Corpus Callosum Lesion Associated With COVID-19–Psychosis

Laura Rosas, MD[1] ▪ Shivani Kumar, MD[1] ▪ Lala Park, MD[1] ▪ Stephanie Eng, MD[1] ▪ Royce Lee, MD[2]

Abstract

This case report presents a patient with acute onset psychosis in the setting of a COVID-19 infection. Magnetic resonance imaging of the brain was ordered to evaluate for organic etiologies which revealed cytotoxic lesions of the corpus callosum. These lesions can be associated with infectious diseases which cause inflammation. She was treated with an antipsychotic and later also with an antiepileptic. This case demonstrates that COVID-19 can affect multiple systems. Neuropsychiatric symptoms are possible and neuroimaging may be helpful, especially if symptoms are acute in onset.

Key words: psychosis, COVID-19 complication, cytotoxic lesions

A woman in her 20s was brought to the emergency department (ED) by her parents with acute-onset psychosis. She reported auditory and visual hallucinations, paranoia, and false beliefs of being a twin and pregnant.

History

At baseline, the patient was a high-functioning college student who had transferred closer to home at the beginning of the COVID-19 pandemic. Over the past year, her parents noticed a decline in motivation and grades. Three days prior to her presentation, she attended a social event.

On the day before her presentation, she smoked marijuana, which she believed was laced with another drug after she developed abdominal pain. She also had a remote history of untreated depression.

Mental examination

On mental status examination, she was observed to be responding to internal stimuli. Her thought process was tangential and disorganized. Her affect was euphoric and labile. Routine urine toxicology was positive for cannabinoids only.

Treatment and management

Given the patient's acute behavioral changes, admission to the psychiatric unit was planned. The patient underwent a required COVID-19 polymerase chain reaction (PCR) test before admission to the psychiatric unit, the results of which were positive. Therefore, she was instead admitted to the medicine service with psychiatry and neurology on consult. Given our patient showed only neuropsychiatric symptoms without respiratory symptoms in the setting of positive infection, directed treatment for COVID-19 was not initiated. Treatment for COVID-19 at this time during the pandemic was commonly used only for patients with respiratory symptoms. She improved before additional intervention was needed.

AFFILIATIONS:
[1]Resident Physician, Department of Psychiatry & Behavioral Neuroscience, University of Chicago, Chicago, IL
[2]Associate Professor of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL

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CORRESPONDENCE:
Laura Rosas, MD, University of Chicago, Billings Hospital, 5841 South Maryland Avenue, Chicago, IL 60637 (Laura.rosas@uchospitals.edu)

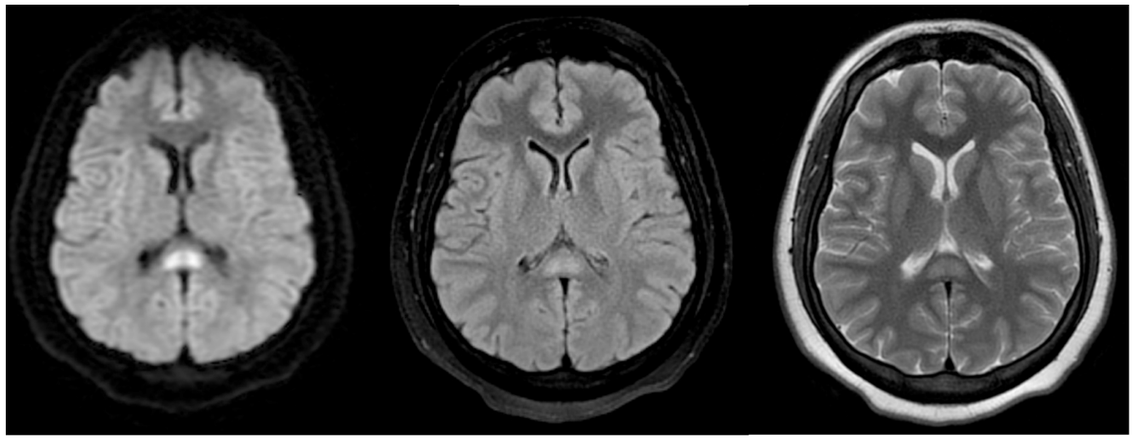

Figure 1. Patient's initial axial MRI brain images (sequences from left to right are DWI, FLAIR, T2). CLOCCs can be visualized posterior midline.

Laboratory testing revealed elevations in erythrocyte sedimentation rate (ESR), C-reactive protein, lactate dehydrogenase, creatine kinase, and hemoglobin A_{1C} levels.

An extended electroencephalogram was normal. On hospital day 3, magnetic resonance imaging (MRI) of the brain with contrast showed a cytotoxic lesion in the splenium of her corpus callosum, seen on diffusion weighted imaging (DWI), T2-weighted imaging (T2WI), and T2-FLAIR sequences in the top row of **Figure 1**. A computed tomography scan of the chest, abdomen, and pelvis showed nonspecific prominent retroperitoneal and right-lower quadrant lymph nodes. A pelvic ultrasound was normal. Cell count, glucose, and protein levels in the patient's cerebrospinal fluid (CSF) were within normal limits; CSF studies for routine infectious, autoimmune, and paraneoplastic etiologies were negative, however, a COVID-19 PCR test was not done.

Before transfer to the psychiatric unit, hospital policy required patients to have two consecutive negative COVID-19 PCR tests in a 48-hour period. Over the course of a 23-day admission, the patient received six COVID-19 PCR tests, with fluctuating positive and negative results. There were no consecutive negative tests (+, -, +, -, +, +, -). By hospital day 23, her psychosis had mitigated to the degree that she no longer met criteria for psychiatric admission. She was discharged home with a referral to a virtual intensive outpatient program.

Thirty days after initial diagnosis of COVID-19, the patient underwent a repeat outpatient brain MRI, which showed complete resolution of the cytotoxic lesion in the bottom row of DWI, T2WI, and T2-FLAIR sequences of **Figure 2**. Thirty-seven days after initial diagnosis, she returned to the ED due to a several-hour period of staring and hesitant movement, interspersed by periods of psychomotor and verbal agitation. Because she was agitated and attempted to escape the ED, haloperidol 5 mg and lorazepam 2 mg were administered for safety. Several hours later, her Bush-Francis Catatonia Rating Scale score of 10 was concerning for catatonia. Laboratory testing revealed elevations in IL-6 and white blood cell count and a persistently elevated ESR. After receiving a negative COVID-19 PCR test result, she was transferred to the inpatient psychiatry unit.

At the time of discharge, the patient was taking risperidone 3 mg twice daily and oxcarbazepine 300 mg every 12 hours. Seven days after discharge, and 3 months after her first presentation, her psychotic and catatonic symptoms resolved completely. Her only remaining concerns were fatigue and new-onset sleep paralysis. Risperidone was decreased to 3 mg every night at bedtime and oxcarbazepine was discontinued.

Discussion

Previous viral pandemics have been followed by the recognition of secondary neuropsychiatric syndromes, such as encephalitis lethargica after the Spanish Flu.[1] Similarly, there is a growing recognition of the relationship between infection with the SARS-CoV-19 virus and neuropsychiatric disorders.[2] COVID-19–psychosis—the appearance of psychotic symptoms in the setting of correlated infection—is believed to be related to the presence of the virus in the brain or the immunologic sequelae of infection.[3,4] Interestingly, not all cases of COVID-19–psychosis occur in the context of viral encephalopathy. In those cases, the psychotic symptoms may be best understood as global dysfunction in cerebral and subcortical brain networks involved

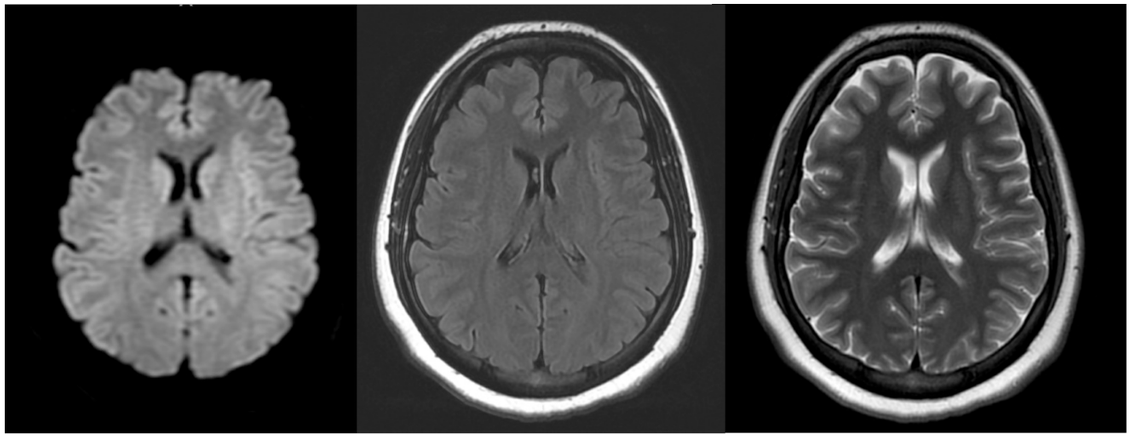

Figure 2. Patient's repeat axial MRI brain images one month later (sequences from left to right are DWI, T2WI, T2-FLAIR) demonstrating resolution of cytotoxic lesions of the corpus callosum.

in predictive encoding.[5] These cases raise the possibility that infection with the virus or sequelae of infection may more directly affect brain functions that underlie psychotic disorders. We present a case that highlights some of these issues. Our patient had no diagnosed psychiatric history but presented with the abrupt onset of psychosis, rapid resolution of symptoms with recovery from infection, specific brain MRI findings that resolved, and elevated markers of immune activation.

Because of the patient's history with marijuana prior to her presentation, a substance-induced psychotic disorder was considered, as cannabis alters the microstructural integrity of the corpus callosum, particularly the splenium, which was the site of our patient's brain lesion.[6] However, given cannabis has anti-inflammatory effects and has even been proposed as a treatment option for COVID-19 to dampen immunologic response, this diagnosis was less likely.[7]

Because of the acute onset of psychotic symptoms in the setting of COVID-19 infection, a psychotic disorder due to a medical condition seemed most likely. Supporting this diagnosis was the initial MRI brain findings that resolved on follow-up imaging and inconsistently positive nasal swabs suggestive of greater central than peripheral infection.[8] A recent retrospective cohort study of over 200,000 COVID-19 survivors reported one-third of patients had neuropsychiatric diagnoses in the 6 months following infection; 2.77% of patients had a diagnosis of a psychotic disorder.[2] This percentage is consistent with an earlier study that noted 10 of 153 patients (6.5%) with COVID-19 infection developed new-onset psychosis.[9]

Since the onset of the pandemic, several case reports have linked COVID-19 to psychotic symptoms.[10,11] One case described a 53-year-old man with no psychiatric history who attempted suicide by drinking bleach, reported command auditory hallucinations, and was found to have COVID-19 pneumonia. He was treated with ceftriaxone, azithromycin, and hydroxychloroquine with as needed olanzapine.[10] Another case reported a middle-aged man with no previous psychiatric history who presented with acute onset of paranoid and persecutory delusions, disorganized thought process, and auditory and visual hallucinations without evidence of cognitive impairment. He was treated with aripiprazole, later cross-tapered to risperidone due to persistent psychosis, admitted to a psychiatry unit when medically appropriate, and then recovered within 6 weeks.[11]

Our patient's brain MRI demonstrated cytotoxic lesions of the corpus callosum (CLOCCs). There are at least two reports of COVID-psychosis with CLOCCs.[12,13] However, these patients had severe physical COVID-19–related symptoms. One patient died from multisystem organ failure before starting antipsychotics,[12] and the other recovered.[13] CLOCCs are nonspecific for various entities, including infection, drugs, malignancy, and trauma.[14] The most common neurologic presentations are confusion (50%-60%), ataxia (33%-43%), dysarthria (13%-43%), and seizure (10%-40%).[15] In our case, the psychotic symptoms occurred in the context of mild COVID-19 illness and in the absence of global encephalopathy, which may provide novel insight into the pathophysiology of psychotic illness.

Volume loss in the corpus callosum has been implicated in psychiatric diseases, such as schizophrenia and bipolar disorder.[16] One possibility is that the splenium of the corpus callosum plays a role in predictive encoding in the brain.[4] Lesions here may disrupt the integration of bottom-up sensory information and top-down predictive models of the world. As reflected in our case, CLOCCs are frequently reversible.[14] Although our patient's recovery was time-lagged after resolution of the CLOCC, it is possible that MRI cannot detect subtle, persistent changes in synaptic function.

It was unlikely that our patient had multiple false-positives given high sensitivity and specificity of testing. In a recent systematic review and meta-analysis, a COVID-19 nasopharyngeal swab nucleic acid amplification testing (NAAT) had a pooled sensitivity of 84.8% and specificity of 98.9%.[17] Of note, studies describe that, of patients with confirmed COVID-19 infection on nasopharyngeal swab and a neuropsychiatric sequelae, only a minority had viral RNA in the CSF. The largest retrospective RT-PCR screening of CSF samples in patients with confirmed COVID-19 showed that only two of 23 patients were positive for the virus, to which the authors concluded was likely due to blood contamination.[18] We were unable to obtain this testing of our patient's CSF, but currently there are no published reports on the sensitivity and specificity of COVID-19 CSF NAAT.

Neuropsychiatric symptoms generally arise between 1 and 14 days after the beginning of peripheral COVID-19 infection symptoms.[19] This timeline was consistent with our theory that our patient had been exposed to the virus at a social event shortly before hospitalization. Her fluctuating results may have indicated low viral shedding in the nasopharynx later in the course of the infection, with viral loads hedging the threshold of positivity. It is not yet understood why some patients have persistently positive COVID-19 tests. In this case, brain sequestration is a possibility, but only positive brain biopsy would provide confirmation and a negative biopsy would remain inconclusive.

Because SARS-CoV-19 is a novel virus, we do not yet know the complete pathophysiologic mechanism of its neuropsychiatric symptoms. The virus enters the central nervous system via the olfactory nerve, causing inflammation and demyelination; this is supported by 49% of patients infected with COVID-19 reporting olfactory and gustatory symptoms.[4] Alternately, the spike protein may bind to ACE-2 receptors in the capillaries, allowing the virus to cross the blood-brain barrier; once in the brain, it may bind neurons, which have a high density of ACE-2 receptors.[2] The virus may remain latent in the neurons even after the acute neuropsychiatric symptoms resolve. Subsequent demyelination and neurodegeneration may increase the long-term risk of neuropsychiatric disorders.[5]

At least three hypothesized pathophysiological mechanisms have been proposed. First, the virus may have a directly deleterious effect on neurons, perhaps mediated by ACE-2 receptors in the brain.[20,21] Second, there may be an inflammatory response to viral infection, including the release of cytokines.[22] Third, there may be alterations in the microvascular structure of the brain; this novel hypothesis emerged from the postmortem discovery of megakaryocytes stuck in small blood vessels of the brain.[23]

Risk for neuropsychiatric diagnoses is greater for patients with more severe disease.[2] However, our patient's psychosis occurred in the context of otherwise mild COVID-19 symptoms. Regardless of severity, pharmacotherapy targeting inflammation may be helpful for patients with neuropsychiatric effects. Various studies have highlighted a paradoxical anti- and pro-inflammatory action of antipsychotics, making it difficult to predict how each one may work. However, aripiprazole, ziprasidone, and risperidone decrease IL-6 cytokine levels.[24] Given persistent elevated inflammatory markers upon our patient's return to the ED, it is possible that patients with COVID-19–psychosis may benefit from adjunctive treatment with anti-inflammatory medications, such as intravenous immunoglobulin (IVIG), tetracyclines, and tocilizumab (IL-6 inhibitor).[1,25] However, there are no reports of COVID-19–psychosis treated with IVIG or tetracyclines. One case series described psychotic symptoms from COVID-19 developing in a patient who was previously treated with tocilizumab, which was not attributed to the drug itself.[26]

Conclusion

Patients with COVID-19 infection may experience neuropsychiatric illness. Brain imaging is an important component of the diagnosis. Further research is needed on the neuropsychiatric pathophysiology of CLOCCs and the treatment of patients with COVID-19 and neuropsychiatric symptoms.

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