Psychosis in a Patient With Asymptomatic SARS-CoV-2 and Secondary Adrenal Insufficiency

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In addition to the psychological distress associated with the coronavirus disease 2019 (COVID-19) pandemic, the direct effects of the virus itself and the subsequent immune response of the host on the central nervous system (CNS) continue to be elucidated.[1] We present the case of a patient with secondary adrenal insufficiency and no psychiatric history who developed a psychotic episode after a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Case Report

Our patient was a 41-year-old black woman with a medical history significant for hypothyroidism and secondary adrenal insufficiency who presented to our emergency department with paranoid delusions of 2 days duration. Eight days prior to admission, the patient was hospitalized for 2 days due to adrenal crisis from nonadherence to outpatient prednisone. The patient had tested positive for SARS-CoV-2 infection and denied CNS/psychotic symptoms but had a C-reactive protein (CRP) level of 0.9 mg/dL. COVID-19 pneumonia was considered in the differential diagnosis. Our patient was discharged on hydrocortisone 20 mg at 8:00 AM/10 mg at 4:00 PM and levothyroxine 100 mcg/d.

During the current admission, the patient was asymptomatic of COVID-19. She denied constitutional/gastrointestinal symptoms, headache, ageusia, and anosmia. Her vital signs were within normal limits, her pulse oximetry was > 94%, and the chest x-ray was unremarkable. Blood/urine cultures, urine drug screen, and blood alcohol were negative. The laboratory evaluation was remarkable for serum cortisol < 0.85 mcg/dL, adrenocorticotrophin hormone (ACTH) < 1.1 pg/mL, sodium of 130 mmol/L, and thyroid-stimulating hormone of 5.7 mU/L. Despite low ACTH and cortisol levels, the patient demonstrated no signs or symptoms of adrenal crisis. Computed tomography (CT) of the brain and lumbar puncture, including cerebrospinal cultures, protein, and glucose, were unremarkable. The psychiatric consultation team was consulted due to paranoid delusions.

During our evaluation, except for the previously mentioned paranoid delusions, she denied other psychotic symptoms (auditory/visual hallucinations). Her speech was goal directed. She admitted nonadherence to both prednisone and levothyroxine for 6 days. She was oriented x 3 and the Confusion Assessment Method[2] yielded a negative result. Magnetic resonance imaging of the head and pulmonary and head/neck CT angiography revealed no acute findings. Pertinent positive results included elevated levels of CRP (1.3 mg/dL) and interleukin 6 (IL-6; 8.1 pg/mL).

As the patient was not thought to be in adrenal crisis, she was admitted to the hospital when hydrocortisone 20 mg/d was initiated. Risperidone 0.5 mg twice/d was started, and her paranoid delusions abated after 3 days of treatment. Hydrocortisone was tapered on day 4 of treatment, and prednisolone 5 mg/d was started. Our patient continued without psychosis until discharge 10 days later. Interestingly, her CRP and IL-6 levels were within normal limits after 3 days of hydrocortisone treatment. She was discharged on prednisolone and levothyroxine, but risperidone was discontinued on the day of discharge.

Discussion

SARS-CoV-2 may gain entry to the CNS and possibly induce neuropsychiatric symptoms, such as psychosis, by 2 routes: hematogenous or neuronal transmission (Figure 1).[3–9] There is emerging evidence about psychiatric manifestations as a potential complication of SARS-CoV-2 infection.[10] In 1 study,[11] and similar to our patient, two-thirds of patients infected with SARS-CoV-2 who developed psychosis had no reported psychiatric history. Also, over 50% psychiatrically symptomatic individuals were either asymptomatic (38%) or mildly symptomatic (16%) for COVID-19, a finding that is similar to our patient.[11]

Despite unremarkable neuroimaging and lumbar puncture, our patient did have elevated IL-6 and CRP levels. While review of psychoimmunology is beyond the scope of this report, enhanced inflammation in psychosis has been confirmed by meta-analyses in chronic schizophrenia and drug-naive patients in first-episode psychosis. Furthermore, high levels of IL-6 in adolescents correlate positively with occurrence of psychosis later in life.[12] One limitation is while psychosis is rare in adrenal insufficiency, there are reports of new-onset psychosis in adrenal crisis.[13,14] However,

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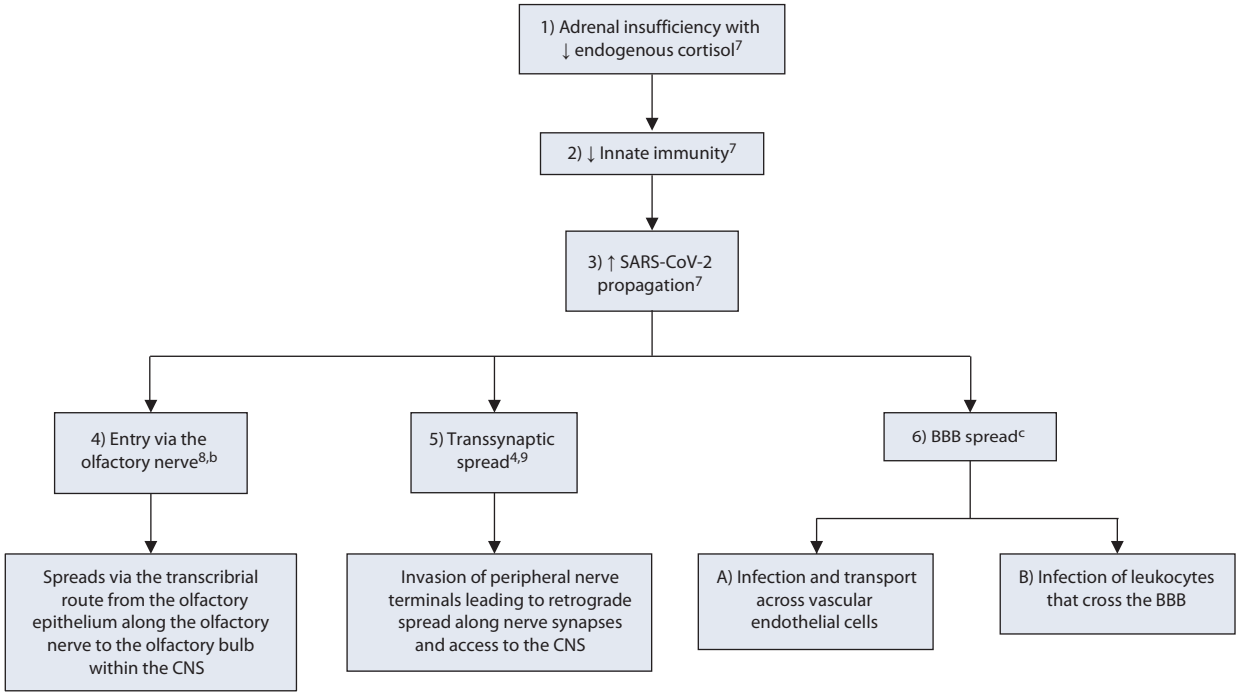
Figure 1. Proposed Pathogenesis of the Patient's Psychotic Symptom



[a]The figure does not account for potential hypoxia, brief psychotic disorder, and potential psychotomimetic effects, in a dose-related manner, of exogenous glucocorticoids.
[b]ACE2 is a functional receptor for the SARS coronavirus, which associates with cellular receptors to mediate infection of their target cells.
[c]Mechanisms of spread across the BBB: (a) Infected vascular endothelial cells have been shown to spread SARS-CoV-2 to glial cells in the CNS. Following a respiratory tract infection characteristic of the virus, SARS-CoV-2 may disseminate into the systemic circulatory system. Upon reaching the BBB, SARS-CoV-2 may invade host endothelial cells by interaction with the ACE2 receptor, altering tight junction proteins formed by BBB endothelial cells, or phagocytosis by immune cells. (b) Known as the Trojan horse mechanism, infected leukocytes from the periphery can cross the BBB to infect the CNS. (c) In sum, as for neuropsychiatric symptoms, it is posited that despite BBB, the brain and spinal cord communicate with the peripheral immune system, and, hence, systemic inflammation can affect the CNS. In the context of COVID-19, the damage to the BBB mediated by a massive increase in circulating proinflammatory factors is highly likely. Compromised BBB allows an inflammatory storm to engulf the CNS, leading to functional damage and is the suggested pathophysiology of neuropsychiatric manifestations of SARS-CoV-2 infection.
Abbreviations: ACE2 = angiotensin-converting enzyme 2, BBB = blood-brain barrier, CNS = central nervous system, COVID-19 = coronavirus disease 2019, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

our patient was determined to not be in adrenal crisis. Nonetheless, we recommend that further studies regarding neuropsychiatric symptoms of SARS-CoV-2 infection are warranted.

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