CASE REPORT

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A Case of Neuroleptic Malignant Syndrome After COVID-19 Vaccination and Possible Mechanisms of Vaccines in the Formation of This Syndrome

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ABSTRACT

Neuroleptic malignant syndrome is characterized by muscle stiffness, hyperthermia, autonomic dysfunction, elevation in serum creatine phosphokinase, and changes in consciousness, which usually occur due to the side effects of life-threatening neuroleptic and antipsychotic drugs, and it can cause high mortality. A few cases of neuroleptic malignant syndrome associated with coronavirus disease 2019 infection and vaccination have been reported in the literature. Our case presented with epileptic seizure and neuroleptic malignant syndrome signs 10 days after receiving a single dose of the BNT162b2 vaccine when under low-dose olanzapine treatment with a diagnosis of autism and epilepsy. According to the laboratory test, the creatine kinase value was very high, there was hyponatremia, and the iron value was low. The patient died. Our aim in reporting this case is to draw attention to the possibility that coronavirus disease 2019 vaccines may trigger neuroleptic malignant syndrome, which can be a fatal complication in patients taking antipsychotics, albeit very rare among the large vaccinated population.

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare but sometimes fatal side effect that has been described in patients receiving neuroleptic therapy. Neuroleptic malignant syndrome can occur due to the use of conventional and atypical neuroleptics, tricyclic antidepressants with D2 receptor antagonists, metoclopramide, and the abrupt discontinuation of dopaminergic drugs for the treatment of Parkinson's disease. It is mainly characterized by fever and rigidity. In addition, findings such as impaired consciousness, autonomic instability, and laboratory findings, for example, elevated creatine kinase (CK), leukocytosis, elevated liver enzymes, and low serum iron (Fe) or potassium levels, can occur.[1] The coronavirus disease 2019 (COVID-19) pandemic has been affecting the world for 2 years. Strict quarantine measures are insufficient to contain the spread of the virus. It is widely accepted by the scientific community across the world that vaccination is the most important weapon in the control of the pandemic. Different vaccines have been developed against the virus causing the disease, using viral vectors, mRNA technology, and inactivated vaccine (using the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) techniques.[2] Due to the persistence of the pandemic, its impact on the whole world, high mortality and morbidity rates, additional burden on the health systems of the countries and damage it causes, vaccines have started to be used without waiting for the results of phase 4 on a global scale. Therefore, we do not yet have any clear information about the long-term side effects and rare side effects associated with vaccination.[3,4] In this article, we report a case of NMS as a possible complication after BNT162b2 vaccination.

CASE PRESENTATION

A 30-year-old male patient, who was followed up with the diagnosis of autism and epilepsy and had been using olanzapine 5 mg/day for a long time, was referred to the emergency department by his family with the complaints of persistent fever lasting for 3 days, drowsiness, widespread pain, and seizures that had started on the day of presentation. The patient, who was known to have not used any antiepileptic drugs for about 12 years and had no seizures for 15 years, was administered intravenous

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midazolam 5 mg due to a generalized tonic-clonic epileptic seizure lasting about 15 minutes. Convulsions ended after the treatment. It was determined that the patient had been examined by a physician 3 days earlier and prescribed 1500 mg/day paracetamol and 2000 mg/day ceftriaxone due to a high fever, which could not be controlled. According to his medical history, he had long been followed up by psychiatry for autism and he had been regularly taking olanzapine at 5 mg/day due to behavioral problems, with no change in dose. It was also determined that the patient had received the first dose of the BNT162b2 vaccine 10 days earlier as part of the vaccination program against COVID-19. The results of the neurological examination showed a poor general condition and unconsciousness. Widespread rigidity and the cogwheel sign were detected in all 4 extremities, pupils were isochoric, direct and indirect light reflexes were bilaterally normal, and the plantar response was bilaterally flexor. At the time of admission, his body temperature was measured as 40.1 ˚C, and he was resistant to antipyretic therapy. His arterial blood pressure was 80/55 mmHg, and his heart rate was 152 beats per minute. No pathology was detected in brain computed tomography (CT) imaging and thorax CT. Since the patient weighed 140 kg, cranial magnetic resonance imaging (MRI) could not be performed because the MRI device in our center is not suitable for obese patients. The laboratory values of the patient are shown in Table 1. The CK value was over 30 699 986 U/L and was too high to be explained by a 15-minute epileptic seizure. This value was attributed to the very severe rhabdomyolysis in the patient. In addition, the sodium value was 111 mEq/L, indicating severe hyponatremia; the serum Fe value was 13 µg/dL; and the serum albumin value was 3 g/dL. No abnormality was observed in the complete urinalysis or blood-urine cultures. There was no primary focus of infection to explain the patient's fever. After the examination and laboratory findings, the patient met the diagnostic criteria for the NMS[5] diagnosis and was admitted to the intensive care unit. The patient was intubated and started on norepinephrine, bromocriptine, and hypertonic fluid support. Cardiac arrest developed about 3 hours after hospitalization. The patient was declared dead in the third hour of his hospital stay.

Table 1. Laboratory Values

Serum level	Value in the Case	Reference Range
CK	30 699 986	30-200 U/L
AST	281	0-50 U/L
ALT	58	0-50 U/L
LDH	1004	90-250 IU/L
Urea	18.2	15-45 mg/dL
Creatinine	1.27	0.5-1.25 mg/dL
Na	111	136-148 mmol/L
K	4.2	3.5-5.2 mmol/L
Cl	90	96-116 mmol/L
Ca	7.6	8.4-10.6 mg/dL
CRP	0.19	0-0.5 mg/dL
ESR	97	0-15 mm/h
Fe	13	60-160 µg/dL
WBC	19.63	4.6-10.2 × 10^3/µL
Hg	13.7	12.2-18.1 g/dL
Hct	39.7	37.7-53.7%
Trb	305	142-424 × 10^3/µL
Albumin	3	3.5-5.5 g/dL

CK, creatine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Fe, serum iron; WBC, white blood cell; Hg, hemoglobin; Hct, hematocrit; Trb, thrombocyte.

Informed consent form approval was obtained from the patient's family for this case report.

MAIN POINTS

- Vaccines can have complications affecting the central nervous system, peripheral nervous system, and muscular system.
- Although the pathophysiology of neuroleptic malignant syndrome (NMS) has not been clarified, it is considered to be due to decreased dopaminergic activity. Recently, it has been emphasized that NMS is associated with the acute phase response due to decreased dopaminergic activity.
- This is the second reported and first fatal NMS case diagnosed after the BNT162b2 vaccination.
- Rare complications of vaccines are now more frequently reported due to vaccination programs being implemented in large populations. Vaccination can trigger the acute phase response, and, although rare, it can have the potential to create NMS in patients using antipsychotics.

DISCUSSION

Neuroleptic malignant syndrome is a life-threatening syndrome with a high mortality rate, which mostly occurs as a result of the side effects of neuroleptics and antipsychotics.[6] Therefore, the risk of death is between 10% and 30%, and the most common causes of death are arrhythmia, respiratory failure, kidney failure, and severe dysfunction of the cardiovascular system.[7] Muscle stiffness, hyperthermia, autonomic dysfunction, elevated serum CK and transaminase levels, leukocytosis, and changes in consciousness (confusion, agitation) can be observed in this syndrome.[8] Several opinions have been suggested for the pathophysiology of NMS, but the underlying cause has still not been fully revealed. The primary explanation is the functional impairment of dopaminergic receptors. The second explanation mainly implicates muscle mitochondrial dysfunction as a cause of NMS. Another explanation suggests that a functional disorder of the sympathetic nervous system triggers the event. Regarding the etiopathogenesis of NMS, there has recently been an interest in the role of

acute-phase reactants and inflammatory response in NMS. Yet, it remains unclear whether this is a causal factor or a consequence of NMS.[9] Hyperthermia is explained by the decrease in dopaminergic activity in the hypothalamus, and rigidity findings are explained by the decrease of dopaminergic activity in the nigrostriatal pathway. However, since this view is insufficient to explain all symptoms, other neurotransmitters are considered to accompany the pathophysiology.[10] Neuroleptic malignant syndrome can occur after a single dose of a neuroleptic or after many years of treatment with the same active ingredient at the same dose. It is not a dose-related condition, but the use of higher doses is a risk factor for NMS. In addition, a recent or rapid dose increase, switching from one drug to another, and parenteral administration have been reported as other risk factors.[10] It has also been suggested that acute phase response may cause NMS.[11] It is known that vaccination and administration of antigens to the body stimulate macrophages and dendritic cells, resulting in an acute phase response by increasing the release of inflammatory cytokines. The plasma levels of a number of microminerals including Fe can cause changes in disorders of homeostasis during the acute phase response.[12] Fe is necessary for dopaminergic receptors to perform their normal function, and its deficiency causes a disorder of dopaminergic activity.[13,14] The serum Fe value measured in our case was 13 µg/dL, which was considerably lower than the normal limit. We think that this may explain the decrease in dopaminergic activity. In addition, the patient also had a low albumin value, which is a sign of the acute phase response. The serum concentrations of the drugs used may vary due to fluctuations in serum protein levels and decreased serum albumin expression levels during the acute phase response.[12] Olanzapine binds to plasma proteins at a rate of 93%, with most of these proteins being albumin and α1-acid glycoprotein.[15] Due to the decrease in serum albumin, the amount of free olanzapine may increase, causing a dose increase-like response. In an article by Anglin et al[11], it was suggested that viral infection might lead to decreased tolerance to drugs by changing immune regulation, and accordingly NMS might be associated with a virus–drug interaction by triggering a fulminant acute phase response of a predisposing viral disease to antipsychotic drugs.[11] Soh et al reported NMS in 2 patients followed up due to SARS-CoV-2 pneumonia. The first case was associated with the use of fentanyl, propofol, midazolam, and favipiravir, while the second case was associated with the use of favipiravir and risperidone.[16] In February 2021, Alfishawy et al reported the first case of NMS associated with the BNT162b2 vaccine. The patient was a 72-year-old male patient with dementia and bipolar disorder, who was using quetiapine. The patient was vaccinated with the BNT162b2 vaccine 16 days prior to the development of NMS.[17] Our case is the second reported NMS case after COVID-19 vaccination. It differs from the first reported case because laboratory parameters at admission were compatible with NMS, the prognosis was clinically poor, and the patient died. The neurological complications of the BNT162b2 vaccine that affect the central and peripheral nervous systems, such as Guillain-Barre syndrome, lumbar radiculopathy exacerbation, transverse myelitis, syncope, and seizure have also been described.[13] mRNA vaccines including BNT162b2 have been reported to act as both an antigen and an adjuvant. mRNA vaccines are recognized by endosomal toll-like receptors and cytosolic inflammatory components, triggering inflammation and immune response. Moreover, molecular similarities in vaccines and viruses can trigger inflammation and immune response.[18] It has been shown that patients with a history of NMS have significantly more autoantibodies against neurotransmitter receptors compared to healthy control patients.[11] In this context, vaccines may have the potential to trigger NMS by activating the acute phase response or immune response. In the current case, a decrease was observed in the ratio of serum Fe and albumin, which are negative acute phase reactants. The presence of a systemic infection that would trigger the acute phase response was excluded by blood-urine culture analysis, thorax CT, and complete urine analysis. In addition, there was no elevation in C-reactive protein to explain the fever resistant to antipyretics. Since the patient did not have a significant inadequacy of oral intake until the last day, a nutritional disorder that would cause severe dehydration and hypoalbuminemia was not considered. There was also no change in the dose of antipsychotic medication used by the patient recently. Paracetamol and ceftriaxone, which were administered due to a high fever, have not been associated with any cases of NMS. No risk factors that could trigger the acute phase response, other than vaccination, were identified for this case. No lesion was observed on brain CT that could explain the deterioration in consciousness. The autoimmune encephalitis panel could not be studied since our patient died at the third hour of hospitalization. The laboratory results were consistent with many articles in the literature reporting the association of hyponatremia with NMS and hyponatremia.[19] Hyponatremia is a risk factor for the formation of NMS[20] and one of the electrolyte disorders that accompany this syndrome. Yet, this condition has been associated with cerebral salt loss that develops during NMS.[19] A serum sodium level below 120 mmol/L can cause neurological symptoms.[21] Deep hyponatremia in our patient may have adversely affected clinical manifestation, by triggering an epileptic seizure and worsening consciousness.

In the literature, NMS is observed more often in people with speech and behavioral disorders, and a history of neurological diseases, which are evaluated as risk factors for NMS.[22] However, there are no studies suggesting that epilepsy increases the risk of NMS. In our case, the patient had not had a seizure or used antiepileptics for a long time. Therefore, we did not consider epilepsy to be the cause of

NMS. However, the seizure triggered during resistant fever may have contributed to an increase in the level of CK. This may have had a negative effect on the prognosis.

Our limitations in evaluating this patient include the inability to perform a cerebrospinal fluid examination or study the autoimmune encephalitis panel since the patient died within the first 3 hours of hospitalization. We were also not able to perform cranial MRI due to the patient being obese. Our aim in reporting this case is to draw attention to the possibility that COVID-19 vaccines may trigger NMS, which can be a fatal complication in patients taking antipsychotics today, albeit very rare among the large vaccinated population.

Informed Consent: Informed consent form approval was obtained from the patient's family for this case report.

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