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Case Report

Adrenal Crisis Secondary to COVID-19 Vaccination in a Patient With Hypopituitarism

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ABSTRACT

Background/Objective: Adrenal crisis (AC) is an acute life-threatening condition that can occur in patients with primary or secondary adrenal insufficiency who are already receiving glucocorticoid replacement therapy or can be a first presentation of adrenal insufficiency. Vaccination with tetanus, diphtheria, and pertussis, influenza, and pneumococcal vaccines has been reported as a cause of AC. Here, we aimed to present a case of AC precipitated by COVID-19 messenger RNA vaccination in a patient with hypopituitarism.

Case Report: A 74-year-old male patient with hypopituitarism received the second dose of the messenger RNA (BNT162b2) COVID-19 vaccine and after a few hours developed lethargy and confusion followed by fever. In the next day, the patient was more somnolent and unable to converse. His temperature and heart rate were 103.5 °F and 105 beats/min, respectively, and his blood pressure was 145/84 mm Hg, which decreased to 107/71 mm Hg. The patient was stuporous, responsive only to painful stimuli. A stress dose of glucocorticoids was started with improvement in all symptoms in 24 hours of treatment initiation.

Discussion: Vaccination with ChAdOx1 SARS-CoV-2 vaccine has been recognized as a cause of AC in patients with adrenal insufficiency. The present case report additionally demonstrates that different types of COVID-19 vaccines may be a cause of AC in patients with adrenal insufficiency.

Conclusion: A twofold to threefold increase in the maintenance dose of glucocorticoid is recommended if the patient is experiencing any symptom after COVID-19 vaccination. This treatment may reduce the risk of AC occurring after COVID-19 vaccination in patients with hypopituitarism.

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Introduction

Adrenal crisis (AC) is an acute life-threatening condition that can occur in patients with primary or secondary adrenal insufficiency who are already receiving glucocorticoid replacement therapy that does not meet the increased need for cortisol or can be a first presentation of undiagnosed adrenal insufficiency. AC may be precipitated in patients with primary or secondary adrenal insufficiency by infection and other major stresses, such as surgery, psychological stress, extreme physical activity, and forgetting or

discontinuing glucocorticoid therapy.^{1,2} Vaccination with tetanus, diphtheria, and pertussis (Tdap), influenza, and pneumococcal vaccines on the same day is also reported as a cause of AC.³

Recently, a case series⁴ of 5 patients who developed actual or incipient AC after ChAdOx1 SARS-CoV-2 vaccination in the United Kingdom was published. Of these patients, 2 had hypopituitarism, and 3 had Addison disease before vaccination.⁴ Here, we report a case of AC precipitated by COVID-19 messenger RNA (mRNA) (BNT162b2) vaccination in a patient with hypopituitarism. Informed consent was obtained from the patient.

Case Report

A 74-year-old male patient presented to the emergency department (ED) with altered mental status and fever. His past medical history was significant for prolactinoma with surgical

Abbreviations: AC, adrenal crisis; ED, emergency department; mRNA, messenger RNA; Tdap, tetanus; diphtheria, and pertussis.

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resection (in the 1980s) and subsequent hypopituitarism on hormone replacement therapy, type 2 diabetes mellitus, and essential hypertension. The patient received his first dose of COVID-19 mRNA vaccine (BNT162b2) on March 09, 2021, and the second dose of the same vaccine 3 weeks after the first dose at 1 PM; after a few hours, he experienced lethargy and confusion. Overnight, the patient developed fever, which was treated with acetaminophen. In the next day, patient was unable to converse and was more somnolent and sleeping for >24 hours. The Emergency Medical Services was called; the patient was found to have a blood glucose level of 20 mg/dL and bilateral miosis and was treated with intravenous dextrose and naloxone without improvement of mentation. The patient did not have any recent sick contact, travel, change in medications, or illicit drug use. At-home medications for hypopituitarism included hydrocortisone 10 mg twice daily, levothyroxine 150 mcg daily, desmopressin 0.1 mg half of tablet twice daily, testosterone gel, and diabetes mellitus treatment with insulin glargine 20 units at bedtime, glipizide 2.5 mg twice daily, and sitagliptin 100 mg daily. On arrival to the ED, the patient's vital signs were significant for fever of 103.5 °F, heart rate of 105 beats/min, and blood pressure of 145/84 mm Hg, which subsequently decreased to 107/71 mm Hg. The patient was stuporous, responsive only to painful stimuli with no focal deficit on physical examination. Workup in the ED revealed a serum blood glucose level of 143 mg/dL and normal complete metabolic panel and complete blood cell count results. Further workup included cortisol, thyroid-stimulating hormone, and free thyroxine levels of 1.91 µg/dL, 0.006 µIU/mL, and 1.90 ng/dL, respectively. The urinary toxicology screening result was negative, and the blood alcohol level was undetectable. The findings of computed tomography of the head and computed tomography angiography were negative for any acute central nervous system pathology. During the first day of hospital stay, lumbar puncture was performed, and the cerebrospinal fluid analysis results were within the normal limits with negative viral and bacterial cultures. The patient was started on parenteral glucocorticoids and after 24 hours of intravenous hydrocortisone 50 mg every 6 hours patient had significant improvement in mental status, became more awake, oriented to himself, place, and eventually time. He was discharged on oral hydrocortisone with plan to taper the dose down to his maintenance dose.

Discussion

Here, we described a clinical presentation of AC due to mRNA COVID-19 vaccine in a patient with hypopituitarism. AC is an acute life-threatening condition that contributes to the excess mortality in patients with adrenal insufficiency for which timely recognition and adequate treatment are needed.⁵⁻⁷

The most common precipitators of AC are gastroenteritis, infections, surgical procedures without adequate steroid coverage, emotional stress, pregnancy, and strenuous physical activity;^{2,6} vaccination is rarely reported.^{3,4}

The incidence of AC because of vaccinations is unknown, and considering that infection is one of the leading causes of AC, adequate immunization against different pathogens in patients with adrenal insufficiency is crucial.³ In addition to the case report³ of AC occurring after administration of Tdap, pneumococcal, and influenza vaccines, recently, a case series⁴ of AC occurring after administration of the first dose of the Astra-Zeneca ChAdOx1 SARS-CoV-2 vaccine in the United Kingdom was published. Five patients experienced AC a few hours to 1 day following immunization, and 2 of them had hypopituitarism and were

Highlights

- This case report additionally describes that different types of COVID-19 vaccines can be a precipitator of adrenal crisis (AC).
- Medical professionals need to be aware of the risk of AC after vaccination in patients with hypopituitarism.
- A twofold to threefold increase in the maintenance dose of glucocorticoid is recommended if the patient is experiencing any symptoms after COVID-19 vaccination.

Clinical Relevance

This is a case report of adrenal crisis (AC) secondary to COVID-19 vaccination with the BNT162b2 vaccine. Considering frailty of the patients with adrenal insufficiency and hypopituitarism, physicians need to be aware of the risk of AC after vaccination, which is most likely related to stress response and adverse reactions. The use of the sick day rule, which means doubling the dose of glucocorticoids if the patient is experiencing any symptoms after vaccination, is recommended.

receiving daily hydrocortisone replacement before vaccination.⁴ This represents the same initial diagnosis and chronology of symptoms occurrence as the present case report but in the settings of 2 different vaccines.

The ChAdOx1 SARS-CoV-2 (Astra-Zeneca) and mRNA (Pfizer/BioNTech) vaccines use different mechanisms with the overall goal of the production of viral protein to initiate immune response. Although ChAdOx1 SARS-CoV-2 vaccine uses recombinant replication-deficient chimpanzee adenovirus vector to deliver the genetic code of the SARS-CoV-2 spike glycoprotein, Pfizer/BioNTech vaccine contains mRNA that encodes the entire S protein containing immunogenic epitopes of the virus.^{4,7} This mRNA is delivered by lipid nanoparticles to prevent quick disintegration of mRNA.⁷ The present case report additionally demonstrates that different types of vaccines used for the first time in humans (mRNA vaccine) can precipitate the same reaction as that of the ChAdOx1 SARS-CoV-2 vaccine, which has a mechanism of action similar to those of prior vaccines, such as the influenza and Middle East respiratory syndrome vaccines. Both BNT162b2 and ChAdOx1 SARS-CoV-2 vaccines have the same main adverse reactions, including pain, erythema and swelling at the injection site, weakness, myalgia, fever, and chills.^{7,8} Major and Chacko³ described that AC in a patient receiving Tdap, pneumococcal, and influenza vaccine on the same day was secondary to fever and gastroenteritis caused by vaccination. Similar to the infection process, Maguire et al⁴ described that acute-onset and marked adverse reactions following ChAdOx1 SARS-CoV-2 vaccination, including high fever and associated stress, can precipitate AC. In the present case report, the second dose of the mRNA COVID-19 vaccine triggered AC in a patient receiving a maintenance dose of glucocorticoids. It is possible that vaccination and immune cell response combined with adverse reactions, including fever, following vaccination represent stress reactions that lead to AC in a frail patient with adrenal insufficiency. However, currently, there is no information about the incidence of AC due to any vaccination and whether different types of vaccines are more likely to cause AC.

The Society for Endocrinology and Korean Endocrine Society recommend using the sick day rule if the patient is not feeling

well and experiences symptoms after COVID-19 vaccination, which would also be our recommendation.^{9,10} The sick day rule means increasing the daily replacement dose of hydrocortisone 2 to 3 times if the patient experiences any symptom after COVID-19 vaccination (most commonly fever, myalgia, and chills).^{9–11} The Pituitary Society based on the recently conducted survey reported that 36% of physicians plan to increase glucocorticoid dosage with COVID-19 vaccination, whereas 64% do not plan to increase the dosage of replacement therapy with vaccine administration but plan to do so if symptoms of fever, myalgia, or arthralgia develops.¹² The established preventive measures of AC in patients with adrenal insufficiency should be continued, including education on stress dosing and parenteral glucocorticoid administration, wearing steroid dependency alert card or medical alert bracelet, and being equipped with emergency hydrocortisone kit.^{2,4,13}

Conclusion

In addition to the ChAdOx1 SARS-CoV-2 vaccine causing AC, we presented a case in which vaccination with the mRNA COVID-19 vaccine (BNT162b2) can also be a precipitator of AC in a patient with adrenal insufficiency. A twofold to threefold increase in the maintenance dose of glucocorticoid is recommended if the patient is experiencing any symptom after COVID-19 vaccination. This treatment may reduce the risk of AC occurring after COVID-19 vaccination in patients with hypopituitarism and adrenal insufficiency.

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Disclosure

The authors have no multiplicity of interest to disclose.

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