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Newly diagnosed autoimmune Addison's disease in a patient with COVID-19 with autoimmune disseminated encephalomyelitis

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SUMMARY

A man in his 20s with a history of acute disseminated encephalomyelitis (ADEM) was brought into the emergency department (ED) after his family found him at home collapsed on the floor unresponsive with a blood glucose of 28 mg/dL at the field. In the ED, the patient was tachycardic, tachypnoeic and hypotensive, requiring pressors and intubation at 9 hours and 12 hours after arrival, respectively. Laboratory results revealed a positive COVID-19 test, serum sodium of 125 mmol/L and persistent hypoglycaemia. The patient was given a high dose of dexamethasone for COVID-19 treatment 1 hour before pressors were started. He was then continued on a stress dose of intravenous hydrocortisone with rapid clinical improvement leading to his extubation, and discontinuation of vasopressors and glucose on day 2 of admission. The patient received his last dose of intravenous hydrocortisone on day 4 in the early afternoon with the plan to order adrenal testing the following morning prior to discharge. On day 5, the aldosterone <3.0 ng/dL, adrenocorticotropic hormone (ACTH) level >1250 pg/mL, and ACTH stimulation test showed cortisol levels of 3 and 3 µg/dL at 30 and 60 min, respectively. The anti-21-hydroxylase antibody was positive. The patient was discharged on hydrocortisone and fludrocortisone. The patient's symptoms, elevated ACTH, low cortisol and presence of 21-hydroxylase antibodies are consistent with autoimmune Addison's disease. This is the first case reporting autoimmune Addison's disease in a patient with COVID-19 with a history of ADEM. The case highlights the importance of considering adrenal insufficiency as a diagnostic differential in haemodynamically unstable patients with COVID-19.

BACKGROUND

The COVID-19 pandemic has resulted in nearly 500 million confirmed cases and over 6 million deaths globally. COVID-19 is primarily a respiratory disease, but SARS-CoV-2 may affect multiple organs, contributing to severe disease and also post-COVID-19 syndrome.[1] An accumulating body of evidence is uncovering the link between COVID-19 and endocrinopathies such as new-onset diabetes, thyroiditis, diabetes insipidus, pituitary apoplexy, hypogonadism and adrenal insufficiency.[2–7] The mechanisms for COVID-19-related endocrinopathies are not fully elucidated but are likely multifactorial, including proinflammatory status, impaired immune function and thrombogenic responses to pathogens.

Several cases of primary adrenal insufficiency in the setting of COVID-19 have been reported (table 1), mostly due to adrenal haemorrhage or infarct.[8 9] One report has suggested that COVID-19, in conjunction with another prothrombotic condition (primary antiphospholipid syndrome), may precipitate these causes of adrenal insufficiency.[9] Furthermore, there is a wide variety of laboratory findings in patients with COVID-19-related adrenal insufficiency, and a majority of cases have been shown to affect patients in their mid to late adulthood, possibly related to the increased prothrombotic risk with age (table 1).[10] Here we describe a novel case of a young adult with a history of multiple childhood episodes of acute disseminated encephalomyelitis (ADEM), an autoimmune demyelinating disorder of the central nervous system, who developed acute primary adrenal insufficiency after presenting with COVID-19 infection.

CASE PRESENTATION

A man in his 20s with a history of three episodes of ADEM in childhood was brought into the emergency department (ED) by emergency medical service after his family found him collapsed on the floor unresponsive at home early morning with a blood glucose of 28 mg/dL at the field. Prior to the presentation, he reported 3 days of sore throat, nausea, vomiting, fatigue, chills and muscle aches, for which he initially tested negative for COVID-19 at an urgent care. At the time of presentation, his mother reported that his only medical history included three admissions at ages 4, 10 and 11 years for ADEM flares and possible optic neuritis. ADEM is an autoimmune demyelinating disease of the central nervous system that typically follows an infection and is more common in childhood. At the time of his diagnosis, our patient was prescribed prolonged courses of prednisone, the longest being 1 year. He never received immunosuppressants and had not been on any other home medications since the resolution of the last flare at age 11 years. He was not vaccinated against COVID-19 because of the family's belief that his ADEM episodes were triggered by various childhood vaccinations. Otherwise, he remained healthy and did not have any additional medical history, surgical history or family history of autoimmune conditions.

In the ED, the physical examination was notable for temperature 39°C, pulse 145/min, blood pressure (BP) 80/42 mm Hg, respiratory rate 39/min

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Table 1 Compilation of various case reports' patient characteristics and laboratory values

Case report	Age (years)	Sex	COVID-19 vaccination status	Required pressors?	Required intubation?	Sodium (mmol/L)	Glucose (mg/dL)	TSH (µIU/mL)	Cortisol (µg/dL)	ACTH (pg/mL)
Present case	20s	M	No	Yes	Yes	125	28	1.89	4	>1250
Asano *et al*[12]	70s	F	n/a	No	No	142	174	n/a	29.7	176.6
Machado *et al*[8]	40s	F	n/a	No	No	Hypo	n/a	n/a	<1.0	807
Elkhouly *et al*[14]	50s	M	n/a	No	Yes	135	n/a	n/a	26.6	n/a
Sheikh *et al*[5]	40s	F	n/a	No	No	139	n/a	1.83	1.1	56
Hashim *et al*[15]	50s	M	n/a	No	No	108	95	2.12	2.03	n/a
Chua *et al*[13]	40s	M	n/a	No	No	136	126	2.99	<1.0	7.1
Heidarpour *et al*[16]	60s	M	n/a	Yes	Yes	135	192	n/a	13	n/a
Frankel *et al*[9]	60s	F	n/a	No	No	129	n/a	n/a	<1.0	207
Kumar *et al*[17]	70s	F	n/a	No	No	112	n/a	n/a	16	Normal
Alvarez *et al*[11]	70s	M	n/a	No	No	127	n/a	n/a	2.1	n/a
Sanchez *et al*[20]	60s	F	n/a	No	No	117	n/a	0.33	2.6	1944
Bhattarai *et al*[10]	Late adolescence	F	n/a	Yes	Yes	110	63	22.4	1.0	26

Case report	Aldosterone (ng/dL)	Presence of anti-21-hydroxylase antibody	Associated conditions	Imaging findings	Treatment
Present case	<3.0	Positive	ADEM	Mild atrophy of bilateral adrenal glands	IV hydrocortisone, followed by PO hydrocortisone and fludrocortisone
Asano *et al*[12]	n/a	n/a	Sjogren's syndrome	Bilateral adrenal infarction	IV hydrocortisone, followed by PO hydrocortisone
Machado *et al*[8]	<3.0	Negative	Positive APL antibodies	Bilateral non-haemorrhagic infarction	IV hydrocortisone, followed by PO hydrocortisone and fludrocortisone
Elkhouly *et al*[14]	n/a	n/a	HTN, right adrenal adenoma	Bilateral adrenal haemorrhages	IV hydrocortisone prior to cardiac arrest and subsequent death
Sheikh *et al*[5]	n/a	n/a	T2DM	n/a	Hydrocortisone
Hashim *et al*[15]	n/a	n/a	None	n/a	Prednisolone
Chua *et al*[13]	n/a	n/a	T2DM	n/a	PO hydrocortisone
Heidarpour *et al*[16]	n/a	n/a	HTN	n/a	IV hydrocortisone, followed by PO prednisolone
Frankel *et al*[9]	n/a	n/a	APLS	Bilateral enlarged adrenal glands w/ surrounding haziness	IV hydrocortisone, followed by PO prednisone and fludrocortisone
Kumar *et al*[17]	n/a	n/a	HTN, HLD	Bilateral non-haemorrhagic adrenal infarction	IV hydrocortisone, followed by PO hydrocortisone
Alvarez *et al*[11]	n/a	n/a	Psoriasis	Bilateral adrenal haemorrhage	IV hydrocortisone, followed by PO hydrocortisone
Sanchez *et al*[20]	<0.3	Positive	Hypothyroidism, T2DM	Unremarkable	IV hydrocortisone, followed by PO hydrocortisone and fludrocortisone
Bhattarai *et al*[10]	n/a	Positive	Raynaud's phenomenon, possible autoimmune thyroiditis	Bilateral adrenals diminutive w/o nodularity or haemorrhage	IV hydrocortisone, followed by PO hydrocortisone and fludrocortisone

ACTH, adrenocorticotropic hormone; ADEM, acute disseminated encephalomyelitis; APL(S), antiphospholipid (syndrome); HLD, hyperlipidaemia; HTN, hypertension; IV, intravenous; n/a, not available; PO, oral; T2DM, type 2 diabetes mellitus; TSH, thyroid-stimulating hormone.

with initially normal oxygen saturation on room air, somnolence and no signs of mucocutaneous hyperpigmentation.

INVESTIGATIONS

Laboratory results on admission revealed a positive COVID-19 PCR test, serum sodium 125 mmol/L (reference range 135–145), potassium 3.1 mmol/L (reference range 3.5–4.1) and persistent hypoglycaemia requiring a dextrose drip. Thyroid-stimulating hormone was 1.89 µIU/mL (reference range 0.45–4.12). Pancultures were sent, and the patient was started on broad-spectrum antibiotics (intravenous vancomycin and piperacillin–tazobactam). The patient remained hypotensive despite receiving 4 L of intravenous fluid boluses and was started on norepinephrine 7 µg/min after 9 hours of his presentation. A dose of dexamethasone 6 mg was given per COVID-19 protocol shortly prior to initiation of pressors. His oxygen requirements steadily increased to a simple face mask of 6 L/min, and he was subsequently intubated with the addition of vasopressin for BP support 3 hours after norepinephrine was initiated. The patient was transferred to the intensive care unit for the management of acute hypoxic respiratory failure and undifferentiated shock.

DIFFERENTIAL DIAGNOSIS

Work-up for cardiogenic aetiologies of shock was unremarkable (ECG showed sinus tachycardia and troponins were within normal limits). A stat echocardiogram and CT angiography of the chest with contrast were ordered to assess for a thromboembolic cause of obstructive shock, though both studies were unrevealing for right heart strain or pulmonary embolism, respectively. The CT of the chest demonstrated pneumonia involving the entire left lung associated with segmental/subsegmental atelectasis in the posteromedial aspects of the left lower lobe. Contrast-enhanced CT of the abdomen and pelvis demonstrated suboptimal visualised adrenal glands, with no thickening, lesions or calcifications. Blood, sputum and urine cultures were drawn to evaluate for other superimposed bacterial or fungal infections leading to septic shock. Given also high clinical suspicion for an adrenal crisis, a 05:00 cortisol was drawn the next

morning which resulted at 1 µg/dL (reference range >18). A second dose of dexamethasone 6 mg was given before endocrine was consulted to help guide the steroid treatment.

TREATMENT

It was noted that the 05:00 cortisol was drawn 14 hours after the first dexamethasone dose. Despite this, there was still high suspicion of possible adrenal insufficiency, and the patient was switched to intravenous hydrocortisone 100 mg every 8 hours in addition to fludrocortisone 0.1 mg daily. The hypotension and hyponatraemia quickly resolved, and vasopressors along with the glucose were discontinued before the patient was extubated on day 2 of his hospitalisation. He remained on intravenous steroids and antibiotics. On day 4, the sputum culture returned positive for methicillin-susceptible *Staphylococcus aureus* (MSSA) (thought to be a contaminant), with no growth seen on the blood and urine cultures. Given clinical stability, all antibiotics were discontinued. He received a final dose of intravenous hydrocortisone in the afternoon with the plan to repeat confirmatory testing for adrenal insufficiency the following morning to guide the management of steroids and mineralocorticoids at discharge.

On day 5—the last day of his admission—a baseline 08:00 cortisol was 4 µg/dL (reference range >18; unknown patient baseline) with adrenocorticotropic hormone (ACTH) level of >1250 pg/mL (reference range 0–45; unknown patient baseline). A high-dose 250 µg ACTH stimulation test followed; cortisol levels were 3 and 3 µg/dL (reference range >18) at 30 and 60 min, respectively. Aldosterone was <3.0 ng/dL (reference range 4.0–31.0), and anti-21-hydroxylase antibody was positive (reference: negative).

OUTCOME AND FOLLOW-UP

The patient was then diagnosed with primary adrenal insufficiency and was discharged on oral hydrocortisone 20 mg in the morning and 10 mg in the afternoon and oral fludrocortisone 0.1 mg daily. On the follow-up phone call, the patient endorsed taking his medications consistently. The patient established care with endocrinology at his primary institution upon discharge from the hospital.

DISCUSSION

Here we report a case of new-onset adrenal insufficiency in a COVID-19-positive patient with a background of ADEM. The patient was an otherwise healthy young man, who presented with symptoms consistent with adrenal crisis (hypoglycaemia, hypotension and hyponatraemia) shortly before the progression of his acute hypoxic respiratory failure due to COVID-19 pneumonia. Work-up for multiple causes of shock, including cardiogenic, obstructive and septic, was unrevealing except for lung findings of bronchiolitis and pneumonia involving the entire left lung along with a positive COVID-19 PCR test (sputum culture returned positive for MSSA, which was a contaminant in the context of negative blood cultures). Since the patient was started on dexamethasone per COVID-19 treatment protocol in the emergency room, primary adrenal insufficiency was diagnosed after his recovery from shock based on his elevated ACTH and reduced cortisol, positive cosyntropin stimulation test and positive anti-21-hydroxylase antibodies, which were collected on day 5 of his admission prior to discharge. Although adrenal insufficiency has been reported in patients with COVID-19, this case has several distinct features.

From previous case reports of COVID-19-related adrenal insufficiency we have compiled (table 1),[5 8–17] the majority of cases are caused by adrenal infarct or haemorrhage, likely because SARS-CoV-2 infection is known to elicit a hypercoagulable state leading to acute thrombotic complications including ischaemic stroke.[18]

In addition to the case reports, a retrospective study of 219 patients with COVID-19 with severe or critical lung disease on CT scan showed that 51 patients with an average age 67 years old exhibited adrenal infarct on imaging.[19] However, the actual number of patients who presented clinically with adrenal insufficiency was only a fraction of that seen on imaging (8%). Of all our compiled cases, two have reported on autoimmune Addison's disease complicated by COVID-19.[10 20] The first case is a woman in her 60s who was diagnosed with primary adrenal insufficiency 5 months after asymptomatic COVID-19 infection. The direct connection of adrenal insufficiency to COVID-19 is less clear. The second case is a woman in late adolescence who presents with adrenal crisis 4 days after a positive COVID-19 test. However, the patient's abdominal MRI showed diminutive adrenal glands, consistent with a chronic pre-existing adrenal insufficiency. Both cases of adrenal insufficiency with positive 21-hydroxylase antibodies have or possibly have Hashimoto's thyroiditis, suggesting some autoimmune background.

A unique feature of our case is our patient's childhood history of ADEM, a rare condition with an average age onset of 3–7 years, and annual incidence of 0.2–0.5 per 100 000 children.[21–23] ADEM is characterised by demyelination in the brain, spinal cord and occasionally the optic nerve, resulting from autoimmune inflammation that occurs in response to a preceding infection or immunisation.[21–23] Most patients affected by ADEM recover completely from the initial acute illness, although a minority of patients may experience relapsing episodes.[24] Our patient had three documented episodes of ADEM. Whether he has a stronger autoimmune background that may have rendered him more susceptible to developing other autoimmune conditions is unclear. Approximately 50%–65% of patients with autoimmune adrenal insufficiency have one or more other autoimmune endocrine disorders (most commonly thyroid disease and type 1 diabetes).[25–29] It is worth noting, however, that ADEM is mostly monophasic and not generally associated with other autoimmune diseases.[24] A literature search did not yield any report of adrenal insufficiency in patients with ADEM. Although many studies suggest an increasing prevalence of Addison's disease across all ages, the annual incidence is estimated to be 0.6 per 100 000.[30–33] Given the similar but very low incidence of ADEM and Addison's disease (especially that ADEM is very rare in adulthood with unknown incidence rates), the co-occurrence of both diseases in the population would be extremely rare. Therefore, although it is still possible that our patient with both conditions may represent a chance association, some intrinsic autoimmune mechanism could have linked his ADEM and adrenal insufficiency. Nevertheless, our case is the first to report the autoimmune Addison's disease in a patient with a history of ADEM.

COVID-19 clearly plays a major role in the patient's presentation of adrenal crisis. It remains speculative whether SARS-CoV-2 infection contributes to the autoimmunity of the patient's adrenal insufficiency. COVID-19 has been associated with multiple autoimmune diseases, including ADEM.[34–41] However, it is usually difficult to determine the causality in most cases. Our patient had detectable adrenal autoimmunity around 8 days after the onset of symptoms (with an additional incubation period of 3–5 days). The time is considered too short for antibody production during SARS-CoV-2 infection, which usually takes

1–3 weeks after an antigenic stimulus.[42 43] We therefore cannot deduce that the COVID-19 infection alone caused the patient to develop autoimmune adrenalitis. More plausible is that the patient has a history of positive anti-21 hydroxylase antibody with subclinical adrenal insufficiency (not yet apparent as radiological adrenal shrinkage), which was precipitated by his COVID-19 infection. Coco *et al* evaluated 48 patients with adrenal cortex autoantibodies, 21% of which developed overt adrenal insufficiency in 4 years.[44] The same investigators reported that of 100 patients with adrenal cortex autoantibodies, the estimated cumulative risk (using a life-table analysis) of developing overt adrenal insufficiency during a mean follow-up period of 6 years was 100% in children and 32% in adults.[44] These data provide plausible evidence that our patient likely had antecedent subclinical adrenal insufficiency, which was precipitated by COVID-19 infection, leading to the development of adrenal crisis.

Hypoglycaemia, especially severe hypoglycaemia, can be seen in children but is uncommon in adult patients with adrenal insufficiency. Our patient experienced severe and refractory hypoglycaemia requiring a dextrose drip to maintain glucose levels. Several mechanisms may contribute to the patient's severe hypoglycaemia. The poor appetite and oral intake due to the combination of adrenal insufficiency and SARS-CoV-2 infection are the apparent factors. As discussed above, the patient likely had a background of adrenal autoimmunity, with an acute precipitation of the adrenal crisis, and the compensatory mechanisms for increasing glycaemic levels may have not been established yet.

As dexamethasone is a standard therapy on the protocol for treating COVID-19 infection, the diagnosis of adrenal insufficiency can be complicated and could be delayed since dexamethasone suppresses endogenous cortisol production. Although cosyntropin-stimulation test in non-critically ill patients who received high-dose dexamethasone treatment within 72 hours can still be informative, data are lacking in critically ill patients treated with high-dose dexamethasone.[32 45] It is crucially important to treat suspected adrenal insufficiency first before the diagnosis is established. Since dexamethasone has minimal mineralocorticoid effects, fludrocortisone should be added. Alternatively, stress doses of hydrocortisone can be used.

It is worth noting that the age of our case's patient (early 20s) and those of previously reported autoimmune Addison's disease with COVID-19 (late adolescence) are significantly younger compared with the median age in the 60s in the other case reports of adrenal insufficiency caused by infarct or haemorrhage. SARS-CoV-2 infection is known to elicit a hypercoagulable state. The risk is likely further increased by the advanced age. Autoimmune adrenalitis, on the other hand, usually occurs at younger ages, with an average of 40 years old (30–50 years).[28 46–48] Therefore, in younger patients with COVID-19 presenting with adrenal insufficiency, it is pertinent to consider autoimmune adrenalitis as an aetiology.

In summary, this case is the first to report autoimmune Addison's disease in a patient with a history of ADEM, although an association with adrenal insufficiency is yet to be proven. Importantly, COVID-19 infection triggers adrenal crisis, which leads to the diagnosis of Addison's disease. The case highlights the importance of the recognition and management of adrenal crisis in haemodynamically unstable patients with COVID-19. Infarcts and haemorrhage are more common aetiologies for adrenal insufficiency, although autoimmune Addison's disease should be considered, especially in younger patients. The standard therapy of administering dexamethasone for COVID-19 may complicate the diagnosis of adrenal insufficiency, but early treatment is crucial. Future case series studies may provide insights into the incidence, aetiology, clinical course and outcome of adrenal insufficiency in patients with COVID-19.

Learning points

- It is important to consider adrenal insufficiency as a diagnostic differential in haemodynamically unstable patients with COVID-19.
- Young patients with an autoimmune history who develop haemodynamic instability during an infection should warrant a work-up for possible autoimmune Addison's disease.
- The standard therapy of administering dexamethasone for COVID-19 may complicate the diagnosis of adrenal insufficiency, but early treatment is crucial.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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