Acute-Onset Psychosis Following Prolonged Hospitalization for COVID-19 Pneumonia

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Patient: Male, 23-year-old
Final Diagnosis: COVID psychosis
Symptoms: Mania • psychological issues • psychosis
Medication: —
Clinical Procedure: —
Specialty: Psychiatry

Objective: Rare coexistence of disease or pathology
Background: SARS-CoV-2 infection presents with a variety of clinical manifestations, from asymptomatic courses to prolonged hospitalizations with severe systemic inflammatory responses and multiorgan failure. One particular sequela of the disease is the sudden onset of neuropsychiatric symptoms in the weeks following recovery from COVID-19 pneumonia. While the pathophysiology for the development of this condition is uncertain, symptoms ranging from mild confusion and anxiety to florid psychosis with manic delusions and auditory and visual hallucinations have been rarely, but increasingly, reported in the literature. The acute development of such symptoms in the post-recovery period can be devastating for patients, their caregivers, and clinicians who may be unaware of effective management options.

Case Report: In this case report, we present a 23-year old man who developed psychotic symptoms, including acute mania, delusions of grandeur, and auditory and visual hallucinations, 1 week following an extended hospitalization for COVID-19 pneumonia. The patient was admitted to our psychiatric unit and treated with a combination of antipsychotic and mood stabilizer medications. After 2 weeks of treatment, the patient’s psychotic and mood-related symptoms resolved, with normal mental status maintained at last follow-up 1 month following discharge from our unit.

Conclusions: The acute development of neuropsychiatric symptoms is a rare but increasingly recognized sequela of COVID-19. Despite the severity of initial presentation, patients can be successfully treated with short courses of typical antipsychotic medications with complete return to baseline, unimpaired functioning, and no lingering psychiatric sequela.

Keywords: COVID-19 • Mood Disorders • Psychiatry • Psychotic Disorders • SARS-CoV-2

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Background

The course of a patient’s infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is variable and likely determined by a confluence of socioeconomic, environmental, and genetic factors in combination with age, body habitus, and the existence of comorbid conditions. While some patients recover quickly after an asymptomatic infection, others experience prolonged hospital stays exacerbated by severe and systemic inflammatory responses, potentially precipitating multiorgan failure and patient death. One troubling finding that has been increasingly reported in the medical literature over the past year is the development of acute psychotic symptoms in the weeks following patient recovery from COVID-19 pneumonia. Such psychiatric symptoms documented in a limited number in case reports range from confusion and paranoia to complex hallucinosis and manic delusions [1]. The sudden onset of COVID-induced psychosis appears to be independent of other manifestations of psychophysical distress that typically present with more insidious presentations and are related to pandemic-related social isolation and distancing measures, including depression [2], PTSD [3], and increased subjective stress and anxiety [4]. While COVID-induced psychosis has so far proven to be a self-limited condition that resolves gradually within weeks following treatment with low-dose antipsychotic medications [5-7], it remains a relatively rare and incredibly distressing phenomenon for unsuspecting providers and family members of patients recovering from COVID-19. In this case report, we present a 23-year-old man who developed acute mania, delusions of grandeur, and auditory and visual hallucinations after an extended hospitalization for COVID-19 pneumonia.

Case Report

A 23-year-old man with no past medical or psychiatric history presented to the Emergency Department with fever, cough, and severe shortness of breath. The patient denied any history of alcohol, tobacco, or illicit drug use. A complete blood count (CBC) at that time showed platelets 128 000/μL and leukocytes (WBC) 4000/μL, with relative neutrophils 74% and relative lymphocytes 18%. Nasopharyngeal swab nucleic acid amplification testing (NAAT) confirmed COVID-positive status and both 10 mg dexamethasone i.v. BID (for 8 days) and 100 mg benzodiazate TID PRN (for 2 days) were administered. Two days after admission, the patient’s condition acutely worsened; SaO2 fell to 79%, with hemoptysis and tachycardia in the range of 120-130 bpm. We started 4 mg baricitinib qd (for 5 days) and 100 mg Remdesivir i.v. qd (for 5 days). SaO2 was stabilized at 90-94% with the use of a non-rebreather mask and 15 L/min flow. CBC showed WBC 12 300/μL, relative neutrophils 88%, relative lymphocytes 7%, and platelets 138 000/μL. Lab values found various elevated serum markers: D-dimer 623 ng/mL, LDH 316 U/L, CRP 307.0 mg/L, and CPK 344 U/L. Elevated procalcitonin raised the suspicion for concomitant bacterial pneumonia, and empiric ceftriaxone and azithromycin were administered. Over the following days, the patient’s condition continued to stabilize and improve. CBC normalized to WBC 8600/μL and platelets 245 000/μL. A psychiatric exam found normal mood and behavior; no altered mental status was noted throughout the patient’s hospitalization. The patient was discharged home 9 days following admission and was prescribed a 5-day course of 5-mg dexamethasone BID. Two days later, the patient was readmitted to the Emergency Department for erythema and anaphylactic airway constriction related to shrimp consumption. He was discharged home on the same day after i.v. diphenhydramine administration, without any additional corticosteroids given. Altered mental status and abnormalities of mood or behavior were also not reported at that time.

Six days following this last discharge, the patient was brought to the Psychiatric Emergency Department by university police after he was found running through the cafeteria and exclaiming that he was the “son of God.” On arrival to our inpatient unit, he was found to be acutely manic, grandiose, restlessly pacing the halls, and wearing a red Super Mario hat, which he believed gave him superpowers. He reported bizarre ideations about experiences within a “pocket dimension,” traveling to Hell and absolving the devil of sin, and seeing a figure in the hallway whom he called “the prophet” and who commanded the patient to perform various tasks. Urine toxicology performed on admission to our unit was negative for the presence of any illicit substances. Over the following days, the patient became increasingly agitated and confrontational with staff, demanding repeatedly to speak with physicians and be discharged. No ideations of self-harm or intent to harm others were ever expressed by the patient throughout his hospitalization.

Collateral information obtained from the patient’s aunt unequivocally corroborated a lack of psychiatric history and denied any previous episodes of mania or depression. The patient had recently taken an academic leave of absence during the 2020 spring semester due to an unspecified “inability to concentrate.” His mother had died in 2018 from complications of alcoholic cirrhosis, after which he received supportive counseling from a therapist at his university for a period of a few weeks. He had reported feeling “depressed” at this time but was not given a formal diagnosis of major depressive disorder and was not prescribed any medication. His family psychiatric history was significant for major depressive disorder, post-traumatic stress disorder, and anxiety on the maternal side due to a long history of intergenerational physical abuse. The patient’s mother and step-father were described by others as being severe alcoholics who were both verbally and physically abusive to...
him throughout his childhood, once resulting in an aunt calling child protective services to separate the patient from them.

On admission to our unit, the patient was started on 2 mg risperidone qHS. The dosage was increased on subsequent days due to only partial efficacy (which did not result in any changes in his manic symptoms) to 2 mg BID, and then 3 mg BID. Early in his treatment course, he was also given 5 mg haloperidol once and 2 mg lorazepam once for acute agitation. After 1 week, the patient began to receive 500 mg divalproex sodium BID in combination with his risperidone. His condition began to improve on day 11 of his inpatient stay; his medication regimen at this time was 3 mg risperidone qHS, 500 mg divalproex sodium qd, and 1000 mg divalproex sodium qHS. The patient remained afebrile throughout his stay in our unit, and CBC was significant only for relative neutropenia (20.1%), which was thought to be caused by his Depakote use. Symptoms of mania resolved with better behavioral control and no delusions of grandeur on day 15 of hospitalization, and the patient was discharged on the following day. At 1-month follow-up, the patient reportedly remained at his baseline neuropsychiatric functioning without any lingering psychotic or mood-related symptoms and was following up with an outpatient psychiatrist for periodic counseling sessions.

Discussion

COVID-19-induced psychosis is an acute-onset psychiatric condition of uncertain pathophysiology. Although the incidence of psychosis following COVID-19 pneumonia is currently unknown due to the relative paucity of case reports in the published literature, the development of neuropsychiatric symptoms following other viral infections has been well-documented, indicating that this phenomenon is not a novel occurrence. The link between multiple strains of the influenza virus and the development of schizophrenia and psychosis has been well-established; a 2010 study found that influenza infection during pregnancy significantly increased the risk of offspring later developing schizophrenia, with an odds ratio of 3.0 [8]. HIV infection has also been implicated in the development of apathy, depression, anxiety, mania, and psychosis in long-term patients [9]. Lim et al estimated the percentage of patients infected during previous coronavirus epidemics (eg, SARS and MERS) who then developed psychotic symptoms to be 0.7%, though they noted that many positive cases were likely confounded by glucocorticoid-induced psychosis [5]. Of the few published cases of COVID-19-induced psychosis, the presentation of symptoms has been variable, ranging from relatively mild confusion and paranoia [6] to severe agitation and complex hallucination – 1 patient was reported to have developed intracranial hematomas secondary to severe self-harm by repeatedly hitting his head against a wall [7]. Fortunately, the condition appears to be self-limited and responsive to standard antipsychotic treatment. A single-center case series from Madrid found that 80% (8/10) of their included patients had psychotic symptoms appear more than 2 weeks following initial COVID-19 diagnosis and then resolve within 2 weeks with treatment with low-dose antipsychotic medication, which included any single agent or combination of olanzapine, risperidone, haloperidol, and aripiprazole [6].

The differential diagnosis for psychotic symptoms following the onset of COVID-19 includes a number of psychiatric conditions that present either concurrently or subsequently as a result of patient hospitalization and treatment. We ruled out delirium as a cause of our patient’s psychosis due to the sudden onset of his symptoms only following recovery from pneumonia and the persistence of his altered mental status while on our unit without a waxing-and-waning quality. Brief psychotic disorder or post-traumatic stress disorder (PTSD) triggered by the psychological trauma of experiencing a life-threatening illness was also considered as a possible cause of the development of our patient’s symptoms; however, no mention of psychiatric symptoms was recorded during his COVID-19 hospitalization or during his second Emergency Department visit for anaphylaxis. The patient also never mentioned any persistent distressing thoughts or flashbacks related to his COVID-19 hospitalization experience during his time on our unit or at 1-month follow-up after discharge. In addition, the exclusionary criteria for a diagnosis of either brief psychotic disorder or PTSD were not met in our case, as both inflammatory and infectious primary processes have been hypothesized to be more likely etiologies for COVID19-induced psychosis. Glucocorticoid-induced psychosis (GIP) has also been suggested as an explanation for psychotic symptoms manifesting secondary to corticosteroid treatment of systemic inflammation or acute respiratory distress syndrome. A literature review conducted by Ciriaco et al found that the presentation of psychiatric symptoms occurred in 86% of cases within the first 5 days following initiation of corticosteroid therapy [10], unlike in the case of our patient. In addition, Judd et al found in a case series of 676 patients that the psychiatric side effects of GIP were dose-dependent, occurring only in 1.3% of cases in which a dose of less than 40 mg was administered daily [11]. In the present case, our patient had only been given low doses of dexamethasone during his inpatient stay, with a maximum administered daily dose of 10 mg dexamethasone i.v. BID. Antibody therapy used for the treatment of COVID-19 pneumonia was also ruled out as a possible psychiatric etiology, as neither Remdesivir [12] nor baricitinib [13] have been associated with the development of neuropsychiatric adverse effects.

The mechanism by which acute psychosis develops following COVID-19 pneumonia is unclear. One proposal is that the onset of psychotic symptoms is the result of an encephalopathic
process secondary to direct CNS infection by SARS-CoV-2 virions. In a case series from Beijing, China, genome sequencing detected the presence of the SARS-CoV-2 virus in cerebrospinal fluid obtained from deceased patients [14], and both cerebral vasconstriction and edema have been found in other patients with COVID-19 [15,16]. In a case series from Wuhan, China, 36.4% (78/214) of patients were recorded as having developed acute neurological symptoms, including headache, disorientation, loss of consciousness, and paralysis, in addition to their symptoms of COVID-19 pneumonia [14]. It is known that along with primary infection of type II pneumocytes in the alveoli of the lungs, infection by SARS-CoV-2 can also occur through invasion of the nasal epithelium, and research has shown the virus can reach the CNS through retrograde neural transport following infection of olfactory neurons [17]. Supporting animal studies in mice have demonstrated that ablation of the olfactory bulb subsequently prevents the development of encephalopathy in studies of murine coronaviruses [18]. Following invasion of the CNS, coronaviruses have been shown to precipitate neural demyelination and can cause flaccid paralysis secondary to spread to the spinal cord [17]. MRI T2/FLAIR imaging in some patients with COVID-19 have demonstrated signal changes in the thalamic nucleus, basal ganglia, hippocampus, and mesial temporal lobe [19], which are areas of the brain that have been implicated in the development of various psychiatric disorders such as schizophrenia and bipolar disorder [20,21].

Discovery of the pathogenetic mechanisms responsible for the variability of clinical presentations following SARS-CoV-2 infection is an area of active research, with the identification of various host factors and nonstructural proteins that facilitate viral replication and propagation over the past year. In particular, multiple studies have implicated the angiotensin-converting enzyme 2 (ACE-2) receptor as the primary cell surface target by which SARS-CoV-2 is able to bind to and infect host cells [22]. It has also been recognized that the expression of this receptor in various human tissues, including on neurons in the CNS, is genetically variable [20]. We hypothesize that the development of neuropsychiatric symptoms in association with COVID-19 is related to this genetic variability in receptor expression on cells in the CNS. This hypothesis would explain not only why specific patients develop neuropsychiatric symptoms following SARS-CoV-2 infection and others do not, it also would contribute to our understanding of the wide heterogeneity in disease severity among patients, determined in part by an individual patient’s unique, genetically-determined level of expression of ACE-2 receptors on their somatic cell [23].

A second hypothesis is that COVID-induced psychosis presents as a sequel to the primary hyperinflammatory response that occurs during COVID-19. Serology studies have shown that SARS-CoV-2 replication within epithelial cells triggers the activation of various pyroptotic signaling pathways, which trigger programmed cell death and production of high levels of pro-inflammatory cytokines [24]. A case series of 99 patients from Wuhan, China, showed most had elevations of various inflammatory markers: IL-6 (52%), ESR (85%), serum ferritin (63%), and CRP (86%) [25]. Many studies have specifically identified a strong correlation between elevated IL-6 levels (>80 pg/mL) and neuropsychiatric involvement in the course of SARS-CoV-2 infection, even in the absence of respiratory symptoms [26]. Markedly elevated serum IL-6 levels (2.6-11.3 pg/mL) results in corresponding increases in the CSF, where, it is postulated, IL-6 interferes with normal serotonergic and glutamatergic signaling pathways [27,28]. Cytokine signaling pathways in the brain have also been found to increase the activity of specific enzymes that deplete the supply of tryptophan and tetrahydrobiopterin in the local chemical environment, thereby disrupting the production of monoamine neurotransmitters [29]. Such neurochemical imbalances have been shown to underlie the symptomatology of various psychiatric disorders, including schizophrenia and depression [30]. Elevations in proinflammatory cytokines, especially in the context of long periods of hospitalization and immobilization, are also associated with hypercoagulability, which can provoke small-vessel ischemic events and produce neuropsychiatric complications due to interrupted blood supply to areas of the brain that process perception and emotional regulation. Other studies have shown that overactive IL-6 signaling can trigger the production of various intrathelial autoantibodies, which results in the development of neuropsychiatric symptoms secondary to autoimmune encephalitides [31]. In particular, the structural similarity between the NR1 and NR2 subunits of the NMDA receptor widely expressed on neurons with viral nonstructural proteins 8 (NSP8) and 9 (NSP9), respectively, can lead to the generation of IgG autoantibodies following COVID-19 [32,33]. Anti-NMDA receptor encephalitis in patients after COVID-19 is thought to be driven by cytokine-mediated overactivation of Th-17 cells, a pathophysiological mechanism implicated in many autoimmune disease processes [32,33].

It is uncertain which of these etiologies were ultimately responsible for the psychiatric symptomatology observed in our patient, as neither CSF serology nor autoantibody analysis were conducted to definitively rule in or rule out any of these possibilities. What is clear from our case report and from the work of others is that a combination of traditional psychiatric medications has proven to be effective for treating COVID-19-induced psychosis, with spontaneous remission and return to baseline, and unimpaired functioning after less than 2 weeks of therapy.

Conclusions
The development of acute-onset psychiatric symptoms following COVID-19 has been increasingly reported in the medical
literature over the past year. Our case report documents a patient who developed symptoms of mania, grandiosity, and auditory and visual hallucinations in the days following prolonged COVID-19 pneumonia hospitalization and was successfully treated with a short course of antipsychotic and mood-stabilizing medications.

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