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Neuroleptic Malignant Syndrome with Adrenal Insufficiency After BNT162b2 COVID-19 Vaccination in a Man Taking Valproate: A Case Report

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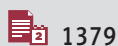
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Patient: Male, 48-year-old
Final Diagnosis: Neuroleptic malignant syndrome
Symptoms: Altered mental status • fatigue • fever • generalized weakness • loss of appetite
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine • Endocrinology and Metabolic • Neurology

Objective: Unusual clinical course
Background: Considering the ongoing coronavirus disease 2019 (COVID-19) pandemic, sufficient information about common and serious adverse events is needed to rapidly distribute COVID-19 vaccines worldwide. We report a case of neuroleptic malignant syndrome (NMS) with adrenal insufficiency after initial vaccination with Pfizer/BioNTech BNT162b2.
Case Report: A 48-year-old man presented to the Emergency Department with fever and an altered mental status 7 days after receiving the first dose of the BNT162b2 COVID-19 vaccine. The patient had a history of end-stage renal disease and epilepsy treated with valproate. He was diagnosed with NMS based on the clinical findings of hyperthermia, muscular rigidity, and an elevated creatine kinase level. Additionally, a reduction in the response of cortisol to adrenocorticotropic hormone (ACTH) stimulation was observed in the rapid ACTH stimulation test. The patient was treated with dantrolene, bromocriptine, and hydrocortisone, and he responded well to treatment. Dantrolene and bromocriptine were tapered off over 4 weeks. Hydrocortisone was also tapered, and the patient was discharged on oral hydrocortisone (30 mg).
Conclusions: The present case suggests a possible link between the BNT162b2 COVID-19 vaccine and NMS with adrenal insufficiency based on the temporal relationship between vaccine administration and disease onset, although the patient was taking valproate, a potential cause of NMS. Having a high level of suspicion is important because the diagnosis of NMS with adrenal insufficiency is often challenging due to non-specific clinical manifestations. However, this case does not negate the utility of vaccination because these complications are extremely rare and can be treated with early diagnosis and proper management.

Keywords: Adrenal Insufficiency • COVID-19 Vaccine • Neuroleptic Malignant Syndrome

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/936217>



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Background

The development of efficient vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is essential to overcome the ongoing coronavirus disease 2019 (COVID-19) pandemic. To date, various COVID-19 vaccines have been authorized for use worldwide [1]. However, COVID-19 vaccination rates remain below the target level required to control the COVID-19 pandemic in most countries [2]. Many people are concerned about vaccine-related adverse events, which is one of the major reasons why vaccination rates remain stagnant. As vaccines have become widespread, reports of unexpected adverse events have increased, in addition to common adverse events such as fever, myalgia, arthralgia, nausea, fatigue, and pain at the injection site [3]. Although most adverse events of the vaccines are mild or moderate in severity and usually resolve on their own, several adverse events are serious and occasionally require intensive care. Further accumulation of evidence is required for the early diagnosis and treatment of serious adverse events associated with hospitalization and death, considering the widespread distribution of COVID-19 vaccines.

Here, we present a case of neuroleptic malignant syndrome (NMS) with adrenal insufficiency after initial vaccination with the Pfizer/BioNTech BNT162b2 COVID-19 vaccine. NMS is an uncommon but potentially life-threatening neurological disorder. To the best of our knowledge, there have only been 2 previous reports of NMS after COVID-19 mRNA vaccination [4,5]; however, this case differed from the previous cases because it was complicated by adrenal insufficiency.

Case Report

A 48-year-old Japanese man presented to the Emergency Department with fever (temperature >38°C), generalized weakness, and an altered mental status, 7 days after receiving the first dose of the BNT162b2 COVID-19 vaccine. The patient also reported fatigue and loss of appetite. These symptoms occurred the day after the vaccination. The patient had a medical history of epilepsy and end-stage renal disease due to glomerulonephritis. The patient was receiving 1200 mg of valproate daily and 1000 mg of levetiracetam daily for seizure prophylaxis and had remained seizure-free for over 5 years without changing his medication. Although he had a history of glucocorticoid therapy for glomerulonephritis, the glucocorticoid was discontinued over 4 years previously. The patient smoked (20 pack-years) and drank socially. On presentation, his temperature was 40.1°C, blood pressure was 118/79 mmHg, heart rate was 132 beats per minute, respiratory rate was 22 breaths per minute, and oxygen saturation was 94% on room air. His Glasgow Coma Scale score was 12.

Table 1. Laboratory data of the patient.

	First hospital day	Second hospital day
Biochemistry/immunology		
Creatine kinase (U/L)	1338	3191
Lactate dehydrogenase (U/L)	311	345
Aspartate aminotransferase (U/L)	89	139
Alanine aminotransferase (U/L)	36	50
Alkaline phosphatase (U/L)	43	41
Total bilirubin (mg/dL)	0.7	–
Blood urea nitrogen (mg/dL)	45	48
Serum creatinine (mg/dL)	6.15	5.68
Estimated GFR (ml/min/1.73 m ²)	8.8	9.6
Serum sodium (mEq/L)	137	135
Serum potassium (mEq/L)	4.7	3.5
Serum chloride (mEq/L)	99	100
Serum calcium (mg/dL)	9.7	–
Serum phosphorus (mg/dL)	2.0	–
Serum albumin (g/dL)	3.2	2.9
C-reactive protein (mg/dL)	19.7	21.8
Antinuclear antibody (titer)	–	1: 40
MPO-ANCA (U/mL)	–	< 1.0
PR3-ANCA (U/mL)	–	< 1.0
Complete blood cell count		
White blood cell (/μL)	8610	6150
Neutrophil (%)	52.4	75.0
Lymphocyte (%)	27.8	9.3
Monocyte (%)	16.3	10.2
Eosinophil (%)	3.0	5.0
Red blood cell (/μL)	356×10 ⁴	332×10 ⁴
Hemoglobin (g/dL)	11.2	10.3
Hematocrit (%)	31.3	29.7
Platelet (/μL)	16.1×10 ⁴	14.1×10 ⁴

GFR – glomerular filtration rate; MPO-ANCA – myeloperoxidase-anti-neutrophil cytoplasmic antibodies; PR3-ANCA – proteinase-3-anti-neutrophil cytoplasmic antibodies.

Table 2. Endocrinological data of the patient.

	Reference range	
Thyroid-stimulating hormone (μIU/mL)	0.488	0.35-4.94
Free thyroxine (ng/dL)	0.79	0.70-1.48
Free triiodothyronine (pg/mL)	1.67	1.68-3.67
ACTH (pg/mL)	7.6	7.2-63.3
ACTH (250 μg) stimulation test		
Cortisol (base) (μg/dL)	1.9	3.7-19.4
Cortisol 30 min (μg/dL)	4.4	
Cortisol 60 min (μg/dL)	5.8	

ACTH – adrenocorticotropic hormone.

A physical examination revealed diaphoresis and muscle rigidity in both the upper and lower extremities. The initial laboratory investigation revealed elevated creatine kinase (CK) of 1338 U/L, elevated C-reactive protein (CRP) of 19.7 mg/dL, and mild elevation in serum aspartate aminotransferase and alanine aminotransferase (Table 1). A complete blood count revealed mild anemia and no leukocytosis (Table 1). The following day, the muscle rigidity worsened, and the CK increased to 3191 U/L. Computed tomography (CT) of the head, chest, and abdomen and magnetic resonance imaging (MRI) of the head showed no cause of fever, including infectious diseases and malignancy. Urine and blood cultures were sterile. The cerebrospinal fluid analysis was unremarkable. Loop-mediated isothermal amplification testing for SARS-CoV-2 was negative. The patient was diagnosed with NMS based on the clinical findings of hyperthermia, muscular rigidity, and elevated CK levels [6]. The patient was started on intravenous dantrolene on the third hospital day, which was gradually increased to 40 mg every 6 h, and started on a 2.5-mg dose of bromocriptine 3 times a day on the seventh hospital day. The muscle rigidity gradually improved within a few days, and the CK level decreased to 65 U/L on the ninth hospital day. However, the fever (approximately 38°C) and elevated CRP (>20 mg/dL) continued. While reviewing the laboratory data at admission, adrenocorticotropic hormone (ACTH) and cortisol levels were relatively low (7.6 pg/mL and 5.1 μg/dL, respectively) despite a high stress condition. To confirm the hypothesis of adrenal insufficiency, hormonal laboratory tests were performed for further investigation (Table 2). The intravenous rapid ACTH (250 μg) stimulation test revealed that the cortisol levels were 1.9, 4.4, and 5.8 μg/dL at baseline, 30 min, and 60 min, respectively, indicating a reduction in the response of cortisol to exogenous ACTH. The fever rapidly improved after the initiation of intravenous hydrocortisone (50 mg every 6 h) on the tenth hospital day. In addition, CRP levels started to decrease

with hydrocortisone treatment and normalized 14 days later. Dantrolene and bromocriptine were tapered over 4 weeks and discontinued. Hydrocortisone was also tapered, and the patient was discharged on a 15-mg dose of hydrocortisone twice a day. Antiepileptics were not discontinued during the hospitalization. The patient has been scheduled for a follow-up consultation with an endocrinologist.

Discussion

NMS is a potentially life-threatening neurological emergency with a mortality rate of 5.6%, and early diagnosis and prompt treatment are required to reduce mortality [7]. NMS usually develops after a sudden increase or decrease in the dose of medications that affect dopaminergic system neurotransmission [8]. Although typical antipsychotics are well-known causative agents of NMS, atypical antipsychotics and antiepileptics, including valproate, can cause or are related to NMS [9,10]. Additionally, several recent papers have described patients who developed NMS during treatment for COVID-19 [11,12]. In our patient, the BNT162b2 COVID-19 vaccine was suspected to be the causative agent, mainly due to the temporal relationship between vaccine administration and disease onset. In this case, valproate was administered; however, the patient had been taking it for a long time, and the dose had been unchanged for more than 5 years before the development of NMS, which was different from the reported cases of NMS associated with valproate [10,13]. Moreover, our patient responded well to the treatment for NMS without withdrawal or change of valproate, although the discontinuation of causative agents is one of the first-line treatments for NMS [14]. Therefore, we concluded that the BNT162b2 COVID-19 vaccine, but not the antiepileptic drug, was the most likely etiology for the NMS. However, considering some evidence suggesting that valproate can predispose to NMS [10,15], valproate might have partially contributed to the development of NMS in this case.

Adrenal insufficiency is also a serious condition that can be potentially life-threatening if not properly treated [16]. Several recent studies have reported the involvement of COVID-19 vaccination in adrenal insufficiency [17,18]. Maguire et al reported that the ChAdOx1 nCoV-19 vaccine precipitated adrenal crises in patients treated for adrenal insufficiency, suggesting that increasing the maintenance glucocorticoid dose may be required when COVID-19 vaccines are administered to patients with adrenal insufficiency [17]. Furthermore, hypophysitis following vaccination with Moderna mRNA-1273 and adrenal insufficiency caused by bilateral adrenal hemorrhage associated with ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia have been described in other cases [18]. Our case was different from the previously reported cases in that there was neither a history of adrenal insufficiency nor

CT and MRI findings showing abnormalities in the hypothal-amo-pituitary-adrenal axis. Our case suggests that everyone with or without a medical history of adrenal insufficiency can develop adrenal insufficiency following COVID-19 vaccination and that people with a history of steroid treatment may need to be carefully followed up. A high level of suspicion for adrenal insufficiency is required because the initial clinical manifestations of adrenal insufficiency, including fatigue, arthralgia, and nausea [19], are often non-specific and they partially overlap with COVID-19 vaccine adverse events.

Several cases of NMS accompanied by adrenal insufficiency have been reported [20,21]. Those patients easily recovered from NMS in response to corticosteroid supplementation. The potential mechanism remains unclear. However, because cortisol regulates dopamine levels [22], it may affect the pathogenesis of NMS. Cortisol deficiency may exacerbate symptoms, including high fever. In our case, corticosteroid supplement therapy ameliorated the symptoms dramatically. Cortisol deficiency seems to have contributed to symptom deterioration.

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Conclusions

This report describes a case of NMS and adrenal insufficiency following BNT162b2 COVID-19 vaccination, and both are difficult to diagnose due to non-specific clinical manifestations and are potentially life-threatening. This case highlights the potential for serious adverse events associated with COVID-19 vaccines, although the patient was taking valproate, a potential cause of NMS. However, we do not intend to negate the utility of vaccination because these complications are notably rare and can be treated with early diagnosis and proper management. More research is required to determine the relationship between COVID-19 vaccines and these complications.

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