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Case Report

A case of adrenal insufficiency during multisystem inflammatory syndrome in children

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Highlights

- To the best of our knowledge, this is the first reported pediatric case with adrenal insufficiency due to MIS-C.
- The hypothalamic-pituitary-adrenal axis may be impaired during the coronavirus 2019 (COVID-19) pandemic.
- Due to individual hypersensitivity, pediatric endocrinologists should evaluate children with COVID-19 for adrenal insufficiency, especially those taking steroids.

Abstract. Multisystem inflammatory syndrome in children (MIS-C) is a disease related to coronavirus disease 2019 (COVID-19). Although the effects of COVID-19 on many systems are known, there is limited data regarding its effects on the endocrine system. This study aimed to discuss the effect of COVID-19 on cortisol dynamics in a patient who developed adrenal insufficiency after COVID-19 infection. An 11-yr-old boy with polymerase chain reaction-proven COVID-19 one month previously was referred with a five-day history of fever, vomiting, and rash. On admission, he had hypotension, tachycardia, and severe hyponatremia. After the evaluation, he was diagnosed with MIS-C and glucocorticoid therapy was initiated. During follow-up, the patient experienced adrenal insufficiency, and hydrocortisone treatment was initiated at a crisis dose. Four months later, the adrenal axis function had not recovered. The adrenocortical response in COVID-19 patients may be significantly impaired, resulting in increased mortality or morbidity.

Key words: coronavirus disease 2019 (COVID-19), cortisol, adrenal insufficiency

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Introduction

Multisystem inflammatory syndrome in children (MIS-C) associated with pediatric coronavirus 2019 (COVID-19) was first defined in April 2020. MIS-C, with symptoms similar to those of Kawasaki disease, has variable treatment options, one of which is glucocorticoids (1). Although the effects of COVID-19 on the endocrine system are not yet fully understood, COVID-19 reportedly rarely affects adrenal function and causes both primary and secondary adrenal insufficiency (2). Possible mechanisms include a direct effect of infection on the hypothalamic-pituitary-adrenal (HPA) axis mediated through cytokines, such as IL-6 and toll-like receptors (TLR), or indirect effects due to glucocorticoid use during treatment that modifies the inflammatory effect of MIS-C (2–4). Here we present the case of an 11-yr-old boy who was followed up for MIS-C and developed adrenal insufficiency.

Case Report

An 11-yr-old boy was referred to our center with a five-day history of fever, vomiting, and rash. He had a history of COVID-19 infection one month previously and had recovered within two days. On initial examination, he had a high body temperature (39°C), hypotension (80/50 mmHg), tachypnea (26 breaths per min), sinus tachycardia (138 beats per min), and rashes that faded under pressure. His weight was 46 kg and height was 156 cm (0.6 SD and 1.3 SD, respectively).

He had elevated C-reactive protein, erythrocyte sedimentation rate, D-dimer, *N*-terminal pro-brain-type natriuretic peptide (NT-proBNP), and IL-6 levels. His serum glucose was 85 mg/dL, sodium was 124 mmol/L, and potassium was 3.19 mmol/L, while other biochemical markers were normal (**Table 1**). Immunoglobulin M to SARS-CoV-2 was 1.83 (< 10) and immunoglobulin G was 6.1 (< 1.4). He was evaluated by the rheumatology and infectious disease departments and diagnosed with MIS-C. The patient had normal blood pressure after fluid and inotropic treatment.

The patient then continued a maintenance dose of isotonic saline. He was started on methylprednisolone therapy (60 mg) daily after receiving a dose of intravenous immunoglobulin (IVIG) for the treatment of MIS-C. On the second day of treatment, he developed hyperglycemia (venous glucose, 288 mg/dL; insulin: 2.4 uIU/mL, c-peptide, 0.95 ng/mL; HbA1C, 5.4%), which was considered stress hyperglycemia. His condition was unresponsive to treatment, so the glucocorticoid regimen was changed on the third day of treatment to methylprednisolone (500 mg) daily for the following three days. Subsequently, the dose of methylprednisolone was reduced to 60 mg daily on the sixth day of treatment. On the eighth day of treatment, while receiving methylprednisolone (40 mg) and a maintenance dose of isotonic saline, the patient deteriorated, with severe fatigue and low blood pressure, and his sodium level decreased from 140 to 129 mmol/L (**Table 2**). The patient was euvolemic with no signs of dehydration or edema. The patient was not taking diuretics.

Venous blood testing revealed a pH of 7.30, pCO_2 of 28 mmHg, $cHCO_3$ of 16 mmol/L, and an anion gap of 14 mmol/L. Serum and urine osmolalities were 271 mOsm/kg and 823 mOsm/kg, respectively. His urinary sodium level was 239 mmol/L. Serum IL-6 and NT-proBNP levels were in the normal range (4.6 pg/mL and 114 pg/mL, respectively).

Echocardiography revealed no change in cardiac

Table 1. Biochemical and hematological variables at admission in a patient with MIS-C and adrenal insufficiency

Lab variable	On admission	Reference values
White blood cells (10^3/μL)	6.8	3.6–10.2
Neutrophils (10^3/μL)	5.7	1.7–7.6
Lymphocytes (10^3/μL)	0.8	1–3.2
Hemoglobin (g/dL)	11.8	12.5–16.3
Platelets (10^3/μL)	169	152–348
Erythrocyte sedimentation rate (mm/h)	82	< 15
C reactive protein (mg/L)	378.87	0–5
Interleukin-6 (pg/mL)	2330	0.9–71
NT-proBNP (pg/mL)	522	70–133
D-dimer (μg/dL)	6.7	0–0.5
Serum glucose (mg/dL)	85	70–100
Serum sodium (mmol/L)	124	136–146
Serum potassium (mmol/L)	3.19	3.5–5.1
Serum creatinine (mg/dL)	0.4	0.67–1.17
AST (U/L)	30	0–50
ALT (U/L)	28	0–50
Fibrinogen (g/L)	5.6	2–4
Ferritin (ng/mL)	215	23.9–336.2

Normal ranges are shown in the right-hand column. ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-proBNP, *N*-terminal pro-brain-type natriuretic peptide.

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Table 2. Therapy modalities and biochemical variables during follow-up

Time	Serum sodium (mmol/L)	Serum potassium (mmol/L)	Treatment
Day 1	124	3.19	IVIG, MP 60 mg/d
Day 2	131	3.08	MP 60 mg/d
Day 3	133	3.05	MP 500 mg/d
Day 4	135	3.34	MP 500 mg/d
Day 5	138	3.88	MP 500 mg/d
Day 6	139	4.38	MP 2×30 mg/d
Day 7	140	4.79	MP 2×30 mg/d
Day 8	129.9	5.23	MP 2×20 mg/d
Day 9	131.8	4.37	HC 300 mg/m^2/d
Day 10	134.6	3.98	HC 225 mg/m^2/d
Day 11	135.8	3.53	HC 170 mg/m^2/d
Day 12	139.6	3.5	HC 100 mg/m^2/d
Day 13	138.2	3.64	HC 75 mg/m^2/d
Day 18	139	3.7	HC 7 mg/m^2/d
Month 3	138.6	3.9	HC 7 mg/m^2/d
Month 4	138	4	HC 5 mg/m^2/d
Month 6	140	3.9	HC 5 mg/m^2/d
Month 9	139	4.1	–

HC, hydrocortisone; IVIG, intravenous immunoglobulin; MP, methylprednisolone.

function. Therefore, a pediatric endocrinology consultation was requested for the severe hyponatremia. The first assessment of his HPA axis showed serum levels of ACTH of 18 pg/mL [normal range (NR), 0–45]; cortisol, 1.34 µg/dL (NR, 6–22); dehydroepiandrosterone sulfate (DHEAS), 89.7 µg/dL [NR, 24–247], aldosterone, 4.9 ng/dL [NR, 3.7–31]; and plasma renin activity, 0.02 ng/mL/h (NR, 0.06–4.69) indicative of central adrenal insufficiency. Other pituitary hormone levels were within normal limits. The ACTH stimulation test was not performed because the patient was receiving glucocorticoid therapy. The methylprednisolone was discontinued, and hydrocortisone was initiated at the adrenal crisis dose. The dose of isotonic saline administered did not change. Serum sodium and potassium values subsequently normalized (138.2 mg/dL, 3.6 mg/dL, respectively), as did his blood pressure with a good clinical response. The hydrocortisone dose was then gradually reduced to the physiological dose (7 mg/m^2/d). After four months of hydrocortisone treatment, the morning serum ACTH level was 27 pg/mL and cortisol level was 8 µg/dL. The hydrocortisone was discontinued, and a low-dose ACTH stimulation test was performed. During the test, the peak cortisol value was 13.6 µg/dL, which indicated that the HPA axis had not fully recovered. Therefore, physiological hydrocortisone treatment was restarted at a dose of 5 mg/m^2 daily. After six months of treatment, the HPA axis was re-evaluated. The peak cortisol level was 19 µg/dL during the test, and hydrocortisone treatment was discontinued. The last morning values of the patient, who is currently in his ninth month of follow-up, were ACTH 24 pg/mL and cortisol 15 µg/dL.

Informed consent was obtained from the patient's family for the publication of this case.

Discussion

Angiotensin-converting enzyme 2 (ACE2), a metallopeptidase present in the membranes of target cells, is the main receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. This enzyme is expressed in the arterial and venous endothelial cells of many organs, including the adrenal glands (5). Additionally, both pituitary and hypothalamic tissues express ACE2, which may be potential targets for SARS-CoV-2 in COVID-19 (5).

In a study of 28 COVID-19 patients, ACTH and cortisol levels were evaluated; surprisingly, the adrenocortical responses were impaired in a significant percentage of the patients, indicating secondary adrenal insufficiency (6). The authors stated that it was unclear whether this was due to the direct effect of the virus on the hypothalamus or pituitary glands or if it was secondary to a humoral response and the release of inhibitory cytokines.

Endogenous cortisol plays an important role in controlling inflammation. The hypothalamus, pituitary, and adrenal cells are controlled by a variety of hormones, peptides, cytokines, and other factors in the basal condition and during critical illness (7). For example, Toll-like receptor (TLR)-2 and TLR-4 stimulate cortisol production independent of ACTH in adrenocortical cells (4). Activation of the HPA axis and an increase in free cortisol levels secondary to decreased glucocorticoid receptor activity and decreased cortisol clearance are expected in patients with critical illnesses such as sepsis and severe pneumonia (8). Nevertheless, in cases of critical illness-related corticosteroid insufficiency (CIRCI), relative adrenal insufficiency may develop due to the inability of cortisol to meet the increased metabolic

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demand (8). COVID-19-related cytokine storm may be responsible for the development of adrenal insufficiency. In addition, the release of cytokines such as IL-1, IL-6, and tumor necrosis factor-α is thought to reduce ACTH production (9). It was reported that, IL-6 levels are inversely correlated with serum sodium levels among COVID-19 patients (3). However, steroid therapy may cause hypoadrenalism due to HPA axis suppression, especially in patients with individual hypersensitivity (2).

Our patient had no history of adrenal insufficiency before admission. Although he had significant hyponatremia and elevated IL-6 levels at presentation, it is impossible to conclude that he had hypoadrenalism at presentation since adrenal function tests were not performed. Hyponatremia upon admission was attributed to elevated IL-6 levels. Hypotension and clinical deterioration developed while he was receiving high-dose methylprednisolone treatment. Laboratory findings showed severe hyponatremia despite normal serum IL-6 levels. The serum ACTH and cortisol levels measured at this time indicated HPA axis impairment. However, improvement in his clinical picture and laboratory results after hydrocortisone replacement at a crisis dose indicated that he was experiencing central adrenal insufficiency. This finding suggests that patients with severe COVID-19 are predisposed to developing CIRCI and that glucocorticoid treatment during the infection could cause HPA suppression and adrenal insufficiency.

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a common cause of hypoosmolality. It is characterized by inappropriately concentrated urine (> 100 mOsm/kg), natriuresis (> 30 mEq/L), and hyponatremia correction after water restriction. For the diagnosis of SIADH, renal, hepatic, adrenal, thyroid, and cardiac functions must be normal (10). Concentrated urine and natriuresis can be expected in ACTH deficiency, another euvolemic hyponatremia condition, there are some measurements which may be helpful in distinguishing ACTH deficiency from SIADH (11). Compared to patients with hyponatremia due to hypocortisolemia, normal serum bicarbonate levels and a lower anion gap are expected in patients with SIADH (11). The fact that patients with ACTH deficiency have lower serum bicarbonate and aldosterone concentrations than those with SIADH may aid the diagnosis (12, 13). Although inappropriate concentrated urine and natriuresis on day 8 of treatment in our patient with euvolemic hyponatremia may be compatible with SIADH, a low serum bicarbonate level, relatively low aldosterone level, normal anion gap, and improvement with hydrocortisone without water restriction suggested central adrenal insufficiency.

Although low DHEAS levels are expected in adrenal insufficiency, cases of central hypoadrenalism with normal DHEAS levels have also been reported (14). In an adult study conducted by Liza *et al*., endocrinological evaluations of patients with COVID-19 were performed, and central hypocortisolemia was detected in 38.5% of the adults with moderate to severe COVID-19. In addition, most patients with hypocortisolism have normal DHEAS levels (15). Our patient's DHEAS level, which did not increase sufficiently during the critical illness, may be a sign of adrenal insufficiency.

The patient presented here was discharged on a physiological dose (7 mg/m^2/d) of hydrocortisone on day 18 of treatment. The low-dose ACTH stimulation test, performed at month 4 of hydrocortisone treatment, showed that the HPA had not fully recovered; thus, the central adrenal insufficiency continued. After the HPA axis evaluation, hydrocortisone (5 mg/m^2 daily) was administered until normal cortisol values were achieved in month 6. Therefore, we suggest that MIS-C patients be carefully monitored for adrenal insufficiency and, if indicated, pediatric endocrinologists participate in the patient's subsequent management.

Conclusions

To the best of our knowledge, this is the first pediatric case of adrenal insufficiency secondary to MIS-C. COVID-19 may cause both primary and secondary adrenal insufficiency owing to its effects, individual hypersensitivity, and steroid treatment. Clinicians should be aware that the adrenocortical response to COVID-19 may be significantly impaired. The HPA axis should be evaluated, especially in COVID-19 patients with unexplained hypotension and hyponatremia.

Conflict of interests: The authors have nothing to declare.

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