td>No (had fever), abnormal chest X-ray, PCR+, nucleocapsid IgG+</td>
<td>0</td>
<td>Delirium, quadriplegia</td>
<td>Diffuse T2 hyperintensities: medulla, dentate nuclei, periventricular white matter, posterior internal capsule, and subcortical white matter</td>
<td>Protein 98, OCBs 4</td>
<td>NA</td>
<td>Corticosteroids, plasma exchange</td>
<td>Died from neurologic illness</td>
<td>Probable seronegative AE*</td>
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<tr>
<td>3/62/M</td>
<td>Yes, PCR+</td>
<td>23</td>
<td>Delirium and seizures</td>
<td>Normal</td>
<td>Protein 61</td>
<td>Epileptiform discharges, midline anterior</td>
<td>None</td>
<td>Encephalopathy resolved, normal EEG</td>
<td>Possible seronegative AE*</td>
</tr>
<tr>
<td>4/63/M</td>
<td>No (had fever, myalgias), PCR+</td>
<td>0</td>
<td>Delirium, gait ataxia</td>
<td>T2 hyperintensities: bilateral cerebellar peduncles and pons</td>
<td>Protein 99</td>
<td>Diffuse slowing</td>
<td>None</td>
<td>Resolved</td>
<td>Possible seronegative AE*</td>
</tr>
<tr>
<td>5/46/F</td>
<td>No (had fever, myalgia, headache), PCR+</td>
<td>0</td>
<td>Delirium, aphasia</td>
<td>Normal</td>
<td>Protein 78</td>
<td>Diffuse slowing, triphasic waves, and intermittent rhythmic delta activity, bilateral frontal head region (FIRDA)</td>
<td>None</td>
<td>Resolved</td>
<td>Possible seronegative AE*</td>
</tr>
</tbody>
</table>

Abbreviations: − = negative; + = positive; Abs = antibodies; COVID-19 = coronavirus disease 2019; IgG = immunoglobulin G; NA = not available; OCBs = oligoclonal bands (CSF-restricted); WBCs = white blood cells in CSF.

*AE classification according to Graus et al. criteria. CSF normal values: protein, ≤35 mg/dL; OCBs, ≤2; WBCs, ≤5/μL.
Also common is PASC, also known as long COVID. This represents a constellation of symptoms, fatigue being most common, that persists after acute infection in the absence of objective neurologic examination or test findings. Neurologic symptoms include headache, cognitive symptoms (“brain fog”), and dizziness (orthostatic or loss of equilibrium).22-26 In contrast to the 0.05% AE frequency in our study, neurologic PASC symptoms are reported in at least 10% of patients after COVID-19.24

Our study has several limitations. Most people develop detectable SARS-CoV-2 antibodies 7–14 days following infection, so patients who developed neurologic symptoms early in the infection course might have eluded our surveillance. In
addition, we only systemically evaluated sera collected for AE evaluation only, and not sera referred for other indications. Clinically, we only evaluated those patients neurologically referred, and thus it is possible that our study did not account for patients with mild self-resolving AE who went unreferred. Given the ubiquity of the virus, relative infrequent cases of AE encountered in our cohorts, and the heterogeneity of clinical presentations therein, we are not able to exclude the possibility that AE occurred as coincident disease rather than as a direct consequence of the virus. Despite these caveats, the COVID-19 pandemic has provided an opportunity to mechanistically study postinfectious encephalitis. Consistent with our findings, typically neither IgG biomarkers nor virus particles are detected in CSF.\(^1,2^7-29\) A CXCL8 predominant cytokine release syndrome has been described, supportive of periphery-originating, SARS-CoV-2 reactive, macrophage- and neutrophil-initiated inflammation.\(^1,2^9\) Given the usual absence of disease-specific IgG markers in postinfectious AE, future studies should focus on systematic collection of serum, peripheral blood mononuclear cells, and CSF to investigate for diagnostically and pathophysiologically informative cellular and cytokine signatures.

### Study Funding
The authors report no targeted funding.

### Disclosure
C. Valencia Sanchez, E. Theel, M. Binnicker, and M. Toledano report no disclosures relevant to the manuscript. A. McKeon reports patents pending for IgGs (PDE10A, Septins-5 and -7, MAP1B, GFAP, KLCHL11) pertinent to the diagnosis of autoimmune neurologic disorders. Go to Neurology.org/N for full disclosures.

### Publication History
Received by Neurology June 24, 2021. Accepted in final form September 30, 2021.

### Appendix Authors

<table>
<thead>
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### References
Autoimmune Encephalitis After SARS-CoV-2 Infection: Case Frequency, Findings, and Outcomes
Cristina Valencia Sanchez, Elitza Theel, Matthew Binnicker, et al.
Neurology 2021;97:e2262-e2268 Published Online before print October 11, 2021
DOI 10.1212/WNL.0000000000012931

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