

New onset adrenal insufficiency in a patient with COVID-19

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SUMMARY

SARS-CoV-2 is the cause of COVID-19. Since the outbreak and rapid spread of COVID-19, it has been apparent that the disease is having multi-organ system involvement. Still its effect in the endocrine system is not fully clear and data on cortisol dynamics in patients with COVID-19 are not yet available. SARS-CoV-2 can knock down the host's cortisol stress response. Here we present a case of a 51-year-old man vomiting for 10 days after having confirmed COVID-19 infection. He had hypotension and significant hyponatraemia. Work-up was done including adrenocorticotrophic hormone stimulation test. He was diagnosed as suffering from adrenal insufficiency and started on steroids with subsequent improvement in both blood pressure and sodium level. COVID-19 can cause adrenal insufficiency. Clinicians must be vigilant about the possibility of an underlying relative cortisol deficiency in patients with COVID-19.

BACKGROUND

In March 2020, SARS-CoV-2, the cause of COVID-19, reached pandemic level with a high global mortality rate. A striking feature of COVID-19 is its ability to affect multiple organ systems. The COVID-19 virus uses a protein on its surface, which binds to a type of receptor called ACE2 to enter cells in the body of the infected person. ACE2 is present in many cell types and tissues including the lungs, heart, blood vessels, kidneys, liver and gastrointestinal tract. It is also expressed on the arterial and venous endothelial cells of many organs including the adrenal glands. In the lungs, it helps to break down a hormone angiotensin II into another hormone angiotensin I. When the SARS-CoV-2 virus binds to ACE2, it prevents ACE2 from regulating angiotensin II signalling, making more angiotensin II available to injured tissues. The lungs are the primary site of injury by SARS-CoV-2 infection increasing the risk of acute respiratory distress syndrome.¹ The full spectrum of endocrine manifestations of SARS-CoV-2 infection is still unclear. Here, we report a case of adrenal insufficiency as the presenting symptom of COVID-19 infection.

CASE PRESENTATION

A 51-year-old man presented to our hospital's emergency department with two episodes of vomiting. He denied fever, abdominal pain, diarrhoea or any other associated symptoms.

Ten days before current presentation, he was found to have a positive COVID-19 result on PCR testing of a nasopharyngeal sample during a routine screening programme. He was completely

asymptomatic and had stable vital signs. No laboratory tests were carried out but a chest X-ray was normal. No treatment given, as per hospital COVID-19 guidelines, and he was discharged to home quarantine with recommendations regarding airborne and contact precautions.

He was a driver by occupation. He had no medical or surgical history, no family history of chronic or autoimmune diseases, and no previous hospitalisation. He was not on any regular medication. He denied smoking, alcohol intake, sick contact or recent travel.

On examination he was hypotensive with blood pressure 88/58 mm Hg (mean arterial pressure: 70), heart rate of 72 beats/min, respiratory rate of 14 breaths/min, maintaining 100% saturation on room air and afebrile. His physical examination was unremarkable with no weight loss or skin and mucus membrane hyperpigmentation.

INVESTIGATIONS

Laboratory findings showed mild leucopenia of ($3.3 \times 10^9/L$) and normocytic normochromic anaemia with a haemoglobin of 119 g/L. Multiple electrolyte derangements were noted, specifically hyponatraemia (sodium 108 mmol/L), hypochloraemia (chloride 78 mmol/L), mild hypomagnesaemia (magnesium 0.65 mmol/L) and hypophosphataemia, (phosphate 0.60 mmol/L), borderline potassium level of 3.3 mmol/L. The patient was noted to have a non-anion gap metabolic acidosis with CO_2 of 16 mmol/L. His blood glucose was 5.3 mmol/L. Kidney function tests and serum lactate levels were normal. Hyponatraemia work-up was performed and noted a serum osmolality of 240 mOsmol/kg. Urine osmolality and urine sodium were 259 mmol/kg and 24 mmol/L, respectively. Thyroid stimulating hormone was 2.120 mIU/L. Cortisol level at 09:00 was 127 nmol/L. No previous lab results were available to compare. Serum adrenocorticotrophic hormone (ACTH) was not done.

DIFFERENTIAL DIAGNOSIS

Our patient had hypotonic hyponatraemia with hypochloraemia and metabolic acidosis which could not be explained by his presenting symptoms of only two episodes of vomiting and dehydration. This raised the possibility of adrenal insufficiency. Other differentials include syndrome of inappropriate antidiuretic hormone, though urinary sodium was borderline at 24 mmol/L despite good salt intake. Adrenal insufficiency was confirmed by low morning cortisol levels and ACTH stimulation



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test. Our patient had significant improvement in both hyponatraemia and blood pressure with steroids.

TREATMENT

The patient was admitted with a preliminary diagnosis of hypovolemic hypo-osmolar hyponatraemia, and electrolyte disturbance due to vomiting and dehydration. He was started on intravenous fluid hydration with normal saline at rate of 70 mL/hour, and electrolyte replacement.

Repeat laboratory evaluation at 6 hours revealed an improved sodium level of 116 mmol/L. Within 48 hours, the sodium level had corrected 124 mmol/L. The nephrology team was consulted and prescribed sodium chloride tablet 1200 mg two times per day with no notable increase in the serum sodium level.

On day 6 of admission, the sodium level decreased again to 123 mmol/L and the patient continued to have low blood pressure readings with average systolic blood pressure of 80 mm Hg. Endocrinology team was consulted and suggested to perform an ACTH stimulation test, which was consistent with adrenal insufficiency (cortisol baseline 56 nmol/L, cortisol 30 min 197 nmol/L, cortisol 60 min 297 nmol/L). Our final diagnosis was adrenal insufficiency secondary to COVID-19, and the patient was started on 20 mg daily of prednisolone as he could not afford hydrocortisone, with subsequent improvement in blood pressure and sodium level.

OUTCOME AND FOLLOW-UP

On day 10, patient condition improved, and was discharged on 10 mg prednisolone daily with endocrinology follow-up as an outpatient after two negative COVID-19 PCR results. Unfortunately, the patient did not attend the follow-up appointment, so full endocrine screen was not done.

DISCUSSION

Adrenal infections are important, as adrenal gland can be infected by myriad of pathogens including fungi, viruses, parasites and bacteria. Infections can directly or indirectly cause tissue damage and alteration in endocrine function. SARS-CoV-2, like influenza viruses, causes viral amino acid expression which resembles molecules of host's ACTH.² Antibodies produced against virus because of molecular resemblance do not only bind to viral amino acid but also to host own ACTH. This binding limits host's ACTH functionality to stimulate secretion of corticosteroid in response to stress.³

Autopsy studies on patients who died from SARS (the original outbreak in 2003) had shown degeneration and necrosis of the adrenal cortical cells. The SARS-CoV was found in the adrenal glands, demonstrating a direct cytopathic effect of the virus. Hence, cortisol dynamics may be altered in patients with both SARS and COVID-19.² This inadequate corticosteroid response provokes symptoms as a result of a relative adrenocortical insufficiency. Treatment with corticosteroids can relieve the patient's symptoms of adrenocortical insufficiency and provide the corticosteroid levels needed to fight the infection.^{2,4}

SARS (and COVID-19) can cause acute onset adrenocortical deficiency by affecting hypothalamic–pituitary–adrenal (HPA) axis. The ultimate inadequate corticosteroid response provokes symptoms as a result of a relative adrenocortical insufficiency.³

Our patient had no symptoms of weight loss, hyperpigmentation and malaise before this admission. He denies any history of diarrhoea or abdominal pain. His presentation was suggestive of acute rather than chronic adrenal insufficiency due to his recent COVID-19 disease.

However, it is difficult in the absence of a serum ACTH level to determine whether our patient had primary adrenal failure secondary to adrenalitis by viral infection or secondary adrenal failure due to HPA axis disruption. He made good recovery from his symptoms, and was discharged with outpatient follow-up for pituitary gland hormone levels, pituitary and adrenal imaging though he never attended the follow-up clinic.

Leow *et al*⁵ studied hypocortisolism in patients who had recovered from SARS-CoV. Those with an intact HPA axis at the time of acquiring SARS-CoV were included. Three months after recovery, nearly half of the patients had hypocortisolism, of which majority had central hypocortisolism as evident by low ACTH levels. It was noteworthy that the majority of these patients had not received any systemic steroids for SARS ruling out the possibility of HPA axis suppression by exogenous corticosteroid use. Interestingly, hypocortisolism was transient and resolved in two-thirds of the patients within a year.

During the SARS outbreak, indiscriminate use of short-duration, high-dose glucocorticoids was questioned and not found to be universally useful.⁶ However, the RECOVERY trial, launched in March 2020 showed an effect of low-dose dexamethasone in those on critically ill patients on ventilators. There was also an effect on oxygen-dependent patients, but no benefit in mild disease.⁷

A clinical research study on serum cortisol and ACTH changes in patients with severe COVID-19 is ongoing.⁸

Data on cortisol dynamics in patients with COVID-19 are not yet available. Nevertheless, clinicians must be vigilant about the possibility of an underlying relative cortisol deficiency in patients with COVID-19.⁴

Recently, there have been some cases reported with COVID-19 causing adrenal haemorrhage and infarction which further supports our case by highlighting that COVID-19 can affect adrenals by multiple factors including hypercoagulability, direct endothelial damage, microvascular thrombi and susceptibility of adrenals to infarction or haemorrhage due to their vascular anatomy. Physicians should have high index of suspicion for adrenal insufficiency in patients with COVID-19 presenting with hyponatraemia and hypotension.^{9,10}

Contributors MH wrote the initial manuscript and obtained consent. SA initiated the idea and reviewed the Discussion part. WHG finalised the manuscript, edited and revised it for BMJ.

Patient's perspective

I was feeling nervous initially with COVID when my blood pressure started dropping but I feel better now with steroids.

Learning points

- ▶ COVID-19 can affect adrenal function and cause both primary and secondary adrenal insufficiency.
- ▶ High index of suspicion should be there for adrenal insufficiency in patients with COVID-19 with hyponatraemia and hypotension.
- ▶ Routine use of glucocorticoids in patients with COVID-19 is controversial, but clinicians must consider relative cortisol deficiency in these patients.
- ▶ Adrenal insufficiency in COVID-19 might be transient but follow-up is warranted.

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