CASE REPORT

First presentation of Addison's disease as hyperkalaemia in acute kidney injury

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SUMMARY

Addison's disease is a rare endocrine disorder that frequently presents with non-specific symptoms, but may deteriorate rapidly into life-threatening Addisonian crisis if left untreated. Diagnosis can be difficult in patients without a suggestive medical history. We describe a case of a 37-year-old man who was admitted with acute kidney injury and hyperkalaemia, resistant to treatment with insulin/dextrose and calcium gluconate. On clinical examination, he was found to be hyperpigmented; a subsequent random serum cortisol of 49 nmol/L affirmed the preliminary diagnosis of Addison's disease. The patient's hyperkalaemia improved on treatment with hydrocortisone, and a follow-up morning adrenocorticotrophic hormone of 1051 ng/L confirmed the diagnosis.

7.3 mmol/L (3.5–5.3 mmol/L), with acute renal failure: urea 20.1 mmol/L (2.5–7.8 mmol/L), creatinine (Cr) 175 µmol/L (60–125 µmol/L) and estimated glomerular filtration rate 33 mL/min (minimum 60 mL/min). The patient had an elevated creatine kinase (CK) level of 1162 IU/L (60–250 IU/L), was biochemically euthyroid with serum free T4 10.80 pmol/L (7.5–21.1 pmol/L) and thyroid-stimulating hormone 1.69 mIU/L (0.34–5.6 mIU/L), and found to be acidotic with a pH of 7.28 (7.35–7.45) and lactate of 1.0 mmol/L (0.5–1.6 mmol/L) on a venous blood gas. Plasma fasting glucose was 4.4 mmol/L (3.9–5.8 mmol/L). His ECG showed tall, tented T waves in all leads. The urinalysis on admission was negative for protein, blood, leucocytes and nitrites. The urine-specific gravity was 1.020 kg/m³ (1.000–1.030 kg/m³).

BACKGROUND

While one of the 'classic' presenting features of Addison's disease is a combination of hyponatraemia with hyperkalaemia,^{1–3} patients presenting primarily with acute kidney injury (AKI) have also been described.⁴ The current case involved persistent hyperkalaemia in the presence of AKI. This combination led to the delayed diagnosis of adrenal insufficiency, as the hyperkalaemia was initially attributed to kidney injury. As emphasised in previous studies, the clinical examination can be crucial in arriving at a preliminary diagnosis.⁴

CASE PRESENTATION

A 37-year-old man presented with a 7-day history of generalised myalgia, lethargy and limb weakness. He denied any history of trauma, vomiting, diarrhoea, or chest or urinary symptoms, and had no recent foreign travel. Other than an appendectomy as a child, he did not have a significant medical history. He was not on any regular medications but did report an allergy to penicillin noted from childhood. He lived with his partner and two children and worked regular 15 h shifts as a taxi driver. He had quit smoking 1 month previously and had a 20 pack-year history.

On admission, he was noted to be sweaty but afebrile; initial examination was unremarkable apart from cold peripheries and a blood pressure of 95/69 mm Hg, respiratory rate of 20 breath/min, oxygen saturation of 99% on room air and a regular heart rate of 60 bpm.

INVESTIGATIONS

Initial blood tests revealed hyponatraemia 131 mmol/L (133–146 mmol/L) and hyperkalaemia

DIFFERENTIAL DIAGNOSIS

The patient's symptoms and deranged electrolytes were initially considered to be the result of AKI of unknown origin. Rhabdomyolysis was considered as a possible cause; however, although a CK level of more than five-times the upper limit is usually diagnostic of rhabdomyolysis, acute renal failure would require CK levels in excess of 16 000 IU.⁵ Furthermore, the patient had a normal serum calcium value of 2.49 mmol/L (2.2–2.6 mmol/L), a normal serum-adjusted calcium value of 2.41 mmol/L (2.2–2.6 mmol/L), alanine transaminase of 33 U/L (1–45 U/L), alkaline phosphatase of 84 U/L (30–130 U/L) and a serum magnesium value of 0.86 mmol/L (0.7–1 mmol/L). Serum phosphate levels were not requested on admission to definitely determine rhabdomyolysis. In addition, myoglobin was not detected in the urine sample as indicated by the 'negative blood' urinalysis result. An autoimmune screen was therefore requested.

After admission to the emergency department, the patient was treated with 10 mL of 10% calcium gluconate intravenously over 5 min, 2 L stat normal saline and 10 units actrapid with 50 mL of 50% glucose over 20 min. The venous blood gas was subsequently repeated and showed electrolyte levels to have worsened with potassium 7.5 mmol/L, sodium 129 mmol/L and glucose 3.7 mmol/L.

On re-examination of the patient, he was noted to be hyperpigmented. This was particularly noticeable on the forehead, oral mucosa, knuckles and surrounding an old appendectomy scar. On further questioning, the patient admitted to having felt dizzy and thirsty for several days prior to presentation. A diagnosis of primary adrenal insufficiency was suspected, and further blood tests

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revealed a random serum cortisol level, taken at 10.30, of 49 nmol/L (200–750 nmol/L). This test (despite inherent shortcomings due to imprecision in cortisol assays)⁶ has been suggested as a useful first test in suspected Addison's disease before conducting any form of adrenocorticotrophic hormone (ACTH) stimulation test.⁷ In this case, a short Synacthen test was attempted and abandoned, as it was impossible to gain further peripheral vascular access due to intravascular hypovolaemia.

TREATMENT

After the initial course of calcium gluconate, salbutamol, insulin and glucose infusions in the emergency department, the patient was treated with 100 mg intravenous hydrocortisone, as per local treatment protocol for adrenal insufficiency, followed by six-hourly 50 mg intravenous hydrocortisone for 24 h.

Serum potassium levels remained consistently elevated during the first 24 h of admission, despite four subsequent courses of 10 units of actrapid in 50 mL of 50% glucose and regular salbutamol nebulisers of 5 mg and normal saline 1 L every 8 h. The patient reported drowsiness and a burning sensation across his chest after being given calcium gluconate; therefore this was discontinued and he was started on 15 mg calcium resonium four times a day.

Throughout this treatment, potassium levels decreased to 7 mmol/L and then 6.5 mmol/L, but later increased to 7.3 mmol/L before settling at 6.5 mmol/L. Arterial blood gas results showed acidosis and repeated ECGs consistently demonstrated sinus rhythm with tall T waves.

Concerns were raised after the patient did not respond to four courses of insulin and glucose, and discussion with intensive therapy unit (ITU) was considered regarding haemofiltration. However, the patient's symptoms were rapidly resolving and his ECG did not show any arrhythmias. Moreover, he continued to produce good volumes of urine with fluid resuscitation, with an average of 117 mL/h for the first 12 h followed by an average of 100 mL/h for the next 48 h. As such, the patient did not undergo haemofiltration. His potassium eventually decreased to within the normal range after a fifth course and was 4.8 mmol/L on discharge, with sodium 137 mmol/L and glucose 5.0 mmol/L. Throughout these 24 h, the patient was asymptomatic and reported that his myalgia and leg weakness had resolved.

OUTCOME AND FOLLOW-UP

The patient continued to receive intravenous hydrocortisone and intravenous fluids over 3 days, which led to the resolution of both the acute renal failure and the electrolyte abnormalities. The AKI in this case was deemed to be caused by hypovolaemia for several reasons. The patient's disproportionately high levels of urea in relation to creatinine, as confirmed by the blood urea nitrogen (BUN): serum Cr ratio of 28.4 (normal BUN:Cr ratio is 10–15:1),⁸ is an indicator of prerenal azotaemia.⁹ It is important to note that several processes, such as gastrointestinal bleeding and increased protein catabolism, could increase the BUN:Cr ratio due to increased levels of urea. A fractional sodium excretion of <1% could have further confirmed renal hypoperfusion, however, this was not measured. Although BUN:Cr does not differentiate between prerenal azotaemia and acute tubular necrosis,¹⁰ it can be used along with other parameters to indicate prerenal azotaemia. As such, a BUN:Cr >20, in addition to the patient's clinical signs on admission, including hypotension (blood pressure 95/69 mm Hg), cold, clammy peripheries and difficult intravenous access, coupled with the urine-specific gravity of 1.02, indicative of dehydration,¹¹ supported a clinical diagnosis of prerenal azotaemia. Further causes of renal failure were not considered, and a renal ultrasound was not performed

as the patient responded completely to hydrocortisone and fluid resuscitation.

An early morning ACTH measurement taken at discharge revealed an ACTH of 1051 ng/L (reference range for morning ACTH: <30 ng/L), confirming the diagnosis of primary adrenal insufficiency. The patient was discharged on oral hydrocortisone 30 mg three times a day and fludrocortisone 100 mcg once daily. Fludrocortisone is used primarily in adrenal insufficiency due to its potent mineralocorticoid activity. It is used as a replacement for aldosterone, and hence prevents loss of sodium and water, which results in the hypovolaemia and hypotension typically seen in Addison's disease.

The patient was followed up in the endocrinology clinic, for further investigations. The initial autoimmune screen, which was requested for his renal failure, was negative for anti-neutrophil cytoplasmic antibody, antinuclear factor and anti-glomerular basement membrane antibody; 21 hydroxylase autoantibodies, indicative of autoimmune primary adrenal insufficiency, were negative; 21 hydroxylase autoantibodies are present in 80–90% of patients with Addison's disease, but may decrease to 60% if the disease duration has been longer than 15 years.¹² There is an association between autoimmune Addison's disease and other autoimmune endocrine diseases. In autoimmune polyglandular syndrome (APS), thyroid dysfunction and diabetes mellitus may also be present alongside adrenal insufficiency.¹³ The patient in this case was biochemically euthyroid, and did not have a history of diabetes; his glycated hemoglobin was 36 mmol/mol (20–42 mmol/mol). Infectious causes of Addison's disease were considered; however, the patient denied any previous infections, and specifically tuberculosis (TB), this was not further investigated. TB is the leading cause of adrenal insufficiency in developing countries.¹⁴

There are some limitations in the case described above. The patient did not have CT imaging of the adrenal glands during his hospital admission, as infiltrative, haemorrhagic, or neoplastic disease was not suspected. This was later arranged as an out-patient investigation in light of the negative result for 21 hydroxylase autoantibodies. However, the patient did not attend further radiological investigations. Second, despite being regarded as the 'gold standard' test for the diagnosis of Addison's disease, the short Synacthen test was not reattempted, as it would not have added further diagnostic value given the patient's ACTH level and presence of evident adrenal failure. Similarly, plasma renin and renin/aldosterone ratios were not measured.

DISCUSSION

Addison¹ first described the clinical presentation of primary adrenal insufficiency in 1855 in his paper, *On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules*. His description of the cardinal symptoms—fatigue, weight loss, abdominal irritability and skin hyperpigmentation—has barely been altered since, and remains relevant today thanks to the accuracy and fluency of his findings.¹⁵ Despite this, the condition continues to be a diagnostic challenge in the 21st century, mainly due to the slow and non-specific progression of symptoms, which offer a wealth of differential diagnoses.¹⁵

Hyperkalaemia in combination with a marked hyponatraemia occurs classically in Addison's disease.^{4 16} However, when observed in the presence of AKI, as demonstrated by this case, the clinician can be distracted from adrenal insufficiency, which risks leading to a delayed diagnosis, and potential serious morbidity and mortality.

Hydrocortisone treatment in critically ill patients with suspected Addison's disease should be initiated based on clinical

signs and electrolyte levels alone.^{3 6} It is suggested that hydrocortisone should be trialled empirically even in situations where hypothalamic-pituitary-adrenal axis testing (via serum cortisol or ACTH stimulation) is inconclusive, but clinical evidence compelling.⁶ In the present case, this was necessitated by the patient's hyperkalaemia. This has been described previously, in a similar case with a more prominent AKI but without hyperkalaemia, and the importance of prompt initiation of hydrocortisone administration stressed.⁴

In addition, it should be noted that standard treatment for hyperkalaemia with ECG changes (insulin/dextrose and 10% calcium gluconate) may be ineffective in reversing hyperkalaemia in Addisonian crisis, as well as may actually trigger or exacerbate hypoglycaemia.^{3 4} As emphasised by a new National Alert from National Health Service (NHS) England, death from Addisonian crisis still occurs in the UK, as a result of delayed treatment.¹⁷ This can be prevented if a diagnosis of Addison's disease is considered in patients with particularly high and resistant potassium levels.

Finally, this case highlights the crucial importance of the clinical examination. Hyperpigmentation is known to be one of the most common signs of Addison's disease,^{1 16} and specifically of primary adrenal insufficiency,⁶ but is easily missed. Indeed, the hyperpigmentation often predates any other signs or symptoms by long periods of time;¹⁸ and on later questioning, the patient in this case, too, admitted that his skin had darkened over the course of several months.

Learning points

- ▶ This report describes a non-specific presentation of Addison's disease.
- ▶ A high index of suspicion is warranted in patients with persistent hyperkalaemia.
- ▶ Prompt initiation of hydrocortisone treatment is based on preliminary clinical diagnosis.

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