A case of fulminant neuroleptic malignant syndrome with COVID-19

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Dear Editor,

Neuroleptic malignant syndrome (NMS) is a life-threatening neuropsychiatric emergency manifesting hyperpyrexia, rigidity, altered consciousness, and autonomic instability [1]. NMS is associated with the administration of D2 dopamine receptor-blocking antipsychotics or abrupt discontinuation of antiparkinsonian drugs [1]. Although the pathophysiology of NMS is mainly considered acute interruptions of dopaminergic transmission in the basal ganglia and hypothalamus, but there are several risk factors contributing to the development of NMS, including dehydration, agitation, organic brain disorders, and concomitant medical illness [1]. During the ongoing coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), various neurological manifestations and complications of COVID-19 have been reported, ranging from headache, anosmia and ageusia to cerebrovascular disease, seizure, and encephalopathy [2]. However, there are few reports of NMS accompanying the acute phase of COVID-19. We report a rare case of the patient who developed fulminant NMS with COVID-19.

A 51-year-old female patient with a 30-year of history of schizophrenia, presented to the emergency department (ED) with altered mental status and fever. She has been managed with electroconvulsive therapy (ECT); antipsychotic drugs, including 3 mg of risperidone, 5 mg of aripiprazole, and 300 mg of clozapine; and 1mg of lorazepam. She could independently perform her daily activities and reported no recent changes to her medications. She had no history of NMS. She has been diagnosed with COVID-19 four days before admission and had been feeling feverish since then. In the ED, she exhibited a high body temperature (40.2 °C), tachycardia (128 beats per minute), and tachypnea (42 breathes/min). Neurological examination revealed a drowsy and confused mental status and marked rigidity in all limbs. Laboratory tests showed elevated concentrations of creatinine kinase (CK) (27,747 U/L), alanine aminotransferase (90 IU/L), aspartate aminotransferase (424 IU/L), serum sodium (158 mmol/L), and creatinine (4.03 mg/dl). Chest computed tomography revealed peripheral infiltrates in the left lower lung. There were no remarkable abnormalities in the results of brain imaging and cerebrospinal fluid study. The patient was diagnosed with NMS. Emergency intubation was performed and massive hydration was started. However, the urine output gradually decreased and the CK level further increased to above 124,334 U/L. The patient was admitted to the intensive care unit (ICU) and, continuous renal replacement therapy (CRRT) for rhabdomyolysis-induced acute kidney injury was started. In the ICU, she was treated with bromocriptine (a 5 mg
loading dose followed by 2.5 mg doses three times daily via nasogastric tube), and all antipsychotic medications were discontinued. After 5 days of CRRT, the patient was extubated, and the CK and creatinine levels decreased to 3,665 U/L and 2.02 mg/dl, respectively. However, the patient’s urine output had not recovered; therefore, hemodialysis was continued. Additionally, as there was no improvement in rigidity, the bromocriptine dose was increased to 15 mg per day. The patient was more alert than before, but she began to mumble to herself and had delusions and agitation. On hospital day 14, 2.5 mg of risperidone was administered for psychosis management in consultation with psychiatrists. However, risperidone was discontinued because the patient showed worsened rigidity and developed symptoms of catatonia such as mutism, unresponsiveness to stimuli, and immobility (Supplementary Video 1). On hospital day 17, the patient was transferred to the general ward, and the CK level was decreased to 196 U/L. Thereafter, her rigidity and voluntary movements gradually improved. However, the patient had recurring intermittent fever without a specific origin of infection. On hospital day 30, we started tapering off the bromocriptine dose and began administering 12.5 mg of clozapine. On hospital day 47, the patient’s urine volume began to improve from anuria to about 100 ml per 8 hours. The clozapine dose was increased to 50 mg per day. Her rigidity had completely resolved, but residual catatonic symptoms persisted. Eight weeks after admission, the patient resumed ECT for managing her catatonic symptoms while maintaining hemodialysis. After five ECT sessions, the patient’s catatonia and intermittent fever improved, and normal conversation was possible.

NMS is considered an idiosyncratic reaction, and it usually develops within 10 days of beginning the use of neuroleptic agents [1]. The patient with COVID-19 in our report fulfilled Levenson’s criteria for the diagnosis of NMS [3], but she developed NMS despite long-term antipsychotics treatment. There are three published case reports of NMS associated with COVID-19 in patients with schizophrenia or schizoaffective disorder [4–6]. In two cases, NMS was associated with the administration of haloperidol, which is known risk factor of precipitating NMS [4,5]. In the third case, NMS was associated with the re-introduction of atypical antipsychotics, including risperidone and clozapine [6]. Our case illustrates COVID-19 may be a risk factor for NMS development, even in patients receiving a stable dosage of atypical antipsychotics. Previous studies of NMS in patients with Parkinson’s disease reported that intercurrent respiratory or gastrointestinal tract infection could trigger NMS development in the absence of changes in medication [7,8]. Although the mechanism underlying the relationship between infection and NMS remains unclear, stress and dehydration associated with infection may play a role in the development of NMS [7]. In addition, our patient had severe renal failure due to rhabdomyolysis with extremely high CK levels and took a long time to recover from NMS. Further studies are needed to determine how COVID-19 affects the severity and clinical outcomes of NMS.

Neuroinvasion of SARS-CoV-2 reportedly occurs through the angiotensin-converting enzyme 2 (ACE2) receptor on host cells [2,9]. The ACE2 receptor is widely expressed in the central nervous system (CNS), particularly in the substantia nigra, middle temporal lobe, posterior cingulate cortex, and olfactory bulb [4]. The olfactory bulb has been found to be the main route of entry of SARS-CoV-2 into the CNS [9]. Because the olfactory system has complex neuronal connections with the hypothalamus, which is critical for maintaining homeostasis and thermoregulation [9], SARS-CoV-2 infection through the olfactory bulb-hypothalamic network might contribute to the increased likelihood of developing NMS in patient with COVID-19. Furthermore, recent experimental evidence demonstrated that dopaminergic neurons were more permissive to SARS-CoV-2 infection than microglia, macrophages, or cortical neurons [10]. However, the pathophysiologic mechanism by which COVID-19 increases the risk of NMS remains unclear.

In conclusion, our patient with COVID-19 developed fulminant course of NMS despite long-term treatment with atypical antipsychotics. Our case highlights that NMS also need to be considered a neurological manifestation of COVID-19, especially in patient receiving neuroleptics.

Supplementary Material

Supplementary data are available at https://doi.org/10.53991/jgn.2022.00073.

Supplementary Video 1. The video shows a 51-year-old female patient with coronavirus disease 2019 who developed neuroleptic malignant syndrome. She shows catatonic symptoms such as immobility, mutism, unresponsiveness to stimuli, and rigidity of the upper and lower extremities.

Notes

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.
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