

Autoimmune Encephalitis After SARS-CoV-2 Infection

Case Frequency, Findings, and Outcomes

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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

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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.

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.^{1,2} 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.³

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).⁴ 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.⁵ 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).³

Data Availability

Anonymized data used for this study are available upon request.

Results

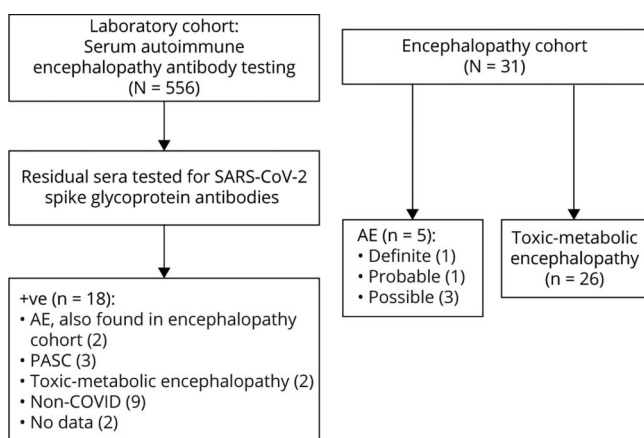
A total of 5 patients met diagnostic criteria for AE (Figure 1 and Table), representing 0.05% of all patients with COVID-19 illnesses evaluated at our institution. All 5 were identified in the encephalopathy cohort, 2 of whom (and no others) were also identified in the laboratory cohort. The 3 AE cases 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.

Figure 1 Laboratory and Encephalopathy Cohorts and Numbers of Autoimmune Encephalitis (AE) Cases



+ve = SARS-CoV-2 antibody positive; Ab = antibody; COVID-19 = coronavirus disease 2019; PASC = postacute sequelae of SARS-CoV-2 infection; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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 (definite, $n = 1$; 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 disturbance. 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 pneumonia, but developed a rhombencephalitis characterized by worsening encephalopathy, quadriparesis, upper motor neuron 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 enhancement (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 hyperintensities 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 improved (definite limbic encephalitis) and 1 died (probable AE).

Discussion

Overall, the number of post–COVID-19 AE cases encountered 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 encephalitis.^{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 encephalitis we encountered is consistent with similarly low numbers reported for Guillain-Barré syndrome in 2020.²¹

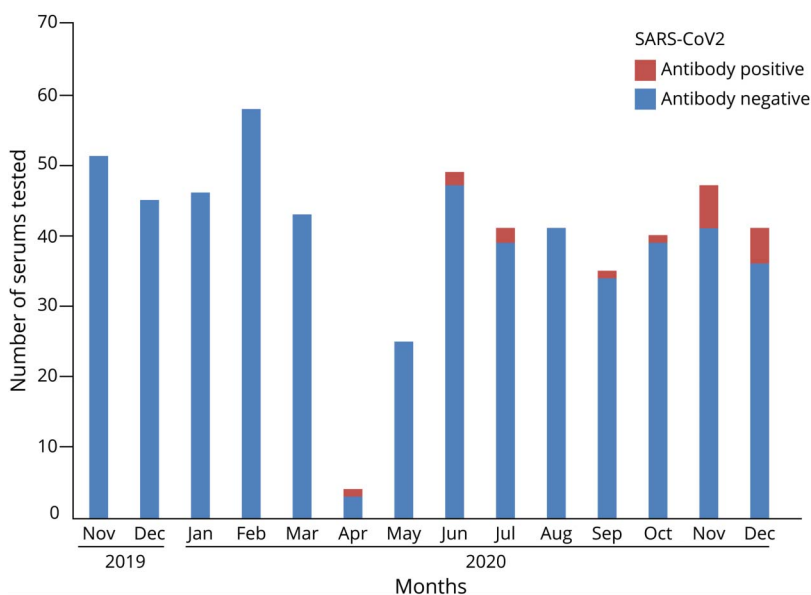
Clinical presentations and test findings in our patients with AE were diverse, and neural IgG testing was universally negative. Three of our 5 cases had a “possible” AE diagnosis only and had spontaneous resolution of symptoms. Differentiation from toxic-metabolic encephalopathy in systemically unwell patients proved challenging, but we erred on the side of specificity in that regard, utilizing established diagnostic criteria with graded levels of diagnostic certainty.³ All 5 patients reported herein had subacute onset encephalopathy, and 4 had no confounding reasons for encephalopathy such as COVID-19 pneumonia. The one patient with pneumonia 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.

Table Characteristics of 5 Patients With Autoimmune Encephalitis (AE) After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

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

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.
^a AE classification according to Graus et al.³ criteria. CSF normal values: protein, ≤ 35 mg/dL; OCBs, ≤ 2 ; WBCs, $\leq 5/\mu\text{L}$.

Figure 2 Distribution of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Serum Antibody Results Between November 2019 and December 2020

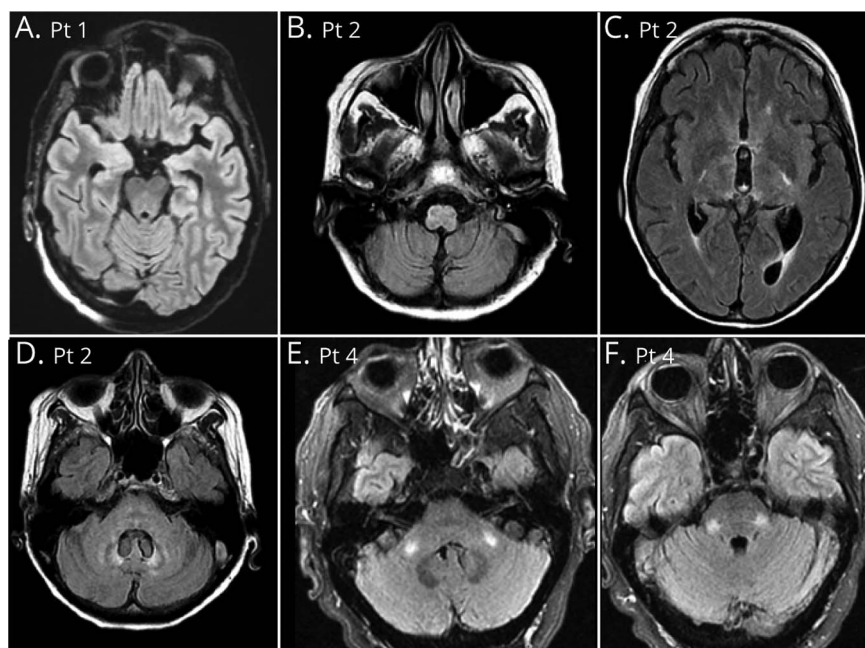


Also common is PASC, also known as long COVID. This represents a constellation of symptoms, fatigue being most common, that persists after acute infection in the absence of objective neurologic examination or test findings. Neurologic symptoms include headache, cognitive symptoms (“brain fog”), and dizziness (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

Figure 3 Three Patients With Autoimmune Encephalitis (AE) After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection With Abnormal Brain MRI



All axial T2 fluid-attenuated inversion recovery brain images (none had enhancement on T1 postgadolinium). (A) Patient 1, volume loss of both hippocampi, 6 weeks after onset of cognitive impairment and seizures. (B–D) Patient 2, hazy, diffuse T2 hyperintensity of the medulla (B), bilateral dentate (C), periventricular white matter, and posterior internal capsule (D). (E, F) Patient 4, T2 hyperintensities in the bilateral middle cerebellar peduncles (E) extending to the pons (F).

addition, we only systematically 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.^{1,27-29} A CXCL8 predominant cytokine release syndrome has been described, supportive of periphery-originating, SARS-CoV-2 reactive, macrophage- and neutrophil-initiated inflammation.^{1,29} 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.

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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](https://www.neurology.org/N) for full disclosures.

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Eitza Theel, PhD	Division of Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Matthew Binnicker, PhD	Division of Microbiology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Michel Toledano, MD	Department of Neurology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Andrew McKeon, MD	Department of Neurology, Neuroimmunology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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