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lesson of the month (1)

Addison's disease presenting with acute kidney injury

This lesson describes a case of Addison's disease presenting with acute kidney injury. The condition is briefly reviewed and a number of learning points are highlighted for clinicians encountering similar presentations.

Lesson

A 54-year-old man was referred to hospital with a four-week history of lethargy, nausea, poor oral intake, weight loss and light-headedness. He reported no thirst, salt craving, diarrhoea or vomiting. His past medical history included hypertension, for which ramipril 2.5 mg had recently been discontinued, and hypothyroidism for which he took levothyroxine.

Examination revealed signs of intravascular hypovolaemia. His blood pressure was 104/76 mmHg without postural drop. His heart rate was 112 beats per minute. No peripheral stigmata of acute or chronic disease was noted.

Investigations included haemoglobin 14.7 g/l, white cell count 6.6×10^9/l, sodium 132 mmol/l, potassium 4.8 mmol/l, creatinine 255 umol/l, estimated glomerular filtration rate 23 ml/min/1.73m^2, urea 18.5 mmol/l, normal liver function tests, calcium 2.64 mmol/l, albumin 47 g/l, glucose 5.9 mmol/l, thyroxine 16.1 pmol/l and thyroid stimulating hormone 6.12 mu/l. Serum immunoglobulins, serum electrophoresis, anti-cytoplasmic antibodies and complement levels were normal. Urinalysis was unremarkable.

Blood results from four months previously included creatinine 132 umol/l, sodium 136 mmol/l and potassium 5.2 mmol/l. His symptoms were therefore attributed, at least in part, to acute kidney injury and uraemia secondary to hypovolaemia. Renal tract ultrasonography was unremarkable and renal biopsy was therefore undertaken. A minority of the tubules showed vacuolisation of the cytoplasm with focal apical blebbing, suggestive of very mild acute tubular injury. Arteriolar hyalinosis and mild atherosclerotic changes were noted. There was no evidence of vasculitis or glomerulonephritis.

There was no improvement in serum creatinine despite fluid replacement with intravenous (iv) normal saline. Furthermore, he developed hyponatraemia (serum sodium concentration 115 mmol/l), low serum osmolality (246 mosmol/kg), raised urinary osmolality (281 mosmol/kg) and raised urinary sodium (42 mmol/l)). A diagnosis of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion was made and, despite the histological suggestion of acute tubular necrosis, a fluid restriction of 1 litre was instituted. Over the next few days, a slight improvement in serum sodium concentration (124 mmol/l) was observed, but there was a deterioration in the serum creatinine concentration (280 umol/l) and hyperkalaemia (6.7 mmol/l) developed. The diagnosis of Addison's disease (AD) was subsequently considered. Re-examination revealed hyperpigmentation of the palmar creases and buccal pigmentation. The diagnosis was confirmed with a short synacthen test (serum cortisol levels of 184 nmol/l at 0 minutes, 191 nmol/l at 30 minutes and 179 nmol/l at 60 minutes).

Commencement of hydrocortisone therapy and iv fluid replacement led to an improvement in the patient's symptoms, normalisation of blood pressure, resolution of electrolyte abnormalities and a return to baseline renal function. The patient was discharged on hydrocortisone and fludrocortisone.

Discussion

Addison's disease describes primary adrenal insufficiency arising from destruction or dysfunction of the entire adrenal cortex. It is a rare but potentially fatal condition occurring with an incidence of 4.7 to 6.2 per million people.[1] Approximately 80% of cases result from autoimmune disease. Less common causes include granulomatous disease (eg sarcoidosis, tuberculosis), haematological malignancies, metastatic malignant disease, infiltrative metabolic disease (eg amyloidosis), congenital adrenal hyperplasia, abdominal radiation and the abrupt cessation of long-term steroid therapy.

Adrenal insufficiency may present acutely with hypotension, hypovolaemic shock, vomiting, abdominal pain and fever. However, an insidious presentation with fatigue, weight loss, nausea and anorexia is more common. A feature specific to primary adrenal insufficiency is hyperpigmentation of the areas exposed to friction, including the palmar creases, knuckles, buccal mucosa and recent scars.

Biochemical abnormalities include hyponatraemia, hyperkalaemia, elevated urea concentration, hypoglycaemia and hypercalcaemia. The diagnosis is confirmed by demonstrating inadequate cortisol production by way of a short synacthen test. Once confirmed, a plasma adrenocorticotrophic hormone concentration should also be measured; a raised concentration will distinguish AD from secondary adrenal insufficiency. Further investigations, including anti-adrenal antibodies and radiological

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imaging of the adrenal glands, are required to determine the underlying cause. Treatment involves the lifelong replacement of glucocorticoid and mineralocorticoid.

Although rarely reported, AD is a well described cause of acute kidney injury.[2] Although not present initially, our patient also developed the classical biochemical picture of hyponatraemia and hyperkalaemia during his hospital admission. Hyponatraemia is the most common electrolyte disturbance seen in hospitalised patients.[3] Hyponatraemia in patients with AD results predominantly from sodium chloride wasting due to the mineralocorticoid deficiency and, in turn, leads to extracellular fluid volume depletion. Aldosterone also increases potassium and hydrogen ion secretion; deficiency is therefore further characterised by hyperkalaemia and non-anion gap metabolic acidosis.

Glucocorticoid deficiency does not cause a negative sodium balance and may, in fact, promote a positive sodium balance. However, the absence of cortisol has major effects on haemodynamics, promoting a decrease in the cardiac index with an inadequate response of systemic vascular resistance to maintain the mean arterial pressure.

The combination of mineralocorticoid deficiency induced extracellular fluid volume depletion and a glucocorticoid deficiency related reduction in cardiac index results in reduced renal perfusion and a reduction in glomerular filtration rate. This was the likely predominant mechanism underlying the renal impairment evident in this patient.

The development of renal microangiopathy and renal failure has been described in two patients with AD.[4] In both cases, renal biopsy identified enlargement of some glomeruli with increased lobularity and deposits of hyaline eosinophilic material. Renal arterioles and some of the intralobular arteries showed fibroblastic intimal proliferation, fibrinoid necrosis and thrombosis. Fibrin deposits in the afferent arterioles and glomerular capillaries suggested intravascular coagulation.

The described case illustrates a number of learning points for nephrologists encountering AD. Firstly, the low incidence and insidious non-specific presentation of AD necessitates that clinicians maintain a high index of suspicion in order to make the diagnosis and avoid unnecessary and potentially harmful investigations; this patient underwent a renal biopsy prior to diagnosis. Approximately 50% of patients have signs and symptoms for more than one year before the diagnosis is established.[2]

Secondly, acute kidney injury may be the presenting feature of AD. The classical biochemical findings of adrenal insufficiency may not always be present – although hyponatraemia occurs in 90% of cases, hyperkalaemia arises in only 65%.[5] When these features are present in association with acute kidney injury, they may erroneously be considered to be a manifestation of the renal failure, increasing the likelihood of a delay in diagnosis.

Thirdly, despite a clinical picture of intravascular hypovolaemia, fluid resuscitation alone (ie in the absence of steroid replacement) will rarely result in resolution of acute kidney injury in patients with undiagnosed adrenal insufficiency, and this should prompt the clinician to consider AD as an explanation of the renal impairment. Furthermore, a limited response to catecholamines, which may be utilised for their inotropic actions in hypotensive patients, should also signal the possibility of the disease.

Fourthly, the presence of hyponatraemia in a patient with clinical signs of intravascular hypovolaemia who is not receiving diuretics is unusual. This too should prompt consideration of the diagnosis of AD.

Fifthly, hyponatraemia with inappropriately raised urine osmolality and sodium concentrations most commonly results from SIADH, for which the first-line treatment is fluid restriction. However, these findings may also arise in adrenal insufficiency, the treatment of which is fluid resuscitation and steroid replacement. Failure to appreciate that adrenal insufficiency must be excluded prior to diagnosing SIADH may therefore result in the inappropriate and life-threatening treatment of a patient with AD.

Finally, hyperkalaemia occurring in the context of AD is potentially life threatening. Clinicians should be aware that treatment with iv insulin and glucose, a component of the standard therapy for hyperkalaemia, should be avoided in patients with AD; not only is it ineffective, it may also provoke or potentiate dangerous hypoglycaemia, to which these patients are already predisposed due to their low levels of glucocorticoid.[6] Intravenous saline and hydrocortisone therapy will correct hyperkalaemia due to adrenal insufficiency.

References

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