*JCEM Case Reports*, 2023, **1**, 1–5
https://doi.org/10.1210/jcemcr/luad079
Advance access publication 14 August 2023
**Case Report**

# Adrenal Crisis Associated With COVID-19 Vaccination in Patients With Adrenal Insufficiency

**Yukako Kurematsu, Takako Mohri, Sadanori Okada, and Yutaka Takahashi**

Department of Diabetes and Endocrinology, Nara Medical University, Kashihara 634-8522, Japan
**Correspondence:** Yutaka Takahashi, MD, PhD, 840 Shijo-cho, Kashihara 634-8522, Japan. Email: takahash@naramed-u.ac.jp.

## Abstract

Vaccination is generally recommended for patients with adrenal insufficiency receiving glucocorticoid replacement therapy because they are at risk of experiencing adrenal crisis during infections. Conventional vaccinations, such as those for influenza virus, have rarely been associated with adrenal crisis in patients with adrenal insufficiency; therefore, increasing the glucocorticoid dose during vaccination is not necessarily recommended. The COVID-19 mRNA vaccines exhibit a higher degree of adverse reactions, including fever and general fatigue, than those of conventional vaccines. Here, we present 3 cases of adrenal crisis associated with mRNA COVID-19 (BNT162b2) vaccination in patients with secondary adrenal insufficiency. Two patients presented with adrenal crisis after the second dose, whereas 1 presented with adrenal crisis after the first dose. Within 24 hours of vaccination, all patients presented with fatigue and appetite loss, and 2 patients were febrile. None of them increased their glucocorticoid dosage at the time of vaccination, leading to an adrenal crisis. To date, 9 cases of adrenal crisis, including ours, associated with COVID-19 vaccination have been reported. Considering the high degree of adverse reactions to COVID-19 vaccination, administration of prophylactic stress dose of glucocorticoids is strongly recommended, particularly in patients with symptomatic adverse reactions, to protect them from adrenal crisis.

**Key Words:** adrenal crisis, adrenal insufficiency, COVID-19 vaccination, glucocorticoid replacement

**Abbreviations:** AC, adrenal crisis; AI, adrenal insufficiency; BP, blood pressure; HC, hydrocortisone; IL, interleukin.

## Introduction

For patients with adrenal insufficiency (AI), increasing the maintenance dosage of glucocorticoid by 2- to 3-folds is recommended to prevent adrenal crisis (AC) during infections [1]; however, no specific recommendation exists regarding its dosage during vaccination. Moreover, AC associated with conventional vaccination has been rarely reported [2].

During the COVID-19 pandemic, several vaccines have been developed and widely used to effectively reduce the risk of infection and severe COVID-19 outcomes [3]. COVID-19 vaccines generally induce high rates of adverse reactions, particularly systemic reactions, compared with conventional vaccines, suggesting an increased possibility of AC associated with the vaccination. In this report, we present 3 cases of AC precipitated by the COVID-19 mRNA vaccination in patients with secondary AI. Furthermore, we provide a literature review on similar cases.

## Case Presentation

### Case 1

A 78-year-old man with idiopathic isolated ACTH deficiency, hypertension, and chronic obstructive pulmonary disease had been under treatment with hydrocortisone (HC) (12.5 mg/d) for 17 years. However, he decided not to take HC on the day he received the second dose of the BNT162b2 mRNA vaccine. The following morning, his body temperature was 37.5 °C and he experienced severe general fatigue, nausea, vomiting, and appetite loss; consequently, he was unable to receive HC since then. Two days later, he visited the emergency department.

## Diagnostic Assessment

He exhibited alert consciousness with a body temperature of 37.7 °C, blood pressure (BP) of 103/60 mm Hg (compared with his usual BP of 138/60 mm Hg), $O_2$ saturation of 98%, and exhibited signs of hyponatremia. The nasopharyngeal swab polymerase chain reaction test for SARS-CoV-2 was negative. The laboratory findings are summarized in Table 1. His chest radiograph was clear, urine showed no signs of infection, and blood culture was negative.

## Treatment

He was administered prednisolone sodium succinate (20 mg) IV, followed by HC (100 mg) and saline infusion.

## Outcome and Follow-up

His symptoms resolved the following day, and electrolyte and inflammatory marker levels normalized on the fifth day. Based on the presence of severe general fatigue, nausea, vomiting, hyponatremia, and relative hypotension, as well as observed clinical improvement after receiving parenteral

**Received:** 24 February 2023. **Editorial Decision:** 9 June 2023. **Corrected and Typeset:** 14 August 2023

**Table 1. Laboratory findings**

| | Normal range | Case1 | Case 2 | Case 3 |
|---|---|---|---|---|
| WBC | 3.3-8.6 ($10^9$/L), 3300-8600 (/μL) | 6.4 ($10^9$/L), 6400 (/μL) | 9.4 ($10^9$/L), 9400 (/μL) | 5.6 ($10^9$/L), 5600 (/μL) |
| Neutrophils | 38.5-80.5 (%) | 47.7 | 46.1 | NA |
| Eosinophils | 0.0-8.5 (%) | 0.9 | 10.9 | NA |
| CRP | <3000 (μg/L), <0.3 (mg/dL) | 261 000 μg/dL (26.1 mg/dL) | 38 000 μg/dL (3.8 mg/dL) | 5000 μg/dL (0.5 mg/dL) |
| Creatinine | 57.5-94.6 (μmol/L), 0.65-1.07 (mg/dL) | 117.6 μmol/L (1.33 mg/dL) | 95.5 μmol/L (1.08 mg/dL) | 76.9 μmol/L (0.87 mg/dL) |
| Blood glucose | 4.05-6.05 (mmol/L), 73-109 (mg/dL) | 4.27 mmol/L (77 mg/dL) | 4.77 mmol/L (86 mg/dL) | 4.61 mmol/L (83 mg/dL) |
| Sodium | 138-145 (mmol/L), 138-145 (mEq/L) | 128 mmol/L (128 mEq/L) | 131 mmol/L (131 mEq/L) | 124 mmol/L (124 mEq/L) |
| Potassium | 3.6-4.8 (mmol/L), 3.6-4.8 (mEq/L) | 3.3 mmol/L (3.3 mEq/L) | 4.3 mmol/L (4.3 mEq/L) | 4.3 mmol/L (4.3 mEq/L) |
| Serum cortisol level | 172.2-496.8 (nmol/L), 6.24-18.0 (μg/dL) | 8.28 nmol/L (0.3 μg/dL) | 5.52 nmol/L (0.2 μg/dL) | NA |

Abbreviations: CRP, C-reactive protein; NA, not assessed; WBC, white blood cell.

**Table 2. The incidence of systemic reactions of the COVID-19 vaccines and influenza vaccine**

| Vaccine | Vaccine type | Number of patients | Dose | Fever ≧38 °C (%) | Nausea, Vomiting (%) | Fatigue (%) | Headache (%) | Chills (%) | Myalgia (%) | Overall systemic reactions (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| COVID-19 vaccine | | | | | | | | | | |
| BNT162b2 (Pfizer/BioNTech)[a] | mRNA | 1 659 724 | 1st | 3 | 8 | 29 | 25 | 7 | 17 | 48 |
| | | 971 375 | 2nd | 14 | 14 | 49 | 40 | 23 | 37 | 69 |
| mRNA-1273 (Moderna)[a] | mRNA | 1 984 194 | 1st | 1 | 9 | 33 | 27 | 10 | 21 | 52 |
| | | 949 497 | 2nd | 16 | 22 | 60 | 53 | 40 | 51 | 75 |
| ChAdOx1 nCoV-19 (AstraZeneca)[b] | Adenoviral vector | 33 869 | 1st | 8 | 23 | 53 | 53 | 32 | 44 | NA |
| | | 31 217 | 2nd | 1 | 9 | 17 | 27 | 5 | 19 | NA |
| Influenza vaccine | Inactivated | NA | | | | | | | | 5-10 |

Abbreviation: NA, not assessed.
[a]Chapin-Bardales J, Gee J, Myers T. Reactogenicity following receipt of mRNA-based COVID-19 vaccines. *JAMA*. 2021;325(21):2201-2202.
[b]MHRA. Information for Healthcare Professionals on COVID-19 Vaccine AstraZeneca. London: GOV.UK. 2022. https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca

HC, he was diagnosed with AC associated with the vaccination [4].

### Case 2

An 80-year-old man, who underwent 3 surgeries for craniopharyngioma with resultant anterior hypopituitarism, was prescribed hormone replacement therapy, including HC (10 mg/d), levothyroxine, and testosterone enanthate. The morning after receiving the first dose of the BNT162b2 mRNA vaccine, he experienced general fatigue and appetite loss. However, because he was afebrile, he decided to continue the maintenance dose of HC. After 5 days, he presented with severe appetite loss, cognitive decline, abnormal behavior, and hallucinations. After 6 days, he was admitted to the emergency department.

## Diagnostic Assessment

On examination, his consciousness level was determined to be E4V4M5 on the Glasgow Coma Scale, his body temperature was 36.8 °C, BP was 123/68 mm Hg, and $O_2$ saturation was 95%. The laboratory findings are summarized in Table 1. His chest radiograph was clear, urine showed no signs of infection, and blood culture was negative. Computed tomography of the head showed no remarkable findings except for postoperative changes.

## Treatment

He was administered HC (100 mg) IV, followed by HC (100 mg) and continuous saline infusion.

## Outcome and Follow-up

After 3 days of hospitalization, his level of consciousness and appetite normalized. Based on the presence of severe general fatigue, hyponatremia, and altered mental status, as well as observed clinical improvement after parenteral HC administration, he was diagnosed with AC associated with the vaccination [4].

### Case 3

A 79-year-old man with idiopathic isolated ACTH deficiency, type 2 diabetes, vasospastic angina, atrial fibrillation, and dyslipidemia had been under treatment with HC (13 mg/d) and insulin for 3 years. Several hours after receiving the second dose of

**Table 3. Clinical characteristics of patients with adrenal crisis associated with COVID-19 vaccination**

| | Case | | | | | | | | Symptom of systemic reactions after vaccination | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | Sex | Vaccine | Dose | Underlying disease | Comorbidities | HC maintenance dose (mg/d) | Onset after vaccination | Fever | Fatigue | Nausea, vomiting | Appetite loss | Other symptoms | HC dose after vaccination |
| Maguire et al [6] | 66 y | F | ChAdOx1 | 1st | AD | Primary hypothyroidism | 20 | 1 day | Y (39.7 °C) | Y | N | N | Headache | Increased to 2-folds |
| | NA | M | ChAdOx1 | 1st | AD | Short bowel syndrome | 30 | 1 day | Y (38.3 °C) | N | Y | Y | Abdominal pain, Diarrhea | Impossible to take |
| | 69 y | F | ChAdOx1 | 1st | AD | APS (type1 DM, POI, vitiligo, thyroidectomy) | 20 | 1 day | N | Y | N | N | Diarrhea | Increased to 1.5-folds |
| | 41 y | F | ChAdOx1 | 1st | Hypopituitarism | Cushing disease post TSS | 15 | 1 day | Y | Y | Y | NA | Headache | Impossible to take |
| | 74 y | M | ChAdOx1 | 1st | Hypopituitarism | Non-functioning pituitary adenoma post TSS | 15 | 1 day | Y | Y | Y | NA | Chills | Impossible to take |
| Markovic et al [7] | 74 y | M | BNT162b2 | 2nd | Hypopituitarism | Prolactinoma post- surgery, type 2 DM, hypertension | 10 | 1 day | Y (39.7 °C) | N | N | N | | Did not take |
| Our cases | 78 y | M | BNT162b2 | 2nd | IAD | Hypertension, COPD | 12.5 | 1 day | Y (37.5 °C) | Y | Y | Y | | Did not take |
| | 80 y | M | BNT162b2 | 1st | Hypopituitarism | Craniopharyngioma post-surgery | 10 | 1 day | N | Y | N | Y | | 10 mg |
| | 79 y | M | BNT162b2 | 2nd | IAD | Type 2 DM, VSA, AF, dyslipidemia | 13 | 1 day | Y (37.6 °C) | Y | N | Y | | 13 mg |

Abbreviations: AD, Addison disease; AF, atrial fibrillation; APS, autoimmune polyglandular syndrome; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IAD, isolated adrenocorticotropic hormone deficiency; NA, not assessed; N, no; POI, premature ovarian insufficiency; TSS, transsphenoidal surgery; VSA, vasospastic angina; Y, yes.

the BNT162b2 mRNA vaccine, he developed a fever of 37.6 °C and experienced general fatigue and appetite loss. An antipyretic was administered, and the maintenance dose of HC was continued. However, as his symptoms persisted, he visited the hospital 10 days later.

## Diagnostic Assessment

He exhibited alert consciousness with body temperature of 36.4 °C and BP of 98/55 mm Hg. Additionally, hyponatremia of 124 mmol/L (124 mEq/L) was observed, without any signs of infection (Table 1).

## Treatment, Outcome and Follow-up

An increased dose of HC (30 mg/d) was administered, following which his symptoms resolved and sodium level normalized. Based on the presence of severe general fatigue, hyponatremia, and hypotension, as well as observed clinical improvement following the increased dose of HC administration, he was diagnosed with AC associated with the vaccination [4].

## Discussion

Reports of AC in patients with AI associated with conventional vaccinations are rare. Major et al reported a case of 32-year-old patient with Addison disease who developed AC after receiving concurrent inoculations for influenza, diphtheria, tetanus, pertussis, and pneumococcal vaccines [2]. In this case, the simultaneous administration of multiple vaccines may have contributed to the development of severe systemic adverse reactions, potentially triggering AC. Based on the extensive search in the PubMed database, we found this to be the only reported instance of AC associated with a conventional vaccination. Therefore, it is reasonable to conclude that conventional vaccinations rarely cause AC in patients with AI.

COVID-19 vaccines, including mRNA and adenoviral vector vaccines, have been extensively used worldwide. Notably, mRNA vaccines had never been used in humans before the COVID-19 pandemic. Both mRNA and adenoviral vector vaccines induce strong humoral and cell-mediated immune responses. In addition to local reactions, systemic reactions such as fatigue and fever are common. The time of onset of systemic reactions is rapid after vaccination [5]. In most cases, the severity of systemic reactions is mild to moderate; however, with mRNA vaccines, moderate or severe reactions are common after the second dose (Table 2) [5].

In this report, we describe cases of 3 patients with secondary AI who developed AC following COVID-19 mRNA vaccination. To date, AC associated with COVID-19 vaccination has been reported in 5 cases using the ChAdOx1 nCoV-19 adenoviral vector vaccine [6] and in 1 case using the BNT162b2 mRNA vaccine [7]. A total of 9 cases, including the 3 cases described in our report, are summarized in Table 3. Interestingly, all patients receiving adenoviral vector vaccines exhibited AC following the first dose, whereas most patients receiving mRNA vaccines exhibited AC following the second dose. In general, adenoviral vector vaccines induce stronger adverse reactions, even after the first dose, than those of mRNA vaccines (Table 2); such a reaction may cause sufficient stress to trigger AC. In contrast, mRNA vaccines can induce strong reactions, especially after the second dose, which may account for the occurrence of AC following the second dose in most cases.

COVID-19 vaccines using mRNA and adenoviral vectors exhibit a higher frequency of systemic adverse reactions than those exhibited by inactivated influenza vaccines (Table 2). These adverse reactions are believed to be associated with COVID-19 vaccine-induced strong immune response, including the release of proinflammatory cytokines. In a clinical trial with the mRNA vaccine BNT162b1, a transient increase in C-reactive protein, particularly after the second dose; increased serum levels of cytokines such as interferon-γ, tumor necrosis factor, interleukin-2 (IL-2), IL-1β, and IL-12p70 were observed. In addition, the lipid nanoparticles of mRNA vaccine increase the level of inflammatory cytokines, such as IL-6 and IL-1β [8]. These data suggest that a profound increase in proinflammatory cytokines following COVID-19 vaccination causes systemic adverse reactions, which can trigger AC as a strong stressor.

We reviewed AC associated with COVID-19 vaccinations and summarized them in Table 3. Among the 9 cases, fever and fatigue were observed in 7 cases each, whereas nausea and vomiting were observed in 4 cases. Additionally, 2 cases did not present with fever. Only 2 cases increased the HC dose, by up to 2-fold, but AC still occurred, whereas 4 cases were unable to receive increased doses because of nausea and vomiting. In case 1, particularly, the patient's failure to take his regular HC dose on the day of vaccination could have played a significant role in triggering AC. In patients experiencing fever of ≥39 °C or diarrhea, even with a 2-fold increase in the HC doses, AC was still observed, indicating that a minimum increase by 3-fold of the regular HC dose may be necessary to prevent AC. Additionally, the IV infusion of HC was recommended when nausea and vomiting were observed.

According to the Pituitary Society survey of patients with AI who received the COVID-19 vaccine, 64% of the clinicians did not recommend automatic glucocorticoid dose escalation with vaccination; among those 88% planned to increase the dose if fever developed, and 47% planned to increase the dose if myalgia or arthralgia developed. Therefore, most clinicians intend to maintain the current glucocorticoid dose and only increase them when fever develops [9]. The Korean Society of Endocrinology recommends that patients with AI should increase the daily replacement glucocorticoid dose 2 to 3 times, following the sick day rule, if the patients experience fever, myalgia, and chills after COVID-19 vaccination [10]. However, in our cases, the degree of fever was mild, and 1 case of AC occurred without fever. Based on these findings, promptly increasing the dose of glucocorticoids in patients with fatigue and appetite loss, regardless of fever, was recommended. In addition, considering that symptoms can be mild or even absent, especially in older individuals, an empirical increase in the HC dose is recommended, particularly when patients have other underlying comorbidities. Notably, older patients often exhibit uncommon symptoms such as cognitive decline as a manifestation of AC, as demonstrated in case 2.

In conclusion, patients with AI may experience AC following COVID-19 vaccination, particularly in cases of systemic adverse reactions. Moreover, a 2-fold increase in HC dose may be insufficient in symptomatic cases, necessitating the administration of at least a 3-fold increased dose of glucocorticoids. Additionally, providing appropriate instructions to

patients and their families is crucial in managing this situation effectively.

## Learning Points

- In patients with adrenal insufficiency and systemic adverse reactions, COVID-19 vaccination may trigger an adrenal crisis.
- Particular attention should be paid to the first dose of adenoviral vector vaccines and second dose of mRNA vaccines.
- Two-fold increase in the hydrocortisone dose may be insufficient in symptomatic cases; therefore, at least a 3-fold increased dose of glucocorticoids should be administered.
- It is essential to provide appropriate instructions to patients and their families.

## Acknowledgments

The authors thank Hiroki Nakajima, Fumika Kamitani, and Miyuki Koizumi, and the members in the department for their assistance.

## Contributors

All authors made individual contributions to authorship. Y.K. was mainly involved in the diagnosis and management of the patients and in manuscript submission. T.M. and S.O. were involved in the management of the patients. Y.K. and Y.T. prepared the manuscript. All authors reviewed and approved the final draft.

## Funding

This study was supported by the Ministry of Health, Labor and Welfare (Hypothalamo-hypophyseal Disorders and Endocrine Syndrome with Sexual Differentiation and Maturation grant to Y.T.).

## Disclosures

None declared.

## Informed Patient Consent for Publication

Signed informed consent obtained directly from the patients.

## Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

## References

1. Quinkler M, Hahner S. What is the best long-term management strategy for patients with primary adrenal insufficiency? *Clin Endocrinol (Oxf)*. 2012;76(1):21-25.
2. Major A, Chacko K. Routine vaccinations as a precipitant of adrenal crisis in adrenal insufficiency. *Intern Med J*. 2018;48(3):360-361.
3. Feikin DR, Higdon MM, Abu-Raddad LJ, *et al*. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet*. 2022;399(10328):924-944.
4. Allolio B. Extensive expertise in endocrinology. Adrenal crisis. *Eur J Endocrinol*. 2015;172(3):R115-R124.
5. Ossato A, Tessari R, Trabucchi C, Zuppini T, Realdon N, Marchesini F. Comparison of medium-term adverse reactions induced by the first and second dose of mRNA BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine: a post-marketing Italian study conducted between 1 January and 28 February 2021. *Eur J Hosp Pharm*. 2021:ejhpharm-2021-002933.30(4).
6. Maguire D, McLaren DS, Rasool I, Shah PM, Lynch J, Murray RD. Chadox1 SARS-CoV-2 vaccination: a putative precipitant of adrenal crises. *Clin Endocrinol (Oxf)*. 2021:10.1111/cen.14566.
7. Markovic N, Lavaud J, Faizan A, Boradia C, Nambi S. Adrenal crisis secondary to COVID-19 vaccination in a patient with hypopituitarism. *AACE Clin Case Rep*. 2022;8(4):171-173.
8. Ndeupen S, Qin Z, Jacobsen S, Bouteau A, Estanbouli H, Igyártó BZ. The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. *iScience*. 2021;24(12):103479.
9. Katznelson L, Gadelha M. Glucocorticoid use in patients with adrenal insufficiency following administration of the COVID-19 vaccine: a Pituitary Society statement. *Pituitary*. 2021;24(2):143-145.
10. Ku CR, Jung KY, Ahn CH, *et al*. COVID-19 vaccination for endocrine patients: a position statement from the Korean Endocrine Society. *Endocrinol Metab (Seoul)*. 2021;36(4):757-765.