Abrupt Late-onset Psychosis as a Presentation of Coronavirus 2019 Disease (COVID-19): A Longitudinal Case Report

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Introduction: **Coronavirus Disease 2019 (COVID-19) is a pandemic infection caused by the Severe Acute Respiratory Syndrome 2 Coronavirus (SARS-2-CoV). Although most prominently associated with pulmonary manifestations, COVID-19 is increasingly implicated in neuropsychiatric complications, including delirium and psychosis. There is a potential causal link between COVID-19 infection and psychotic symptoms; however, case reports to date have been incomplete, as the patients described had known psychiatric histories or other plausible medical causes for altered mental status. We present a longitudinal case of COVID-19 psychosis in a patient who underwent comprehensive diagnostic evaluation. This case is a contribution to the inchoate characterization of neuropsychiatric manifestations of COVID-19 infection.**

Case Report: **We present a case of late-onset psychosis in a middle-aged man with no psychiatric history who tested positive for COVID-19 on admission following a recently resolved upper respiratory illness. His acute presentation—characterized by delusions, hallucinations, and disorganized thought and behavior, for which he required inpatient medical admission and subsequent inpatient psychiatric hospitalization—was successfully treated. During his hospitalization, he underwent comprehensive medical and neurological workup (including neuroimaging; electroencephalography; and serum and cerebrospinal fluid testing) that was grossly unremarkable.**

Discussion: **Despite myriad potential causes of the patient's psychosis, this patient's diagnostic workup was largely unrevealing, apart from his nasopharyngeal SARS-2-CoV reverse transcriptase polymerase chain reaction assay. As such, psychosis secondary to COVID-19 infection emerged as the presumptive diagnosis.**

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Coronavirus Disease 2019 (COVID-19) is a pandemic infection caused by the Severe Acute Respiratory Syndrome 2 Coronavirus (SARS-2-CoV) that has caused nearly 84 million cases and > 1,800,000 deaths worldwide as of early January 2021.[1] Although most prominently associated with pulmonary manifestations, COVID-19 is increasingly implicated in neuropsychiatric complications that include delirium and psychosis.[2]

Before the COVID-19 pandemic, neuropsychiatric symptoms were known manifestations of other emerging coronavirus diseases, including those caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[3,4] During these epidemics, researchers identified an increased prevalence of anxiety, depressed mood, posttraumatic stress symptoms, and delirium in confirmed cases of SARS-CoV-1 and MERS-CoV infections. Psychotic symptoms such as perceptual disturbances and delusions, however, were rare. When reported, such findings were confounded by the administration of psychotomimetic drugs, as most subjects received ultimate diagnoses of steroid-induced psychotic disorder.[5,6]

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Amid the current pandemic, clinicians have observed a spectrum of neurological sequelae in patients with COVID-19 disease, ranging from anosmia and ageusia to dizziness and acute cerebrovascular disease.[7,8] While delirium appears to be the most frequently documented neuropsychiatric symptom in existing literature, the prevalence and nature of neuropsychiatric syndromes in COVID-19 patients have yet to be fully appreciated.[9] In a nationwide collaborative study in the UK, 153 patients who tested positive for COVID-19 demonstrated neuropsychiatric symptoms, 10 of whom had symptoms of new-onset psychosis.[2] A review by Watson et al[10] summarized the literature documenting psychotic symptoms in patients with SARS-CoV-2 infection. The authors found that the diagnostic potential of existing case series and studies, while compelling, remains inconclusive due to confounding variables. The majority of patients described had known psychiatric histories or other plausible psychiatric or medical explanations for their presentations.[11] Most notably, many had been treated with medication, including hydroxychloroquine and corticosteroids, which have known neuropsychiatric side effects.

A case series from New York State described 3 patients admitted with diagnoses of brief psychotic disorder who were found to be COVID-19 positive with elevated inflammatory markers in the absence of systemic symptoms.[12] The bearing of this case series on our understanding of possible COVID-19 psychosis is, however, limited; all 3 patients had psychiatric histories and were younger than 35 years old (and therefore within the typical window for first-episode primary psychosis). A case report from New York City described a middle-aged patient with no psychiatric history who presented with suicidal command auditory hallucinations suggestive of late-onset psychosis.[13] However, the neurological workup for this patient was incomplete, undermining the conclusiveness of the diagnosis. Furthermore, the patient was receiving experimental treatment with hydroxychloroquine, an agent with potential neuropsychiatric side effects, when he first described the psychotic symptoms and suicide attempt leading to his hospitalization.[14] While some of the atypical behaviors predated his presentation to the hospital, the use of this agent may represent a confounding factor in the patient's directly observed symptoms and recollection of the context of his presentation.

We present a case of late-onset psychosis in a middle-aged man with no psychiatric history who was found to be COVID-19 positive on admission with recently resolved symptoms of an upper respiratory illness. His acute symptoms at presentation—characterized by delusions, hallucinations, and disorganized thought and behavior, for which he required inpatient medical admission and subsequent inpatient psychiatric hospitalization—were successfully treated. Despite myriad potential causes of late-onset psychosis, this patient's diagnostic workup, apart from his nasopharyngeal SARS-2-CoV real-time polymerase chain reaction (RT-PCR) assay, was largely unrevealing, suggesting psychosis secondary to COVID-19 infection.

CASE DESCRIPTION

The patient, a 57-year-old man with no psychiatric history and medical history of type 2 diabetes mellitus, hypertension, and coronary artery disease, was brought to the emergency department (ED) by ambulance in May 2020 after he activated Emergency Medical Services to report that he was the target of attempted murder. On arrival at the ED, he was alert and oriented to person, place, and time (month and year but not exact date), but the initial interview was limited by the patient's psychomotor agitation, acute fearfulness, nonsensical thought process with loose associations, and apparent response to internal stimuli with behavior consistent with both auditory and visual hallucinations (eg, erratic, darting eye contact and audible self-talk). His examination was further notable for loud, explosive speech and paranoid and persecutory delusions that included beliefs that his wife was poisoning him, that cameras had been placed throughout his apartment, and that other patients were being murdered in the ED. The patient denied mood symptoms, substance use, and lifetime suicidality or homicidality.

The patient's wife confirmed that he had no history of psychiatric illness and was behaving ordinarily until the day before this presentation: functioning at work as a superintendent of a local building and with unremarkable affect, behavior, speech, and thought. She denied knowledge of any substance use, aside from an occasional glass of wine. She did, however, report that her husband had recently recovered from a self-limited illness characterized by mild cough, nasal congestion, and loss of sense of taste and smell, for which he did not seek medical treatment or take any medication.

During his first day in the ED, the patient required 2 doses of intramuscular haloperidol 5 mg and lorazepam

2 mg for agitation that was unresponsive to verbal deescalation and for which the patient refused oral medication. He ultimately accepted treatment with oral aripiprazole, which was started at 5 mg and chosen because the patient had a prolonged QTc interval of ~490 ms in the setting of an otherwise normal electrocardiogram. The patient's previous medications—antihypertensive agent, dual antiplatelet therapy, statin, and insulin—were restarted.

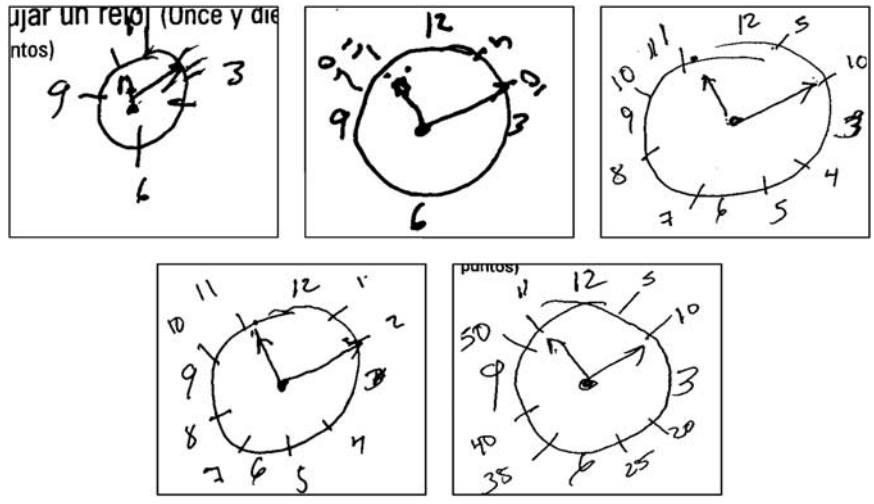
Early in his ED course, the patient's vital signs were temperature 37.1°C (98.8°F), heart rate 82 beats/min, blood pressure 168/76 mm Hg, respiratory rate 17 breaths/min, and oxygen saturation 97% on room air. His physical examination was unremarkable. Of note, his lungs were clear to auscultation bilaterally and results of a brief neurological examination were grossly normal. Laboratory results were notable for positive SARS-CoV-2 RT-PCR assay via nasopharyngeal swab, blood glucose in the 300s mg/dL (normally maintained in the 100s), creatinine of 1.28 mg/dL (reference 0.70 to 1.30 mg/dL) and blood urea nitrogen of 28 mg/dL (reference: 7.0 to 26 mg/dL). Urinalysis and urine drug screen were unremarkable. His erythrocyte sedimentation rate was within normal limits (9 mm/h; reference: 0 to 15 mm/h) and his C-reactive protein was mildly elevated (4.6 mg/L; reference: 0 to 10 mg/L, high > 3.1 mg/L). Following the reinitiation of his regular medications and fluid resuscitation, the patient's blood pressure and laboratory values rapidly normalized, as did his QTc interval. The patient's vital signs, which were taken at minimum once every nursing shift throughout his hospital course, were subsequently unremarkable. Because computed tomography of the head performed in the ED was notable for mild cerebral volume loss and chronic microvascular ischemic changes, neurology was consulted.

Results of a thorough neurological examination (apart from mental status) were normal; however, formal cognitive assessment was postponed, pending resolution of the patient's agitation. Neurology recommended magnetic resonance imaging (MRI) of the brain and lumbar puncture, but neither test could be safely performed without sedation given the patient's behavioral dysregulation. In addition, a lumbar puncture was deemed unsafe until the dual antiplatelet therapy of ticagrelor and aspirin was held for 1 week. The patient was therefore admitted to the neurology service for further medical and neurological workup, at which time the psychiatry consultation-liaison service was called to provide psychiatric management. Of note, following 2 days of antipsychotic therapy in the ED, during which aripiprazole was increased to 10 mg/d, the patient's agitation, hypervigilance, and poor cooperation decreased, but he remained disorganized in thought and behavior and continued to express paranoid delusions that extended to include concerns that hospital staff were spying on him and wished to kill him.

While awaiting lumbar puncture, further medical workup was unremarkable. Serum and urine laboratory tests (ammonia, human immunodeficiency virus-1/2 antigen/antibody, rapid plasma reagin, thyroid-stimulating hormone, B_{12}, urine culture, antinuclear antibody, beta-hydroxybutyrate, ethyl glucuronide, and serum heavy metals) were normal. The patient also converted to a COVID-19-negative status with 4 consecutive negative SARS-CoV-2 RT-PCR tests via nasopharyngeal swab. Twenty-four-hour continuous video-electroencephalography monitoring was unremarkable. MRI of the brain with and without contrast was unremarkable, except for mild cerebral volume loss consistent with the earlier computed tomography of the head. During this waiting period, the patient's calm and cooperative attitude persisted, allowing for serial cognitive testing to be performed. Montreal Cognitive Assessments performed first on day 7 of his admission and twice weekly thereafter demonstrated a degree of cognitive impairment (19/30 on day 7 and 23/30 at discharge). The patient's visuospatial/executive reasoning improved from 1/5 on day 7 to 4/5 on day 11 of the admission, but he made persistent errors in abstraction, language, and attention until the time of discharge (Fig. 1). Despite an increase in the aripiprazole dose to 20 mg/d, the patient's psychosis did not improve; he maintained evolving but rigid paranoid delusions and continued reporting auditory hallucinations of several female voices—per his report, nursing staff—talking about poisoning him. Given the persistence of his psychosis and the normalization of his QTc interval, aripiprazole was cross-tapered to risperidone.

During this cross-taper, the patient underwent interventional radiology–guided lumbar puncture, the results of which were notable only for elevated cerebrospinal fluid glucose to 88 mg/dL and positive toxoplasma immunoglobulin (Ig) G (IgM was negative). Cell count and differential, cultures (bacterial, acid-fast bacterial, and fungal), cryptococcal antigen, (1-3)-beta-D-glucan, meningoencephalitis panel, Epstein-Barr virus quantitative polymerase chain reaction, varicella-zoster IgM/IgG, venereal disease research laboratory test, paraneoplastic and autoimmune (including

FIGURE 1. Progression on the Montreal Cognitive Assessment Clock Drawing Test over a span of 3 weeks, chronologically from top left to top right then bottom left to bottom right.



anti-N-methyl-D-aspartate receptor antibody) panels, and IgG index were all negative. The patient's protein panel was not within the reference range of Alzheimer disease (T-tau, 176.6 pg/mL; P-tau, 36.6 pg/mL; amyloid-β42, 656pg/mL; and Aβ42/T-tau index, 1.46). SARS-CoV-2 RT-PCR was not performed on the cerebrospinal fluid sample due to laboratory limitations.

With his medical and neurological workup complete and grossly unremarkable, the neurology and consultation-liaison psychiatry teams agreed that the patient was likely experiencing acute neuropsychiatric sequelae of his recent COVID-19 infection. Despite the conclusion of the workup, psychiatry concluded that the patient had persistent functional deficits and was unable to care for himself due to his ongoing psychosis, necessitating involuntary psychiatric hospitalization. Upon transfer to inpatient psychiatry, 3 weeks had elapsed since the patient's presentation to the ED. At that point, following his cross-taper from aripiprazole to risperidone (titrated to a total daily dose of 5 mg), the patient was notably more organized, and he consistently denied perceptual disturbances. However, he continued to report ongoing persecutory delusions involving his wife, whom he believed to be unfaithful and the mastermind behind attempts to monitor and poison him before his admission.

Given the patient's transfer to a psychiatric unit on the same medical campus, the consulting psychiatry team followed his course peripherally for the additional week of hospitalization. By the time of discharge, the patient's dose of risperidone had been increased to 3 mg twice daily, and his symptoms had further receded. His thought process was linear, and his thought content was notable for a lack of ongoing persecutory and paranoid delusions. However, some previous delusions had faded to overvalued ideas but these were limited to what had occurred during his period of maximal psychosis. For example, he remained retrospectively paranoid and suspicious of staff on the inpatient neurology unit, albeit less so, but demonstrated no such concerns about the psychiatric staff. On a telephone follow-up call with the consultation-liaison psychiatry team 2 weeks after his discharge, the patient endorsed excellent adherence to his medication. No signs or symptoms of lingering psychosis were noted, and collateral information from his wife was consistent with the patient's self-report. On the basis of his grossly normal examination and his wife's report of a return to baseline functioning, the patient's psychosis had resolved—6 weeks after its abrupt onset in the setting of a recent COVID-19 infection.

DISCUSSION

To date, COVID-19 psychosis, a novel clinical diagnosis of exclusion, has been proposed in case reports and series in which patients without a history of psychosis have experienced positive psychotic symptoms of

delusions, hallucinations, and disorganized thought and behavior.[10,12,13] Our patient's psychiatric presentation following mild COVID-19 symptoms and a positive COVID-19 test was similar to the cases described in those reports. However, the patient's middle age, lack of psychiatric history, and unremarkable extensive medical and neurological workup differentiate this case. Furthermore, the continuity of care over 6 weeks documented in this case offers a unique insight into the course of a rare entity.

Two general mechanisms of central nervous system involvement have been proposed to explain neuropsychiatric symptoms of COVID-19 infections: (1) direct viral invasion of the central nervous system (a) via the olfactory bulb, across the cribriform plate, and into the cerebrospinal fluid or the frontal lobe or (b) via hematogenous spread across the blood-brain barrier and (2) as a sequela of the severe systemic inflammation commonly seen in COVID-19 illness.[15,16] Alternatively, the psychosocial stress of the pandemic has been linked to exacerbation or precipitation of psychiatric symptoms, independent of infection status.[17] In this patient's case, the historical symptoms of anosmia and ageusia, known neurological symptoms of COVID-19, suggest neurological involvement of the SARS-2-CoV virus. In addition, beyond his neuropsychiatric symptoms, the patient did not display signs or symptoms of severe systemic disease or inflammation and denied ruminative or delusional thought content regarding the ongoing pandemic. As such, direct viral invasion appears to be the most likely explanation of his apparent COVID-19 psychosis.

In considering other potential etiologies for the patient's presentation, delirium, the prodrome of a major neurocognitive disorder, acute-on-chronic ischemic disease, and primary psychotic disorder come to the forefront. Despite the observed disturbances in attention and cognition in the setting of the patient's recent infection, his unremarkable electroencephalogram and the relative stability of his mental status are atypical for delirium. Still, the patient's presentation may be on the spectrum of delirium, as notably diverse phenotypes of delirium have been observed in countless patients with severe COVID-19 disease. Given that the patient's examination suggested cognitive impairment, his psychotic symptoms could also be consistent with the early stages of a major neurocognitive disorder. His cognitive impairment characterized by deficits in visuospatial/executive function and attention and late-onset psychosis responsive to atypical antipsychotics are consistent with prodromal presentations of dementia with Lewy bodies.[18] Indeed, while the patient's cerebrospinal fluid protein and lack of significant focal atrophy on brain imaging are inconsistent with Alzheimer dementia, frontotemporal dementia, and Creutzfeldt-Jakob disease, they are in keeping with tau and beta-amyloid protein levels and noncontributory imaging observed in patients with dementia with Lewy bodies.[19] Thus, his acute onset of psychosis with cognitive impairment could be an initial presentation of dementia with Lewy bodies, with the COVID-19 infection serving as a likely precipitant—itself a remarkable case. Alternatively, his scores on the Montreal Cognitive Assessment—having improved in line with reductions in the patient's psychosis—may reflect his distracting psychotic process rather than cognitive impairment *per se*. The patient's hyperglycemia on presentation, which did not meet criteria for a hyperglycemic hyperosmotic state or diabetic ketoacidosis, as well as elevated glucose levels in his cerebrospinal fluid raises the question of a hyperglycemic metabolic encephalopathy, as hyperglycemia has been documented to cause reactive oxidative stress at the neuronal level with concomitant neuropsychiatric symptoms.[20] However, this would not explain the persistence of psychotic symptoms after the rapid normalization of glucose levels to the patient's baseline level. The patient's acute hyperglycemia and his history of diabetes and hypertension—as well as imaging findings consistent with chronic microvascular ischemic changes—suggest the possibility of acute ischemic changes resulting from COVID-19 disease in a susceptible patient.[21] However, imaging of the patient's head—both computed tomography and MRI—failed to demonstrate signs of acute ischemic injury, and thorough neurological examination revealed no focal deficits. In addition, no signs of pulmonary pathology were observed on physical examination nor was hypoxia detected during weeks of frequent vital signs monitoring. Testing of serum and cerebrospinal fluid was also negative for toxic, infectious, paraneoplastic, and autoimmune etiologies, and the absence of focal abnormalities on imaging make other acute encephalopathies unlikely. Finally, a diagnosis of primary late-onset psychosis in the absence of primary mood symptoms, although possible, is rare. Furthermore, the sudden onset of the patient's psychosis makes a primary psychotic disorder unlikely.

Nonetheless, this case is not without its unanswered questions: What would the patient's SARS-2-CoV RT-PCR on cerebrospinal fluid have shown, had this test been possible? What is the role of long-term antipsychotic therapy in his care? What would a baseline Montreal Cognitive Assessment have demonstrated, and were it possible to readminister one now, how would it result? As the pandemic continues, further insight will likely be gained from similar cases. For now, however, our case of apparent COVID-19-induced psychosis in a middle-aged patient without psychiatric history—in whom we describe a complete medical and neurological workup, successful psychiatric treatment, and follow-up over 6 weeks—paints a compelling picture of the potential neuropsychiatric complications of COVID-19 disease.

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