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 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 1 mg 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 breaths/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 na-
sogastric tube), and all antipsychotic medications were discon-
tinued. 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 re-
covered; 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 ad-
ministered for psychosis management in consultation with psy-
chiatrists. However, risperidone was discontinued because the
patient showed worsened rigidity and developed symptoms of
catatonia such as mutism, unresponsiveness to stimuli, and im-
mobility (Supplementary Video 1). On hospital day 17, the pa-
tient 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 re-
curring 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 re-
sidual catatonic symptoms persisted. Eight weeks after admis-
sion, the patient resumed ECT for managing her catatonic
symptoms while maintaining hemodialysis. After five ECT ses-
sions, 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 de-
veloped 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 ad-
ministration of haloperidol, which is known risk factor of pre-
cipitating 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 re-
cieving a stable dosage of atypical antipsychotics. Previous stud-
ies of NMS in patients with Parkinson’s disease reported that in-
tercurrent respiratory or gastrointestinal tract infection could
trigger NMS development in the absence of changes in medica-
tions [7,8]. Although the mechanism underlying the relation-
ship between infection and NMS remains unclear, stress and de-
hydration associated with infection may play a role in the de-
velopment 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 ner-
vous 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 thermoregula-
tion [9], SARS-CoV-2 infection through the olfactory bulb-hy-
pothalamic network might contribute to the increased likeli-
hood of developing NMS in patient with COVID-19. Further-
more, recent experimental evidence demonstrated that dopami-
nergic neurons were more permissive to SARS-CoV-2 infection
than microglia, macrophages, or cortical neurons [10]. How-
ever, the pathophysiologic mechanism by which COVID-19 in-
creases the risk of NMS remains unclear.

In conclusion, our patient with COVID-19 developed fulmi-
nant 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, espe-
cially in patient receiving neuroleptics.

Supplementary Material

Supplementary data are available at https://doi.org/10.53991/
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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 im-
mobility, 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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Conceptualization: DHK, SHL; Investigation: DHK, MGC, JWK, HYK; Methodology: DHK, SHL; Project administration DHK; Writing-original draft: DHK, SHL; Writing-review & editing: all authors.

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References