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Case Report

COVID-19 Psychosis: A Potential New Neuropsychiatric Condition Triggered by Novel Coronavirus Infection and the Inflammatory Response?



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Introduction

Novel coronavirus (COVID-19 or SARS-CoV-2) has caused worldwide anxiety and grief because of its infectivity, lethality, and lack of curative treatment; however, the degree and characteristics of distress, psychopathology, and potential virus-specific neuropsychiatric manifestations have yet to be elucidated. COVID-19, similar to other coronaviruses, is a single-strand RNA virus with a distinct crown-like outer envelope.¹ It can cause a range of manifestations, from no symptoms, to mild respiratory symptoms, to fatal severe acute respiratory syndrome (SARS). Coronaviruses are neurotropic and can enter the brain through various mechanisms, including the olfactory neural pathway, and they can cause a significant inflammatory response, which can cause both peripheral and central nervous system (CNS) manifestations.²

Prior reports from the SARS CoV-1 epidemic identified a range of psychiatric complications in affected patients with SARS, including adjustment-related anxiety, depression, suicidal ideation, as well as organic hallucinosis and organic manic disorder.³ High-dose corticosteroid use has been identified as a significant associated factor in psychotic presentations.^{3–5} Long-term survivors of SARS-CoV-1 were found to have post traumatic stress disorder (54%), depression (39%), panic disorder (32.5%), and obsessive compulsive disorder (15.6%) 31–50 months

after the diagnosis; however, short- or long-term psychosis was not found in this cohort.⁶

To date, there are few reports describing psychiatric symptoms associated with the COVID-19 pandemic. A longitudinal study of psychological symptoms in 1738 respondents from 190 Chinese cities during the initial outbreak in Wuhan, China, repeated 4 weeks later at the peak of the epidemic revealed 28% reported high levels of anxiety, 17% reported depression, and 8% reported stress and distress was stable over time.⁷ An online survey of 1074 individuals from Wuhan yielded similar results, with high rates of anxiety, depression, and alcohol use and decreased mental well-being among respondents, with 21- to 40-year-old individuals reporting higher symptoms than other age groups. Finally, Qiu and colleagues surveyed 52,730 persons throughout China, Taiwan, Macau, and Hong Kong on January 31, 2020, using a COVID-19 Peritraumatic Distress Index which was validated for use in the survey.⁸ In this study, 35% of respondents reported significant psychological distress, with those closest to

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Wuhan, women, individuals aged 18–30 years, the elderly, and more educated individuals reporting the highest levels of distress.⁸ Importantly, none of these studies addressed COVID-19 status in the respondents.

Among COVID-19–infected patients, Mao and colleagues⁹ described neurological manifestations in 36% of hospitalized patients with severe infection, including stroke and alterations in consciousness. Chen and colleagues,¹⁰ in a retrospective report from Wuhan, China, described encephalopathy and persistent alterations in consciousness among patients who subsequently died of COVID-19 disease. These reports raise the specter of neuropsychiatric manifestations of COVID-19; however, the patients had severe respiratory, cardiac, and other systemic complications and were given multiple concurrent medications, including corticosteroid and other treatments, which could explain the neuropsychiatric symptoms.

There is prior evidence to suggest that infection with certain coronaviruses is associated with recent-onset psychotic symptoms; however, new-onset psychosis in otherwise asymptomatic patients infected with COVID-19 has not been described.¹¹ One report documented brief psychotic reaction among 3 patients who were negative for COVID-19, attributed to fear of COVID-19 infection, and another described a case of COVID-19–related delusions in a COVID-19–negative patient who had an underlying diagnosis of schizophrenia.^{12,13}

Since the first regional case of COVID-19 infection was reported in New Rochelle, Westchester County, New York, on March 1, 2020, just 11 miles from our medical center, we have encountered in our emergency department (ED) patients who were asymptomatic for COVID-19 physical symptoms but who presented with new-onset psychotic symptoms and who tested positive for COVID-19. The patients had elevated peripheral inflammatory markers, particularly C-reactive protein (CRP), and responded to medical and psychiatric support and modest doses of antipsychotic medication. We describe 3 such cases here and hypothesize a potential neurotropic and/or neuroinflammatory etiology for these new-onset symptoms that warrants further study.

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The first case, Mr. A, a 30-year-old male, was brought to ED by his wife with bizarre behavior for several

days, including extreme anxiety, suicidal ideation, agitation, suspiciousness, auditory hallucinations of people who were chasing him, decreased sleep, and drinking excessive amounts of water and Pedialyte (Abbott Laboratories, Chicago, IL) for reasons he could not articulate. On examination, he was guarded, internally preoccupied, called himself by an incorrect name, and thought he was being followed. When left alone momentarily, he fled and hid in a cabinet in the ED. He was unable to participate in bedside cognitive testing but was fully oriented. There was no prior history of psychosis, but he had been seen 2 days prior at another local ED and sent home with a diagnosis of panic disorder. He had no respiratory or gastrointestinal symptoms; no history of anosmia or ageusia; and vital signs, complete blood count, comprehensive metabolic panel, chest x-ray, and brain computed tomography (CT) scan were normal. Sequential Organ Failure Assessment score, a measure of mortality risk in patients presenting to the ED, was 0, indicating minimal risk.¹⁴ Acute phase reactants were elevated: CRP was 0.67 (0.0–0.5 mg/dl) and serum ferritin was 421 (180–370 mcg/l). Social history revealed several family members positive for COVID-19, all asymptomatic. Mr. A was tested in the ED and found to be COVID-positive. He was transferred to the medical service for supportive care and also received quetiapine 25 mg daily for 4 days. His psychotic agitation improved, and he was discharged home with psychiatric follow-up.

The second case, a 34-year-old single female, Ms. B, with a history significant for panic disorder, reported that she was walking and trying to take a deep breath, felt anxious, and presented to the ED for evaluation. With the consulting psychiatrist, she was inattentive, pressured, agitated, disorganized, and suspicious, perseverating on bizarre somatic sensations of “fire burning up inside” and migratory numbness and tingling, which family stated had never occurred previously. She was fully oriented but would not cooperate with bedside cognitive testing. She had no respiratory or gastrointestinal symptoms, anosmia, or ageusia, and her comprehensive metabolic panel, chest x-ray, and brain CT and all vital signs were normal. She had low white blood cell count of 2.8 k/mm³. Sequential Organ Failure Assessment score was 0. She had no known COVID-19 exposure but was tested and found to be COVID-positive. She was given lorazepam 1 mg and aripiprazole 2 mg in the ED with some acute improvement and was then admitted to the medical

service for further evaluation and treatment. CRP was elevated, 1.89 mg/dl, while ferritin was normal. Hydroxychloroquine and azithromycin were prescribed to treat COVID infection, and further antipsychotic medication was avoided out of concern for prolongation of the corrected QT interval. She continued on her outpatient medication fluoxetine 10 mg daily, while clonazepam 0.5 mg twice daily and melatonin 3 mg at bedtime were initiated. She was transferred voluntarily to our specialized psychiatric unit for COVID-positive patients because of ongoing anxiety and psychotic symptoms, where she continued to be physically asymptomatic, her antimicrobials were stopped, and aripiprazole 5 mg daily was added to her regimen.

The third case, a 33-year-old white male, Mr. C, with opioid use disorder on methadone maintenance 120 mg daily but no prior history of psychosis (verified by his brother), presented to the ED for evaluation of auditory hallucinations paranoid and persecutory delusions of his ex-wife and “people with knives and guns in a blue van outside” trying to kill him and severe agitation for 4 days. Mini-Cog examination was normal. He reported no respiratory or gastrointestinal symptoms, anosmia, or ageusia, and his vital signs, complete blood count, comprehensive metabolic panel, chest x-ray, and brain CT scan were unremarkable. Sequential Organ Failure Assessment score was 0. Because he had become homeless and had recently stayed in shelters in New York City and New Rochelle, he was tested in the ED and found to be COVID-positive. He was admitted to the medical service for further evaluation and treatment. CRP was elevated (1.9 mg/dl), but ferritin, d-dimer, and chest x-ray were normal. He was provided medical support and started on quetiapine 50 mg twice daily until he could be transferred to our COVID psychiatric unit.

Discussion

These cases all presented similarly, with new and recent-onset severe anxiety, agitation, paranoia, disorganized thinking, and none of the typical COVID-related respiratory or gastrointestinal symptoms or disturbances in taste and smell. Two of the patients reported auditory hallucinations. These cases are strikingly similar to those described recently by Martin¹² in the metropolitan Boston area, who reported 3 cases of new-onset paranoid psychosis related to the

fear of COVID-19. While the presentation is similar, the patients we saw were not overtly expressing COVID-related concerns. Furthermore, because of the new-onset presentation and our ability to obtain rapid COVID testing in addition to other medical workup, they were able to be diagnosed COVID-positive, raising new differential diagnostic considerations.

The etiology of the psychotic symptoms described here may have been related to uncovered or unarticulated stress of the COVID pandemic in psychiatrically vulnerable individuals. However, the lack of COVID preoccupation in these patients, the presence of COVID infection, and elevated inflammatory markers, particularly CRP, raise the possibility of a virus-associated inflammatory trigger. Delirium must also be considered in the differential diagnosis of these patients. Psychotic symptoms can be observed in the context of delirium, and these patients had recent, sudden-onset psychosis, and 2 of the 3 patients were disorganized and, while fully oriented, could not otherwise participate in bedside cognitive testing, all consistent with the diagnosis. However, the patients were not physically ill and had minimal laboratory derangement with the exception of inflammatory markers, and we did not observe characteristic fluctuations in the level of alertness or in the psychotic symptoms, making the diagnosis less likely.

Profound inflammatory response to COVID-19 infection (“cytokine storm”) is thought responsible for the severe, sometimes fatal, pulmonary and cardiac complications of the disease and has been postulated to produce neuropsychiatric symptoms through immunological mechanisms.^{15,16} Immune-based triggers have long been implicated in the pathogenesis of psychiatric illness, including depression, psychotic disorders such as schizophrenia, and neuropsychiatric manifestations of HIV infection and other viruses.^{17,18} CRP, which was elevated in all 3 of our patients, has been studied as a potential peripheral marker of immune activation, which is postulated to have a causal or triggering role in schizophreniform psychosis.¹⁹ It has been hypothesized that human coronaviruses and other respiratory viruses may act as opportunistic pathogens of the CNS as they have been shown to have neuroinvasive qualities, due to either autoimmunity or viral replication.² In fact, CNS penetration and neuroinflammation from other coronaviruses have been associated with new-onset psychotic disorders or CNS infection.^{5,16}

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Troyer and colleagues¹⁶ reviewed literature on viral neuropsychiatric symptoms associated with influenza, H1N1, encephalitis lethargica, and SARS-CoV-1, among other viruses, and postulated that COVID-19 may produce similar neuropsychiatric symptoms through direct viral infiltration of CNS, transmigration into CNS through blood leukocytes, and central and peripheral cytokine activation causing CNS inflammation and blood-brain barrier compromise. Proinflammatory cytokines interleukin (IL)-6, tumor necrosis factor-alpha, IL-8, IL-10, and IL-2R and CRP are all elevated in patients with COVID-19 and reflect disease severity.^{7,20} Immune-modulation therapies such as IL-6 inhibitor agents and melatonin are under investigation for COVID-19,^{21,22} and other therapies such as intravenous immunoglobulin, cytokine-blocking medications, and Janus kinase inhibitors have been suggested.¹⁶

The present case series describes a potentially novel clinical presentation, however, is limited by the small sample and lack of uniform medical and neuropsychiatric workup. The absence of brain CT abnormalities is not unexpected in these cases and does not exclude CNS pathology that might be detected by more sensitive functional imaging studies such as magnetic resonance diffusion weighted imaging and spectroscopy, which can better detect white matter and inflammatory changes. Neuropsychological screening tools or fuller assessment as contact risk would allow could have elucidated concurrent cognitive abnormalities and contributed to differential diagnosis. Furthermore, measurement of a broader array of cytokines, including CRP, IL-6, tumor necrosis factor-alpha, IL-8, IL-10, and IL-2R and others in peripheral blood and cerebrospinal fluid (via lumbar puncture) would better characterize immune activation both peripherally and centrally. Measurement of COVID-19 RNA in

cerebrospinal fluid could indicate virological invasion into CNS. Finally, reliance on self-report and collateral history made it difficult to determine the precise nature and time course of onset of psychosis in relationship to acquisition of the infection. Nonetheless, the onset within just a few days before COVID diagnosis and the presence of concurrent immune activation suggest psychosis may have similar onset to other types of COVID symptoms in the active stage of infection.

Conclusion

Despite the presence of multiple potential stress-related and physiological causes of psychosis in these COVID-19-positive patients, we report that a new-onset psychosis associated with COVID-19 infection and the potential immune-mediated neuropathogenesis described here warrant further investigation. In particular, we are interested in further investigating clinical characteristics, cognitive abnormalities, onset, course and prognosis, and their association to peripheral and central inflammatory markers, including CRP, IL-6, and others. If a COVID-19-psychosis relationship exists, treatment of the psychotic symptoms with antipsychotic medication, while potentially effective for treating symptoms, would likely be obviated or mitigated by effective treatments of the underlying COVID-19 infection and its associated inflammation.

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