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Neuroleptic Malignant Syndrome Concurrent with COVID-19 Infection: A Case Report

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ABSTRACT

Neuroleptic malignant syndrome (NMS), which most often occurs after the use of antipsychotics, is a rare but life-threatening condition. In this article, a 56-year-old male patient with a diagnosis of bipolar affective disorder (BPD) who developed NMS after a COVID-19 infection will be presented. The patient had been brought to the emergency room with high fever, fatigue, and slowness of movements that had been going on for two days. The examination revealed tachycardia, tachypnea, lethargy and rigidity. Upon further investigation the COVID-19 test came out positive and the serum levels of creatine kinase were considerably high. He was admitted to the psychiatric ward with diagnoses of COVID-19 infection and NMS. COVID-19 infection might have been a risk factor for NMS in this patient. Especially in patients who are taking antipsychotic drugs, if COVID-19 is present, the risk of NMS should be taken into consideration.

Keyword: COVID-19, Neuroleptic Malignant Syndrome, Risperidone, Antipsikotik, Enfeksiyon

INTRODUCTION

Coronaviruses are known as viruses that have an affinity to the nervous system (van Vuren et al. 2021). During the pandemic, there have been different peripheral and central neurological symptoms seen in COVID-19 patients. These symptoms have varied from loss of smell/taste and headaches to delirium and impaired consciousness (Mao et al. 2020). There have been different studies put forward during this period, which claim that the COVID-19 infection has effects on the central nervous system thus causing neurologic and psychiatric symptoms.

Neuroleptic malignant syndrome is a neurological emergency involving the central nervous system. We believe that COVID-19 infection might make patients who are using antipsychotics susceptible to the development of NMS. To our knowledge, five similar cases have been reported so far (Kajani et al. 2020; Soh et al. 2020; Burad and Kodange 2021; Espiridion et al. 2021). In this study, we present a COVID-19 patient with neuroleptic malignant syndrome (NMS).

CASE

A 56-year-old male patient with a diagnosis of bipolar affective disorder and a treatment history of about 10 years was brought to the emergency department due to altered consciousness. The patient was reported to be using 6 mg/day of risperidone and 1000 mg/day of valproic acid. Due to the history taken from the relatives, he had not experienced mood changes within the year and there had been no changes in his medications in the last three months. The patient was under regular follow-ups in our hospital. According to previous patient records and the history taken from his relatives, it was found out that he has not experienced any adverse effects of the extrapyramidal system before.

He had been experiencing high fever, fatigue, and slowing of movements for the last two days. The first assessment of vitals showed a fever of 40.5 °C while his blood pressure was 100/50 mmHg and his sPO2 was 95%. Tachycardia and tachypnea were observed. During the physical evaluation, it had been detected that the patient had confusion, somnolence (drowsiness), short incoherent responses to sound, and rigidity of all four limbs.

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Laboratory results showed that the blood levels of creatine kinase were 1947 IU/L; d-dimer was 2347 μg/L; white blood cells were 2690/mm^3 with lymphopenia and thrombocytopenia, and CRP was 98 mg/L. A combined nasopharyngeal swab test for COVID-19 was performed via PCR and it turned out to be positive. Chest CT revealed consolidation in the middle lobe of the right lung and ground-glass opacity in the lower lobe of the right lung.

Fever, altered mental status, and autonomic instability were interpreted to be related to the COVID-19 disease. However, additional creatine kinase increase and rigidity led to the consideration of neuroleptic malignant syndrome.

According to Levenson Criteria (Baltacıoğlu and Hocaoğlu 2019), the patient had 3 major (fever, high serum levels of creatine kinase, and rigidity) and 4 minor (altered consciousness, tachycardia, changes in blood pressure, and tachypnea) criteria of neuroleptic malignant syndrome. The diagnoses of COVID-19 disease and neuroleptic malignant syndrome were concluded and due to his autonomic instability and altered mental status, the patient was admitted to the Intensive Care Unit.

Broad-spectrum antibiotics (piperacillin-tazobactam, Moxifloxacin) and faripiravir were started for the empirical treatment of COVID-19 and pneumonia. Support treatments (dopamine, enoxaparin sodium, hydration, PPIs) and lorazepam were also given to the patient. Lorazepam was started with a dosage of 6 mg/day and the dosage was gradually reduced. There was no need for tracheal intubation due to sufficiently-high saturation follow-ups. Intermittent non-invasive mechanical ventilation with a nasal cannula (and reservoir mask when needed) was administered. During the observation and investigation period, starting drug therapy for NMS (bromocriptine, dantrolene) had not been necessary. With supportive therapy, the creatine kinase (CK) values began to decrease, and the patient's rigidity considerably improved on the third day of hospitalization (3rd day CK levels: 1245 U/L, 7th day CK levels: 566 U/L). Renal failure had not developed. Favipiravir treatment was completed in the hospital. Antibiotic therapy was stopped on the 10th day. The patient gained full consciousness, the clinical condition improved and he was discharged on the 12th day of hospitalization with informed consent.

DISCUSSION

NMS is associated with the use of antipsychotics, especially at high doses. There are various criteria for the diagnosis of NMS (i.e. Levenson, Lazarus, and Nierenberg).

According to Levenson criteria, at least 3 major criteria or 2 major and 4 minor criteria need to be present to make an NMS diagnosis (major criteria: hyperthermia, rigidity, high serum CK levels; minor criteria: altered mental status, tachycardia, changes in blood pressure, tachypnea, diaphoresis, leukocytosis).

Lazarus' criteria include "taking antipsychotic drugs in the last 7 days", while Nierenberg's criteria have "recent use of antipsychotic drugs". DSM-5 criteria indicate that during the last 72-hour period before the symptoms start, the patient needs to have taken a dopamine antagonist (Baltacıoğlu

Table 1. Neuroleptic Malignant Syndrome Diagnostic Criteria

Levenson Criteria	Lazarus Criteria	Nierenberg Criteria	DSM-5 Criteria
Major criteria -Hyperthermia -Rigidity -Elevated serum CPK (>1000 İU/L) Minor criteria -Altered consciousness -Tachycardia -Changes of blood pressure -Tachypnea -Diaphoresis - Leukocytosis	Major criteria -Treatment with neuroleptics within 7 days of onset (2-4 weeks for depot neuroleptics) -Hyperthermia -Rigidity Minor criteria -Altered consciousness -Tachycardia -Changes of blood pressure -Tachypnea -Elevated serum CPK or myoglobinuria - Leukocytosis	Essential criteria -Receiving or recently received an antipsychotic drug -Receiving another dopamine antagonist drug -Recently stopped therapy with a dopamine antagonist Major criteria -Hyperthermia (>38C°) -Muscular lead-pipe rigidity -Elevated serum CPK levels (>3 times normal) -Autonomic dysfunction -Altered consciousness Minor criteria -Other manifestations of autonomic dysfunction (e.g., urinary incontinence, arrhythmia or one of tachycardia, sweating, elevated or decreased blood pressure) - Leukocytosis -Other signs of EPS -Respiratory problems	-Exposure to dopamine antagonist within 72 hours prior to the beginning of the symptoms -Hyperthermia -Diffuse muscular lead-pipe rigidity and other neurological symptoms that are non-responsive to anti-Parkinson drugs -Elevated serum CPK levels (>4 times normal limit) -Altered consciousness -Tachycardia -Diaphoresis -Hypertension -Urinary incontinence -Tachypnea - Leukocytosis
Diagnosis: 3 major criteria or; 2 major + 4 minor criteria	Diagnosis: All three major criteria + 3 minor criteria	Diagnosis: 4 major criteria or; 3 major+3 minor criteria	

(Baltacıoğlu and Hocaoğlu 2019). DSM-5: The Diagnostic and Statistical Manual of Mental Disorders.

and Hocaoğlu 2019). It was determined that according to Levenson, Nierenberg, and Lazarus criteria, the patient had NMS (Table 1).

To our knowledge, five cases of NMS in COVID-19 patients have been reported so far. In the first patient presented by Soh et al., (2020) midazolam and fentanyl were seen as the causative agents, and these drugs were discontinued. In the second case, risperidone, which had been the causative agent, was discontinued and the deterioration of the condition was prevented. In the case report of Kajani et al., (2020) the patient was using haloperidol decanoate. In the study of Burad et al., (2021) the patient who had been observed for COVID-19 developed NMS after they were started on quetiapine. In the case study of Espiridion et al. (2021), a patient who had already been taking clozapine and risperidone developed NMS during their COVID-19-followed hospitalization. In our patient, we had seen the risperidone taken in regular daily doses by the patient as the risk factor and we stopped the risperidone use. Soh et al., (2020) also detected a connection between elevated CK levels and favipiravir treatment in influenza so they pointed out that favipiravir might be causing rhabdomyolysis. They underlined the possible connection between the use of favipiravir and NMS. On the other hand, in the case report of Kajani et al., (2020) the COVID-19 infected patient was not taking favipiravir, so they indicated that the effect of COVID-19 on the central nervous system might make patients more susceptible to the development of NMS. Other than these five cases, there was also a patient with ongoing quetiapine use who reportedly developed NMS after the COVID-19 vaccine, so the researchers warned the readers about the possible future adverse effects of the vaccine (Alfishawy et al. 2021).

Some patients with COVID-19 infection present with neurological and psychiatric symptoms. It is suggested that the SARS-CoV-2 virus causes neurological symptoms using Angiotensin Converting Enzyme (ACE2) receptors located in the nervous system. In addition, psychiatric disorders were thought to be related to COVID-19-caused biological stress. It was also claimed that a pre-existing psychiatric disease or psychotropic drug use might increase the risk of a COVID-19-related psychiatric condition (van Vuren et al. 2021).

Our patient had a bipolar disorder diagnosis and was using risperidone when he developed NMS. The patient had experienced fever, rigidity, alteration in consciousness, autonomic instability, and they had high serum CK levels. These symptoms were present before the favipiravir use. As seen in our patient, we believe that COVID-19 infection makes patients more susceptible to NMS development because of the infection's central effects.

The first step of the NMS treatment is to cease the predisposing antipsychotic drugs in time. After that, the treatment follows a supportive care and supportive pharmacotherapy (Pleggi and Cook 2016). In the case we presented, even the cessation of the antipsychotic drug, which was possibly the cause, was enough to improve the condition with some supportive treatment. NMS is a rare but highly mortal adversity of antipsychotics (Ware et al. 2018). For adequate measurements, NMS needs to be recognized fast (Ware et al. 2018). Therefore, when antipsychotic treatment is needed during any infection, especially in COVID-19, the risk of NMS should be taken into consideration when making psychiatric treatment choices for conditions such as agitation or delirium.

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