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Possible COVID-19 Psychosis in Patient with Post-Infectious Seizure Disorder– A Case Report

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Abstract

Since the beginning of the COVID-19 pandemic, there has been various reports of unique sequelae of the disease. From the development of long-term anosmia to worsening diabetes, there is a long list of COVID-19 sequelae. More recently, neuropsychiatric diseases have also been reported post-infection. These include seizure, encephalitis, acute psychosis, hallucinations, and suicidal behavior. Here we describe a unique case of possible COVID-19 psychosis in an individual who has developed post-infectious seizure disorder. Our patient presented with new-onset psychosis and altered mental status with no respiratory symptoms just three months after COVID-19 infection. This case report adds more evidence to the direct association between psychosis and SARS CoV-2 infection and highlights the need for further laboratory research to improve the accuracy of diagnosis.

Key Words: severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), COVID-19, acute psychosis, schizophrenia, seizure disorder, neuropsychiatry.

Introduction

Since the beginning of the COVID-19 pandemic, there has been various reports of unique sequelae of the disease. From the development of long-term anosmia to worsening diabetes, there is a long list of COVID-19 sequelae [1]. The secondary effects of COVID-19 include several neurological processes such as encephalitis, stroke, seizure, transverse myelitis, Guillain-Barré syndrome (GBS), and acute disseminated encephalomyelitis (ADEM) [2-6]. These neurologic manifestations occur in more than 35% of infected patients with increased frequency in severe cases of COVID-19 [5,6]. More recently, this list of sequelae has begun to include psychiatric disorders including exacerbation of existing psychiatric conditions and new-onset psychosis [7,8]. There have been several case reports and case series describing psychosis in the setting of both severe and mild COVID-19 infection with minimal or absent viral/respiratory symptoms [4,5,8-10].

Before the COVID-19 pandemic, there was a hypothesis that inflammatory effects of viruses on the brain can cause psychotic disorders such as schizophrenia [7]. There was evidence of post-viral psychosis as early as the 17th century and then later during the Spanish influenza pandemic of 1918 [4,7,11]. Recently, many studies have established a clear association between development of psychotic disorders with recent hospitalization for treatment of severe infection. The COVID-19 respiratory viral infection has been shown to cause acute psychosis, post-infectious psychosis, and altered neurodevelopment due to maternal immune activation [7].

In 2011, a study by *Okusaga et al.* showed HKU1 and NL63 (two seasonal coronaviruses) to be associated with increased risk of developing psychosis, however there was also evidence of coronavirus seropositivity associated with a history of mood disorders [7]. Systematic reviews have shown that 0.7% of SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) patients develop acute mania and/or psychosis [7,9]. This statistic includes psychosis attributed to acute infection as well as the use of

corticosteroids as treatment. Other studies report psychotic symptoms such as hallucinations at a rate between 2-5% in the acute and post-acute infection phases. However, it is difficult to separate psychotic symptoms of general delirium from those of an acute infection phase [7].

To establish a clear role of SARS-CoV-2 in the development of neuropsychiatric disease, the social determinants of health should also be addressed. Various social and cultural factors such as heightened stress, socio-economic hardship, social isolation, or substance misuse secondary to COVID-19 infection may impact the psychopathology of the virus [7,9]. Countries around the world have displayed various prevalence of psychiatric sequelae due to differences in governments funding mental health initiatives and creating social distancing regulations [11]. Early reporting of COVID-19 related psychosis was mainly centered on somatic delusions of being infected with the virus, obsessional fear of infecting family members, and auditory hallucinations stating individuals or family members have the virus [7,9]. Now there have been numerous reports of sleep disturbances, catatonia, persecutory delusions, suicidal behavior and auditory hallucinations that are unrelated to the fear of the virus [9].

Here we describe a unique case of possible COVID-19 psychosis in an individual who has post-infectious seizure disorder in hopes of adding more evidence to the direct association between psychosis and COVID-19 infection. Our patient presented with new-onset psychosis and altered mental status with no respiratory symptoms just three months after COVID-19 infection. Perhaps this case report will also help answer the question of whether or not there is something biologically unique about the SARS-CoV-2 virus which predisposes infected individuals to psychosis.

Case Report

Our patient is a 68-year-old male who first had a positive COVID-19 test on December 28th, 2020. He quarantined with his wife, who also tested positive, at home for a little over one week. Then he was brought to the emergency department (ED) by his wife on January 11th, 2021 for progressively worsening confusion and possible seizure activity. In the ED, our patient underwent a STAT computed tomography (CT) of the head/brain without contrast and CT angiogram of the head & neck with contrast which ruled out acute hemorrhage, infarct, aneurysm, hydrocephalus, and brain herniation. An electroencephalogram (EEG) in the ED showed nonconvulsive status epilepticus and the patient was subsequently admitted to the hospital.

The patient was given 2 mg Ativan for breakthrough seizures and started on a loading dose of 1500mg Keppra followed by 1000mg Keppra twice daily with improvement. Acute delirium and metabolic encephalopathy were ruled out with complete blood count, comprehensive metabolic panel, vitamin B12, vitamin B6, and thyroid stimulating hormone (TSH) levels. The patient underwent continuous video EEG monitoring the following day which showed nonconvulsive status epilepticus again. Then, he was started on a loading dose of 1000mg Phenytoin followed by 100mg Phenytoin every eight hours. Magnetic resonance imaging (MRI) of the brain with contrast was performed and demonstrated generalized cerebral volume loss and findings of chronic microvascular ischemic disease. There was also noted bilateral frontal sinusitis, but MRI was otherwise negative for any acute intracranial pathology. With no clear diagnosis, a lumbar puncture was performed by interventional radiologists to rule out infection or autoimmune causes of seizure. The cerebrospinal fluid was analyzed and tested for herpes simplex virus, West Nile virus, and full autoimmune encephalitis panel. However, this study was also negative.

During the patient's entire hospital admission, his oxygen saturation remained greater than 90% on room air and he did not require Remdesivir or any corticosteroids. In addition, his chest x-ray on admission showed chronic left basilar subsegmental atelectasis, otherwise no acute cardiopulmonary abnormality. After a total of 10 days in the hospital, our patient's mental status returned to baseline and he was discharged home with the diagnosis of nonconvulsive status epilepticus. He was placed on a regimen of 750mg Keppra twice daily and 100mg Phenytoin once daily and he followed up with his primary care physician and neurologist on an outpatient basis.

Then about eight weeks later, the patient returned to the ED accompanied by his wife for similar symptoms of altered mental status and seizure. Though, this time, the wife started noticing acute insomnia and behavioral changes in the patient. She reported the patient was only sleeping about two or three hours each night and then she would find him talking to himself and chanting in Hebrew. Our patient is a native Spanish speaker but became interested in and started learning Hebrew about six years ago. Apparently, since he was discharged from the hospital, the patient developed a preoccupation with God and would randomly start yelling Hebrew prayers. He also experienced confusion, had difficulty finding his words, and would get agitated frequently with family members. The patient mentioned that he had not left the house at all since he recovered from COVID-19. He denied any symptoms and repeatedly stated that he felt fine. On further questioning, he was found to only be oriented to person and place and he was unsure why he was in the hospital. His physical exam was unremarkable.

The patient was readmitted to the hospital once acute stroke, hemorrhage, infarct, etc. were ruled out in the ED. An EEG was normal and lab studies showed no evidence of acute infection. The patient tested negative for COVID-19 active infection but tested positive for COVID-19 IgG antibodies. The neurology team was consulted. They ruled out seizure and recommended discontinuing Keppra due to concerns of Keppra-induced psychosis and follow-up EEG in 2 weeks. Afterwards, the psychiatry team was consulted as the patient's symptoms were declared primarily to be psychosis. They recommended 1mg Risperidone twice daily and 2.5mg Haloperidol or 1mg Lorazepam by mouth or intramuscularly as needed for agitation every six hours. On the first day of admission, the patient had a negative urinalysis, urine drug screen, and syphilis panel. C-reactive protein and sedimentation rate were also within normal limits. However, he continued to experience psychosis symptoms including visual hallucinations of an angel, paranoid delusions that someone is going to hurt him, auditory hallucinations of hearing that demons were inside of him, and intermittent episodes of agitation and yelling.

Over the next eight days, the patient was continued on

Risperidone daily and Haloperidol for agitation with gradual improvement of symptoms and he became fully oriented. It was then determined that the patient was stable for discharge home with 1 mg Risperidone twice daily and continued 100mg Phenytoin every eight hours. He was scheduled for an outpatient MRI and given referrals for follow-up with neurology and psychiatry.

Other than the newly diagnosed seizure disorder, our patient does not have any significant past medical history. Although, he has a positive family history of Alzheimer's dementia, schizophrenia, and bipolar disorder. The history of present illness in our patient is similar to other case reports of COVID-19 psychosis. Comparably, we were left with these differential diagnoses: Keppra-induced psychosis, first episode of psychosis or brief psychotic disorder in the context of an obvious stressor/social isolation, or a direct sequela of COVID-19 infection.

Keppra (also known as Levetiracetam) is an antiepileptic drug (AED) with one of the highest rates of psychosis and aggressive behavior compared to other AEDs. Other common psychiatric and behavioral adverse reactions (PBARs) of Keppra include depression, insomnia, irritability, hostility, anxiety and depression. PBARs from AEDs tend to occur more in patients with a personal or family history of psychiatric disorders and this may be related to genetic chromosomal rearrangements. Interictal dysphoric disorder may occur in patients with epilepsy and presents as psychiatric symptoms between seizures. These peri-ictal symptoms include insomnia, reduced energy, mood swings, and outbursts of irritability/aggressive behavior. Postictal psychosis is associated with religious, persecutory, and paranoid ideas/delusions and can be a complication of chronic epilepsy. Unfortunately, it is difficult to separate these aforementioned phenomena from adverse drug effects since they present so similarly [12]. Due to the patient's complex history of seizure disorder treated with Keppra, family psychiatric history, and recent COVID-19 infection, we are still uncertain of the exact cause of his acute psychosis.

Discussion

Epidemiological studies have established a dose-dependent association between developing psychosis and proximity to COVID-19 infection. However, there is no clear mechanism of how SARS-CoV-2 viral infection leads to the development of acute psychosis [7]. Several underlying mechanisms have been hypothesized including cytokine storm in systemic hyperinflammation, hypoxic brain injury, and severe sepsis [5,7]. It is difficult to separate altered mental state from encephalopathy/encephalitis versus other processes. Numerous reports of encephalitis occur in the setting of negative viral RNA in cerebrospinal fluid analyses. Consequently, the absence of direct neuronal invasion of the virus does not exclude the virus from causing neuropsychiatric syndromes [7].

Direct neuroinvasion of coronaviruses can occur via retrograde axonal transport and dynein proteins in the olfactory bulb thus allowing the virus to migrate from the respiratory tract to the brain [6,9,10]. Peripheral trigeminal nerves can also act as a conduit from the respiratory system to the central nervous system (CNS) [6]. The virus can take another route into the CNS via hematogenous spread of blood leukocytes [9]. SARS-CoV-2 has potential for neuroinvasion via Integrin beta-1 which is an ACE2 (angiotensin converting enzyme 2) binding protein that is highly expressed on the blood-brain barrier [5,7]. Interaction of the SARS-CoV-2 spike proteins with ACE2 receptors can also cause increased blood pressure and lead to increased risk of cerebral hemorrhage [6]. It is thought that the subsequent neuronal cell death, due to neuroinvasion, leads to psychosis [9].

This ACE2 protein interaction has been demonstrated in several *in vitro* studies with murine models, but it is not the only mechanism of how a virus can cause neuropsychiatric disease [7]. Post-infectious autoimmune disorders such as Guillain-Barré Syndrome (GBS) and acute disseminated encephalitis (ADEM) are known sequelae of SARS-CoV-2 infection [2,7]. These diseases are linked to psychosis through antineuronal antibodies targeting NMDA-Rs (N-methyl-D-Aspartate receptors) which leads to axonal damage. In the context of COVID-19, further research is necessary as there may be novel autoantibodies directed against CNS antigens which cause psychosis [7].

Cytokine storm has been observed in some patients with severe COVID-19 as well as H1N1 influenza and occurs due to elevation of pro-inflammatory cytokines such as TNF-alpha (tumor necrosis factor), CRP (C-reactive protein), and IL-6 (interleukin-6) [2,7, 9,10]. Thus, testing for peripheral pro-inflammatory cytokines in CSF may help identify cases of COVID-19 psychosis in the future [7]. In addition, one study found that patients with new-onset psychosis had a higher seroprevalence of IgG against the four human coronaviruses (229E, HKU1, NL63, and OC43) [4,9].

Compared to COVID-infected patients without psychiatric complications, COVID-infected patients with new onset psychiatric illness were found to have higher rates of personal and family history for psychiatric disorders [5,9]. Other risk factors for COVID related new onset psychosis include age, untreated HIV (human immunodeficiency virus) infection, significant social stressors, and social isolation especially with home quarantine and minimal direct human contact [5,9]. Perhaps an additional risk factor may be the development of seizure disorder post COVID-19 infection as in our patient, however this has not been well established.

Conclusion

Neuropsychiatric symptoms may be the first sign of COVID-19 infection [6]. Nonetheless, COVID-19 psychosis can present a few days or a few months after infection and is essentially a diagnosis of exclusion at the moment. When a possible case is presented, it is crucial to rule out acute delirium, encephalopathy, medication side effects (such as corticosteroids, quinolones, and AEMs), psychosocial stressors from the pandemic, and other iatrogenic factors before assigning a diagnosis of COVID-19 psychosis [3,7,10].

Early management with antipsychotic medication is crucial in decreasing morbidity and mortality from COVID-19 psychosis [9]. As time passes from initial COVID-19 infection in patients, more cases of psychosis will be identified, and we will have a better idea of the best treatment course and disease prognosis.

Further laboratory research of specific biomarkers and novel autoantibodies against SARS-CoV-2 is necessary to improve the accuracy of diagnosis of COVID-19 psychosis. Although the number of new infections is decreasing, there is a continued need for additional research in the field in order to care for patients with various long-term effects of COVID-19.

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Conflicts of Interest

None declared. The authors have no financial, consultative, institutional and other relationships that might lead to bias or conflict of interest.

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