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

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Abstract

Background and objectives: Autoimmune encephalitis (AE) cases post-SARS-CoV-2 infection have been reported, but the frequency is unknown. We aimed to determine the frequency and diagnostic features of COVID-19 related AE.

Methods: Residual sera from 556 consecutive Mayo Clinic Rochester patients (laboratory cohort) who underwent autoimmune encephalopathy neural IgG evaluation were tested for total antibodies against the SARS-CoV-2 spike glycoprotein using an FDA-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-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: AE, 2; post-acute sequelae of SARS CoV-2 infection [PASC], 3; toxic-metabolic encephalopathy during COVID-19 pneumonia, 2; diverse non-COVID-19 relatable neurological diagnoses, 9; unavailable, 2. Five of the encephalopathy cohort had AE (16%, including the 2 laboratory cohort cases which 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 ADEM 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.
Introduction

Various neurological disorders associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported during the COVID-19 pandemic.\textsuperscript{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 post-COVID-19. In addition, we cross-referenced our institution’s COVID-19 encephalopathy cohort for cases meeting AE diagnostic criteria.\textsuperscript{3}

Methods

\textit{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.

\textit{Laboratory cohort}

This consisted of 556 patients with available residual serum samples (from 642 submitted during the epoch November 1\textsuperscript{st} 2019 to December 31\textsuperscript{st} 2020) that had been tested for AE-pertinent neural autoantibodies (e.g. NMDA receptor antibody), e\textbf{Appendix 1}.\textsuperscript{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 (ECLIA; Indianapolis, IN), which has received emergency use authorization from the US Food and Drug Administration, and was clinically validated prior to implementation.\textsuperscript{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 neurological evaluation in the inpatient or outpatient setting in the context of contemporary or prior SARS-CoV2 infection (January 1st-December 31st 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.

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 neurological 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-CoV2 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 4/27/2020 and 12/30/2020 (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 Table), the remaining 14 patients had post-acute sequelae of SARS CoV2 infection (PASC), 3; toxic-metabolic encephalopathy in the setting of severe COVID-19 pneumonia, 2; and diverse non-COVID-19 relatable neurological diagnoses, 9. These 9 patients had neurological symptoms prior to the COVID-19 pandemic (n=6) or neurological 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 neurological examinations, neuroimaging, EEG and CSF analyses.

**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 AE patients (definite, n=1; probable, n=1; and possible, n=3) were diverse; all were neural 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 year (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 neurological 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 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 post-gadolinium 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 exam, 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 three weeks after hospitalization with COVID-19 pneumonia. He had epileptiform discharges on EEG, but normal brain magnetic resonance imaging (MRI) and CSF. Patient 4 had delirium and mild gait ataxia on exam, 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 were resident in the immediate vicinity of Mayo Clinic (Olmsted County, which had an overall AE incidence rate of 0.8/100,000 person-years 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-NMDA-R and MOG antibody-associated encephalitides. We did not encounter cases of ADEM, though cases have been reported in the literature. One other patient previously reported from our institution, who died from systemic complications of SARS-CoV-2, had ‘ADEM-like’ neuropathological features, but also diffuse microscopic infarcts. The low frequency of possible post-COVID19 immune-mediated encephalitides we encountered is consistent with similarly low numbers reported for Guillain-Barre syndrome in 2020.

Clinical presentations and test findings in our AE patients 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. 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 autoimmune encephalitis.

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 neurological examination or test findings. Neurological symptoms include headache, cognitive symptoms (‘brain fog’), and dizziness (orthostatic or loss of equilibrium). In contrast to the 0.05% AE frequency in our study, neurological PASC symptoms are reported in at least 10% of patients post-COVID19.

Our study has several limitations. Most people develop detectable SARS-CoV-2 antibodies 7-14 days following infection, so patients who developed neurological symptoms early in the
infection course might have eluded our surveillance. In addition, we only systematically evaluated sera collected for autoimmune encephalopathy 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 unrefereed. 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 completely 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 post-infectious encephalitis. Consistent with our findings, typically neither IgG biomarkers nor virus particles are detected in CSF.\textsuperscript{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.\textsuperscript{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.
Table. Characteristics of 5 patients with AE post-SARS-CoV2 infection.

<table>
<thead>
<tr>
<th>Pt/Age/Sex</th>
<th>COVID-19 (other) symptoms, testing data at evaluation</th>
<th>Days RS to NS</th>
<th>Neurological 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 &amp; seizures</td>
<td>T2 hyperintensities mesial temporal lobes</td>
<td>WBCs 30 (92% lymphs)</td>
<td>Bitemporal seizures</td>
<td>Corticosteroids, plasma exchange</td>
<td>Improved. Seizure free. Residual mild anamnestic cognitive impairment &amp; mood disturbance</td>
<td>Definite limbic encephalitis*</td>
</tr>
<tr>
<td>2/53/F</td>
<td>No (had fever), abnormal chest Xray, PCR+, nucleocapsid IgG +</td>
<td>0</td>
<td>Delirium, quadripareisness</td>
<td>Diffuse T2 hyperintensities: medulla, dentate nuclei, periventricular white matter, posterior internal capsule, &amp; subcortical white matter</td>
<td>Pro 98, OCBs 4</td>
<td>NA</td>
<td>Corticosteroids, plasma exchange</td>
<td>Died from neurological illness</td>
<td>Probable seronegative AE*</td>
</tr>
<tr>
<td>3/62/M</td>
<td>Yes, PCR+</td>
<td>23</td>
<td>Delirium &amp; seizures</td>
<td>Normal</td>
<td>Pro 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 &amp; pons</td>
<td>Pro 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>Pro 78</td>
<td>Diffuse slowing, triphasic waves &amp; intermittent rhythmic delta activity bilateral frontal head region (FIRDA)</td>
<td>None</td>
<td>Resolved</td>
<td>Possible seronegative AE*</td>
</tr>
</tbody>
</table>

- = negative; + = positive; AE = autoimmune encephalitis, COVID19 = coronavirus disease 2019, CSF = cerebrospinal fluid, EEG = electroencephalogram, F= female, LE = limbic encephalitis, lymphs = lymphocytes; M= male, MRI= brain magnetic resonance imaging, NS = neurological symptoms, NA = not available, OCBs = oligoclonal bands (CSF-restricted), PASC = post-acute sequela of SARS-CoV2 infection, PCR = polymerase chain reaction, Pro = protein; RS= respiratory symptoms; WBCs = white blood cells in CSF. *AE classification according to Graus et al criteria\(^3\). CSF normal values: pro, ≤ 35 mg/dL; OCBs, ≤ 2; WBCs, ≤ 5/µL.
**Figure legends**

**Figure 1.** Laboratory and encephalopathy cohorts and N of autoimmune encephalitis (AE) cases.

Ab = antibody; PASC = post-acute sequelae of SARS-CoV-2 infection; +ve = SARS-CoV-2 Ab positive

**Figure 2.** Distribution of SARS-CoV-2 serum antibody results between November 2019 and December 2020.
**Figure 3.** Three patients with AE post-SARS-CoV-2 infection with abnormal brain MRI

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


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