Acute Hemorrhagic Encephalitis Related to COVID-19

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Abstract
Purpose of Review: The novel coronavirus, SARS-CoV-2 is the most critical public health challenge in recent history. In this report, we present a case of suspected acute hemorrhagic encephalitis with bilateral intracranial hemorrhages associated with COVID-19 infection

Recent Findings: A 48-year-old female COVID-19 positive patient developed acute changes in her neurological status. A head CT with CT angiography demonstrated extensive bilateral parietal and occipital intraparenchymal hemorrhage with intraventricular extension and acute hydrocephalus. The patient was treated with an external ventricular drain (EVD) and a CSF sample was tested for SARS-CoV-2 but was found to be negative.

Summary: The underlying mechanism for developing acute hemorrhagic encephalitis in viral illnesses may be autoimmune in nature and warrants further investigation. The initial neurologic presentation of COVID-19-related hemorrhagic encephalitis is altered level of consciousness which may prompt further neurologic examination and imaging to exclude this feature.

Take-Home Points:
- Features attributable to central nervous system involvement by COVID-19, are rare though were described in an early population-based studies.
- Acute hemorrhagic encephalitis is a rare complication of viral illness, including COVID-19.
- The underlying mechanism in acute hemorrhagic encephalitis is poorly understood, but may be related to an autoimmune process
- Intraparenchymal hemorrhage related to COVID-19 may be exacerbated by systemic anticoagulation.
- The initial neurologic presentation of COVID-19-related hemorrhagic encephalitis is altered level of consciousness which may prompt further neurologic examination and imaging to exclude this feature.
Introduction:

COVID-19 is a newly identified respiratory illness caused by a novel coronavirus, SARS-CoV-2. Since the first reported cases in December 2019, COVID-19 has grown into a global pandemic and has become one of the most critical public health challenges in modern history. Although current data suggest that as many as 93% of infected individuals may be asymptomatic, symptoms generally include fever, dry cough, sore throat, and diarrhea. Serious complications can arise from COVID-19 infection, including pneumonia, acute respiratory distress syndrome, multi-organ failure, and death.

There is relatively limited data addressing the neurological complications of COVID-19. The most robust study to date suggests that approximately 1/3 of patients can have neurologic complications that can vary from benign (headache, dizziness) to altered mental status and seizures. Additionally, there have been reports of encephalopathy in elderly patients, and one case report of hemorrhagic necrotizing encephalopathy related to COVID-19. In this current report, we present the unique case of a 48-year-old patient who developed acute hemorrhagic encephalitis with bilateral intracranial hemorrhage associated with COVID-19 infection.

Case Presentation:

A 48-year-old previously healthy female who was admitted to our institution after experiencing two weeks of myalgia, dry cough, shortness of breath and fever. Upon presentation, the patient was hypoxic, prompting intubation and admission to the intensive care unit (ICU) where COVID-19 status was confirmed to be positive by SARS-CoV-2 polymerase chain reaction (PCR) testing. Pulmonary computed tomography (CT) demonstrated characteristic features including extensive bilateral ground glass opacity with areas of consolidation and interlobular septal thickening. The patient received hydroxychloroquine (oral, two doses of 400 mg and 5 doses of 200 mg) and two doses of tocilizumab. The hydroxychloroquine was stopped due to development of supraventricular tachycardia and prolonged QT. Bloodwork demonstrated markedly elevated d-dimers with severe hypoxemia and she was started on intravenous heparin infusion on post admission day 10, with only a single pTT outside of therapeutic range, which was promptly corrected. Bloodwork also demonstrated elevated Ferritin at 920 µg/L, and a mildly elevated CRP of 11.7 mg/L. On post admission day 15 she was found to have equal and non-reactive pupils bilaterally with absent cough, gag, and corneal reflexes. A head CT with CT angiography demonstrated extensive bilateral parietal and occipital intraparenchymal hemorrhage with intraventricular extension and acute hydrocephalus. There was no evidence of an underlying vascular lesion including venous thrombus or aneurysm. Heparin infusion was stopped immediately and reversed with protamine sulfate. Hyperosmolar therapy was initiated and an external ventricular drain (EVD) was inserted for intracranial pressure management. Post EVD insertion, the patient’s brainstem reflexes returned, and she was demonstrating extensor posturing to central pain. A repeat CT scan 48 hours later demonstrated stability of the hemorrhages. Magnetic resonance imaging (MRI) failed to demonstrate any underlying ischemia but showed cortical gadolinium enhancement with hyper-intense T2 and FLAIR signal surrounding the hemorrhages, in keeping with vasogenic edema previously seen on CT (Fig 3). PCR testing on cerebrospinal fluid (CSF) taken from the EVD within 24h of...
insertion was negative for SARS-CoV-2. (Table 1). The CSF had 76 x 10^6/L nucleated cells (65% neutrophils) in the presence of 33,000 x 10^6/L erythrocytes. Of note, the CSF IgG ratio was 0.35 with an IgG index of 1.05. A digital subtraction angiogram was not performed due to the patient’s COVID-19 status and unstable condition. The patient was eventually extubated, and is currently recovering with severe neurologic deficits. She is currently undergoing rehabilitation.

Discussion:

One of the biggest challenges facing physicians and healthcare workers addressing the COVID-19 pandemic is the wide variability in presenting features, which range from completely asymptomatic individuals to severe acute respiratory distress requiring mechanical ventilation, unconventional treatments, and extensive life saving measures. Features attributable to central nervous system involvement by COVID-19, are rare though were described in an early population-based study from Wuhan.

We present a suspected case of acute hemorrhagic encephalitis in a previously healthy 48-year-old COVID-19 positive patient. This is only the second reported case of this feature, and the first with a parieto-occipital distribution which may help other clinicians identify and manage neurologic outcomes when treating patients with COVID-19. Acute hemorrhagic encephalitis is believed to be a post-infectious process that is a severe variant of acute disseminated encephalomyelitis and has been described in other viral respiratory infections such as H1N1 Influenza. Another similar entity is acute necrotizing hemorrhagic encephalopathy, although lack of thalamic involvement in our case makes this less likely.

The first case of acute hemorrhagic encephalitis associated with COVID-19 was reported in Detroit, Michigan in March 2020. In that case, thalamic involvement suggested the underlying diagnosis was acute hemorrhagic necrotizing encephalopathy. The patients are demographically similar; however, the cases differ in location and extent of intracranial features (Table 1). It is suspected that the large bilateral intraparenchymal hemorrhage with intraventricular extension was related to the presence of full anticoagulation. This was initiated because the patient’s elevated D-dimer; at that time, anticoagulation was deemed the appropriate treatment.

Imaging was completed to determine the underlying etiology of the bilateral parietal-occipital intraparenchymal hemorrhage. An MRI and a CT-angiogram (timed to optimize assessment of arterial and venous phases) demonstrated patency of arterial and venous structures. There was no evidence of vasculopathy, aneurysm (including peripheral mycotic lesions) or vascular malformation. The pattern of edema and hemorrhage were inconsistent with watershed infarct. Posterior reversible encephalopathy syndrome (PRES) was considered unlikely due to the extensive hemorrhage and progressive nature of the findings despite supportive care. It is noted that the patient was briefly treated with tocilizumab, for which there is one case report of associated PRES. No other precipitating factors for PRES were identified. Small vessel vasculitis was not suspected based on the available imaging. A digital subtraction angiogram would have definitively ruled out small vessel vasculitis; however, given the patient’s diagnosis and unstable condition, this procedure could not be performed.
Having ruled out other differential diagnoses and with the absence of virus in the CSF, the presumed diagnosis of exclusion was one of acute hemorrhagic encephalitis. There are many proposed mechanisms by which SARS-CoV-2 virus can cause nervous system injury, including neural expression of angiotensin-converting enzyme 2 (ACE2) receptors, retrograde neuronal transport, vascular dissemination, systemic or focal hypoxic injury, or as a consequence of cytokine storm\textsuperscript{11 5 12}. Acute hemorrhagic encephalitis may be related to an autoimmune process with an inflammatory response leading to perivascular demyelination and associated edema, hemorrhage and necrosis\textsuperscript{13}. Support for this comes from the finding that CSF for viral PCR is often negative, as it was for this patient, which suggests that the process is not due to direct viral infiltration of brain parenchyma\textsuperscript{14 15}. Similarly, the presence of an elevated IgG index with elevated CSF IgG ratio\textsuperscript{8}, and a neutrophil predominant CSF leukocyte count\textsuperscript{7} is in keeping with an inflammatory process rather than a direct viral effect. However, an inflammatory process could only be confirmed with biopsy, which the patient did not undergo. Furthermore, it is also possible that the CSF neutrophilia was influenced by the presence of intraventricular hemorrhage. Although treatment strategies directed towards mitigating the inflammatory response have been used in acute hemorrhagic encephalitis, such as intravenous immunoglobulin, plasma exchange or corticosteroids, the outcomes in the few reported adult cases suggests that prognosis is poor\textsuperscript{14}.

The extensive hemorrhage was most likely related to the use of systemic anticoagulation. There is ongoing debate regarding the appropriate management of patients with COVID-19 who display features consistent with a pro-thrombotic state, with or without evidence of tissue thrombosis. The present case highlights the need for ongoing neurologic surveillance and the clear risk of neurologic complications in patients with COVID-19. This is particularly true when anticoagulation is deemed the appropriate treatment strategy, and even more so when clinical assessments are limited because of the use of sedation and paralytics to assist in ventilation.

**Conclusion:**

We present a case of a previously healthy 48-year-old female with COVID-19 who developed acute hemorrhagic encephalitis, a complication which has been rarely-described to this point. The underlying mechanism for developing such complication is believed to be autoimmune or para-viral in nature and warrants further investigation. At present, it appears the initial neurologic presentation of COVID-19-related hemorrhagic encephalitis is altered level of consciousness which may prompt further neurologic examination and imaging to exclude this feature. The observed intraparenchymal hemorrhage was most likely exacerbated by systemic anticoagulation and highlights the potential for neurologic complications in these severely ill patients with COVID-19. These findings may inform risk assessment and medical management in these patients, particularly as it pertains to the use of systemic anticoagulation and to the importance of ongoing neurologic assessment.
References:
**Table 1: Comparison of case-study patient demographics presented here, and in literature**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Current Study</th>
<th>Poyiadji et al.</th>
<th>Filatov et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Late 40s</td>
<td>50s</td>
<td>72</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td>None</td>
<td>Unknown</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardioembolic Stroke</td>
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<td></td>
<td></td>
<td></td>
<td>Parkinson's Disease</td>
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<td></td>
<td></td>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recent Cellulitis</td>
</tr>
<tr>
<td><strong>Presenting Symptoms</strong></td>
<td>Shortness of breath</td>
<td>Fever, cough, altered</td>
<td>Fever, cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mental status</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic Symptoms</strong></td>
<td>Altered mental status</td>
<td>Altered mental status</td>
<td>Decreased level of consciousness</td>
</tr>
<tr>
<td></td>
<td>(intubated) then weak</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cough, poor corneals</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Timeline</strong></td>
<td>2 weeks after initial</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>presentation; 5 days after</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>therapeutic heparin infusion initiated</td>
<td></td>
<td></td>
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<tr>
<td><strong>Initial CT</strong></td>
<td>Bilateral parietooccipital hematoma &amp; extensive edema causing hydrocephalus</td>
<td>Hypoattenuation within bilateral medial thalami</td>
<td>Nil acute Encephalomalacia (prior stroke)</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>No watershed infarct</td>
<td>Extensive enhancement</td>
<td>Hemorrhagic rim enhancing lesions within bilateral thalami, medial temporal lobes and subinsular regions.</td>
</tr>
<tr>
<td></td>
<td>and cortical involvement in hemorrhage area.</td>
<td>and cortical involvement in hemorrhage area.</td>
<td></td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>Mild diffuse slowing</td>
<td>Unknown</td>
<td>Diffuse slowing &amp; sharply contoured waves, characteristic of encephalopathy</td>
</tr>
<tr>
<td></td>
<td>characteristic of</td>
<td></td>
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<tr>
<td></td>
<td>encephalopathy, rare left temporal epileptiform discharges</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CSF Analysis</strong></td>
<td>Negative for COVID19</td>
<td>Traumatic – negative</td>
<td>Negative for infection</td>
</tr>
<tr>
<td></td>
<td>Erythrocytes 33,000 x 10^6/L</td>
<td>for infection</td>
<td>(WBC 4, protein 68, glucose 75)</td>
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<tr>
<td></td>
<td>IgG ratio 0.35 (0-0.23)</td>
<td></td>
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<tr>
<td></td>
<td>IgG index 1.05 (0.25-0.85)</td>
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<tr>
<td></td>
<td>Negative for VZV, HSV, and ENV</td>
<td></td>
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<tr>
<td><strong>Outcome</strong></td>
<td>Extubated with significant neurological deficits. Currently receiving rehabilitation.</td>
<td>Unknown</td>
<td>In critical condition in the intensive care unit.</td>
</tr>
</tbody>
</table>

**Note:** Table 1 compares the demographics of the case-study patient presented here with those from previous studies. The current study is a case report of a patient with acute hemorrhagic leukoencephalitis, presenting with symptoms of shortness of breath, fever, cough, and altered mental status. The patient was treated with therapeutic heparin infusion and had a favorable outcome with extubation and rehabilitation. Further investigation into the presumed source of the infection and the role of comorbidities such as atrial fibrillation, COPD, and stroke is warranted.
Fig 1: Unenhanced Axial CT of the Thorax.

An axial image through the level of the carina demonstrating bilaterally extensive ground glass opacity with early consolidation and interlobular septal thickening.

Fig 2: Unenhanced CT of the Head.

Axial and coronal reformatted unenhanced CT images demonstrating extensive intraparenchymal hemorrhage in bilateral parietal and occipital lobes with intraventricular extension and acute hydrocephalus.
Figure 3: Axial MRI of the Head.

DWI-ADC images (A-B) demonstrating diffusion restriction limited to areas of hemorrhage demonstrated on MPGR images (C). T2 images (D) demonstrate extensive associated edema. Post-contrast T1 images (F) demonstrate extensive enhancement in addition to intrinsic T1 related to blood products on pre-contrast images (E), including involvement of cortex.