Managing an acute case of Addison's disease

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The immediate management and investigation of an acute endocrine presentation in general practice is discussed in this section. It is inspired by, but not based on, a real patient situation.

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Glenda, a 59-year-old retired interior decorator, presents to you, a GP, on a Monday morning, seeking an antiemetic. It is the first time you have met Glenda. She says she developed vomiting and diarrhoea over the weekend, and is unable to tolerate oral fluids. She thinks this may be due to having eaten undercooked chicken while out at Sunday lunch.

On further questioning, she describes several months' history of lethargy, generalised headaches, abdominal pain, intermittent loose stools and nausea. She has also unintentionally lost 10 kg of weight over the past six months, and now feels dizzy on standing up. Her past medical history includes autoimmune Hashimoto's thyroiditis treated with thyroxine 150 µg daily, but she is otherwise in good health. She takes no other medications and no over-the-counter preparations. Her family history includes a 3-year-old granddaughter who was recently diagnosed with pernicious anaemia and vitamin B_{12} deficiency.

What are your initial thoughts?

Answer: Although Glenda could have gastroenteritis, the 'red flags' are her inability to tolerate oral fluids, her dramatic weight loss and concomitant longstanding history of abdominal symptoms. She also has a personal and family history of autoimmune disease that increases her lifetime risk of developing several other autoimmune conditions. Differential diagnoses include an infective or inflammatory gastrointestinal process, malignancy such as lymphoma, and autoimmune conditions, including adrenal insufficiency and coeliac disease.

It is important to assess Glenda's thyroid status given her history of hypothyroidism and current thyroxine replacement. Over-replacement of thyroxine may result from increased absorption or undetected changes in her thyroid function if not tested recently. This can lead to weight loss and hyperdefaecation.

How do you examine Glenda?

Answer: You assess the severity of Glenda's volume depletion and assess for any other factors to pinpoint life-threatening diagnoses.

On general inspection, Glenda has a body mass index (BMI) of 22 kg/m^2, with global hyperpigmentation, heart rate of 89 beats per minute, respiratory rate 18 breaths per minute and oxygen saturation 98% on room air. She is afebrile. Her blood pressure is 135/60 mmHg supine, falling to 95/50 mmHg on standing with symptomatic dizziness. She is clinically euthyroid without a palpable goitre. She appears mildly dehydrated, but has normal results on cardiovascular and respiratory examinations. There is mild tenderness in her epigastrium, but no evidence of guarding or rigidity. There is no palpable lymphadenopathy in the cervical, axillary or inguinal regions. There is no evidence of bruising or petechiae.

How has the examination refined your differential diagnoses?

Answer: The presence of global hyperpigmentation in the context of known autoimmune disease and active abdominal symptoms, weight loss and postural hypotension highlights a need to exclude hypocortisolism.

It is reassuring that Glenda appears clinically euthyroid, but it is important to formally check her thyroid function. There are no signs to suggest underlying malignancy or infection.

It is concerning that there is such a large postural drop in blood pressure (>10 mmHg with erect hypotension and postural symptoms). This places Glenda at risk of syncope or dangerous hypotension under stress conditions. As a diagnosis of hypocortisolism is being considered, it is important to urgently refer her to the local emergency department to expedite investigation and management.

What investigations are needed to confirm your differential diagnoses?

Answer: Given the history of nausea and vomiting, baseline investigations should include biochemical tests of liver and kidney function, electrolytes and haematology to assess for signs of infection and

haematological malignancy (see Table 1 for results of initial blood tests).

What are the most striking features in the initial investigations and how do you investigate these further?

Answer: The striking abnormality is the hyponatraemia (sodium level 114 mmol/L), with a low osmolality despite recent vomiting. Glenda also has hyperkalaemia and borderline asymptomatic hypoglycaemia (likely due to increased insulin sensitivity from weight loss and glucocorticoid deficiency), despite not being on any previous hypoglycaemic agents.

As Addison's disease is one of the differential diagnoses, a morning serum cortisol level and adrenocorticotrophic hormone (ACTH) level should be ordered, as well as thyroid function tests (see Table 2 for results).

How do you interpret these endocrine results?

Answer: Thyroid function tests are all within normal limits, excluding hyperthyroidism as a cause of her symptoms. Importantly Glenda's morning cortisol level is low at 83 nmol/L with a markedly elevated ACTH level of 367 pmol/L. A morning cortisol level of less than 100 nmol/L combined with the very high ACTH level confirms a diagnosis of primary hypocortisolism due to adrenal dysfunction. A morning cortisol level of 500 nmol/L or above effectively excludes Addison's disease. If cortisol and ACTH levels are not clearly abnormal, an outpatient short Synacthen test may be required for definitive diagnosis. Clinical acumen and consideration is the key to diagnosis of Addison's disease. Investigation and subsequent treatment of this condition is potentially life-saving.

Table 1. Initial blood test results

Test (units)	Result	Reference range
Sodium (mmol/L)	114	134–145
Potassium (mmol/L)	5.6	3.2–5.0
Chloride (mmol/L)	84	95–110
Bicarbonate (mmol/L)	23	22–32
Anion gap (mmol/L)	13	12–20
Urea (mmol/L)	5.2	2.5–6.5
Creatinine (μmol/L)	73	45–90
Estimated glomerular filtration rate (mL/min/1.73 m^2)	71	>59
Corrected calcium (mmol/L)	2.58	2.15–2.55
Magnesium (mmol/L)	0.7	0.70–1.10
Phosphate (mmol/L)	1.30	0.75–1.50
Random glucose (mmol/L)	3.4	3.6–6.0
Full blood count	Normal	
Osmolality (mmol/L)	258	280–300

Table 2. Endocrine investigation results

Test (units)	Result	Reference range
Cortisol, 9 am (nmol/L)	83	200–600*
Adrenocorticotrophic hormone (pmol/L)	367	2–10
Thyroid-stimulating hormone (mIU/L)	2.49	0.4–4.0
Thyroxine (pmol/L)	14.2	9.0–19.0
Triiodothyronine (pmol/L)	3.1	2.6–6.0
Parathyroid hormone (pmol/L)	1.2	1.0–7.0

* Laboratory reference range must be interpreted with caution given diurnal secretion of cortisol. For example, a serum cortisol level of 201 nmol/L is likely to be normal in the afternoon but may be inadequate at 8 am.

What are the possible causes of hypocortisolism?

Answer: Adrenal insufficiency (hypocortisolism) is a relatively rare but important disease to diagnose. It can present insidiously and with nonspecific symptoms, with the diagnosis often delayed for two to three years.

Hypocortisolism can occur due to adrenal disease or pituitary disease (pituitary disease accounts for over 80% of cases). The ACTH level should be measured before administration of glucocorticoids. A low or normal ACTH level suggests a diagnosis of secondary or pituitary causes, whereas an elevated ACTH level, as in Glenda's case, points to an adrenal cause. Addison's disease refers to an autoimmune adrenalitis leading to pancortical adrenal hypofunction, resulting in decreased glucocorticoid, mineralocorticoid and androgen production. This may occur gradually and not be detected until a catastrophic crisis.

Autoimmune adrenal insufficiency was first described by an English physician Thomas Addison in 1855. The incidence is 0.8 per 100,000 population/year and the prevalence is 4 to 11 per 100,000 people, with higher incidences in white populations. Interestingly, six years earlier in 1849 Thomas Addison also made the first description of pernicious or 'Addisonian' anaemia, which is also present in Glenda's family history.

How can the symptoms, signs and investigation results be explained by the presence of Addison's disease?

Answer: Hyponatraemia occurs because of mineralocorticoid deficiency causing sodium

Table 3. Adrenal Investigation results

Test (units)	Result	Reference range
21-hydroxylase antibody (U/mL)	34.8	<1
Renin (mIU/L)	479	3.3–41
Aldosterone (pmol/L)	146	100–950

Table 4. Bone mineral density

Site	BMD (g/cm^2)	T score	Z score
Lumbar spine	0.991	-0.8	-0.1
Left femoral neck	0.802	-1.2	-0.2

and water depletion, and increased antidiuretic hormone levels due to glucocorticoid deficiency. Loss of sodium with concomitant retention of potassium and intravascular depletion with an associated trend towards metabolic acidosis promote hyperkalaemia, and in some cases associated ECG changes. Glucocorticoid deficiency is also associated with bone hypermetabolism, leading to mild parathyroid hormone-independent hypercalcaemia in some cases.

Hyperpigmentation occurs due to loss of cortisol-induced negative feedback in the hypothalamus and pituitary, leading to increased production of proopiomelanocortin (prohormone of ACTH and alpha melanocyte-stimulating hormone), resulting in increased melanin synthesis. Pigmentation is generally global, with the hallmark being hyperpigmentation of nonsun-exposed areas and areas of increased friction or pressure, such as joints, shoulders and belt marks. The oral mucosa can also be affected. Rarely vitiligo can occur due to associated autoimmune destruction of melanocytes.

If patients with Addison's disease present with a major illness, they may become acutely and rapidly unwell, with hypotension, tachycardia and shock. This can be in the context of an acute physical injury, acute infection or organ failure and is often unresponsive to fluid resuscitation in the absence of recognition for immediate emergency glucocorticoid replacement. In this case, Glenda appeared to have had symptoms over the past several months, but rapidly deteriorated over the previous 24 hours due to concurrent gastroenteritis.

Glenda is escorted by her sister to the emergency department. You phone ahead to provide the history to the admitting officer, so that Glenda is triaged appropriately, and prompt fluid resuscitation and parental glucocorticoid cover can be initiated.

How should Glenda be treated?

Answer: If acutely unwell and during an Addisonian crisis, oral glucocorticoids are poorly absorbed. Hence prompt administration of intravenous hydrocortisone at 50 to 100 mg every six to eight hours depending on the clinical urgency is indicated. Mineralocorticoid replacement is not required as part of initial resuscitation, as deficiency is corrected with normal saline supported by the mineralocorticoid activity of hydrocortisone at stress doses. Fluid restriction should not be initiated in this patient as she is intravascularly depleted from long-standing unrecognised Addison's disease. Concurrent fluid restriction and glucocorticoid replacement can lead to over-rapid correction of hyponatraemia and a risk of central myelinolysis syndromes.

Glenda receives glucocorticoid replacement therapy with intravenous hydrocortisone 100 mg eight hourly, resulting in normalisation of serum sodium, potassium, glucose and calcium levels over 72 hours and resolution of her presenting symptoms.

What investigations should be performed to assess the cause of primary adrenal insufficiency?

Answer: The important causes of adrenal insufficiency include:

- autoimmune adrenalitis, which may be part of polyglandular autoimmune syndrome
- infection, including tuberculosis, disseminated fungal infections and HIV infection
- haemorrhagic infarction, such as in association with meningococcaemia (Waterhouse-Friderichsen syndrome). Use of anticoagulant drugs or heparin therapy, hypercoagulable state, trauma and other severe stress can also predispose a patient to adrenal haemorrhage
- metastatic disease, including lung and breast cancer, melanoma and lymphoma
- use of drugs including inhibitors of cortisol biosynthesis, the anaesthetic agent etomidate, and antimycotics ketoconazole and fluconazole (ketoconazole is used for the treatment of refractory or inoperable Cushing's syndrome).

As Glenda already has a history of autoimmune disease, autoimmune adrenalitis, or Addison's disease, is the most likely diagnosis. To confirm the diagnosis, 21-hydroxylase antibody levels may be measured, which are both sensitive and specific for Addison's disease, being elevated in more than 85% of patients with autoimmune adrenalitis compared with 2.5% of healthy blood donors. This test is available through most laboratories and is now covered by a Medicare rebate. Imaging of the abdomen is also important to exclude infective processes, malignancy or haemorrhage.

Glenda's abdominal CT scan showed bilateral atrophic adrenal glands, without evidence of malignancy, abscesses or haemorrhage. Her 21-hydroxylase antibody level was elevated confirming autoimmune adrenalitis or Addison's disease (Table 3). The elevated renin level reflects mineralocorticoid deficiency.

How should Glenda be treated long term?

Answer: It is important to replace both glucocorticoids and mineralocorticoids in people with primary adrenal insufficiency, in contrast to secondary (pituitary) or tertiary (hypothalamic) hypoadrenalism, as aldosterone is regulated by the renin–angiotensin system, independent of the hypothalamus and pituitary.

The glucocorticoid dose should be weaned from the adrenal crisis dose to a replacement oral dose of cortisone acetate or hydrocortisone 20 to 30 mg/day, usually split into two to three doses across daylight hours, to best

Practice points

- Addison's disease is a rare but important and potentially life-threatening diagnosis.
- Symptoms can be nonspecific but clinical suspicion should be heightened in the presence of fatigue, abdominal symptoms, hyperpigmentation or postural hypotension. Symptoms are completely reversible with appropriate therapy.
- Primary adrenal insufficiency can result in hyponatraemia, hyperkalaemia and metabolic acidosis. In some cases, hypoglycaemia or hypercalcaemia may be present.
- Diagnosis can be established with low morning cortisol plus high ACTH levels; treatment should not be delayed to perform further investigations. In some cases, a short Synacthen test may be required to confirm adrenal insufficiency.
- Initial parenteral glucocorticoid replacement should be promptly given after blood has been drawn.
- Long-term treatment includes glucocorticoid and mineralocorticoid replacement while avoiding and monitoring for signs of over-replacement.
- Monitoring should be guided by symptoms but renin levels may provide a guide for effective mineralocorticoid replacement.
- Vigilance is required for emergence of other autoimmune diseases and consequences of over-replacement.
- Increased risk of Addison's disease or other associated autoimmune disorders for first-degree family members should also be considered.
- Education of patients and their families about adrenal crises, including sick-day management with doubling of glucocorticoid doses, medical alert bracelets and access to intramuscular hydrocortisone, are paramount in the management of Addison's disease.

mimic the natural diurnal variations of cortisol secretion, highest in the morning and lowest at midnight. Other glucocorticoid preparations, such as daily prednisone and dexamethasone may also be used to improve compliance, but do not as accurately reflect endogenous cortisol secretion.

Glenda is discharged on day four on a weaning replacement dose of hydrocortisone 20 mg three times daily (weight 78 kg). At outpatient follow up, this is weaned to a maintenance dose of 14 mg in the morning, 8 mg at 11 am and 4 mg at 3 pm. Fludrocortisone 50 µg daily is also commenced.

What education should be provided for Glenda?

Answer: Although a diagnosis of Addison's disease has now been made, it is important to avoid adrenal crises in the future, which may occur in times of physical stress such as from infection or surgery.

During her outpatient review, a medical alert bracelet and emergency identification card were organised. Glenda was educated on increasing her hydrocortisone dose to double for two to three days during a minor illness, and to alert her GP if she is unable to tolerate her oral dose due to vomiting. Rectal administration of prednisolone is an emergency option in these situations.

If she undergoes general anaesthesia in the future, she must tell her anaesthetist and surgeon, and have a dose of intravenous hydrocortisone at induction of anaesthesia, along with ongoing parental doses while she is 'nil by mouth'. The glucocorticoid dose must never be missed, as she can deteriorate quite rapidly during an adrenal crisis.

Glenda's husband should also be taught how to give intramuscular hydrocortisone (100 mg), in case she becomes seriously unwell and unconscious due to an Addisonian crisis.

How do you monitor patients wtih Addison's disease long term?

Answer: It is important to give the lowest possible glucocorticoid dose to avoid over-replacement and iatrogenic Cushing's syndrome. Higher range dose replacement (>30 to 40 mg/day) has been shown to be associated with increased long-term morbidity and mortality in pituitary-related adrenal insufficiency. Day-curves of cortisol levels may be used to assess replacement efficiency but are time consuming, and in some centres found not to be better than symptomatic monitoring.

Mineralocorticoid replacement should be monitored using: symptoms of volume depletion; signs, including supine and upright blood pressure and pulse; and investigations, aiming for a renin level at the upper end of the normal range and normalised sodium and potassium levels. Hypertension, peripheral oedema and hypokalaemia are signs of excessive mineralocorticoid replacement.

What other conditions are associated with Addison's disease?

Answer: Other autoimmune conditions are more common with Addison's disease. These include endocrine disorders such as type 1 diabetes, autoimmune thyroiditis, Graves' disease, coeliac disease and pernicious anaemia. The combination of autoimmune adrenal insufficiency and other endocrinopathies is termed autoimmune polyglandular syndromes (APS) types I and II. The nonadrenal clinical features include:

- APS I: hypoparathyroidism, mucocutaneous candidiasis, primary hypogonadism and malabsorption
- APS II: autoimmune thyroid disease, Graves' disease, type 1 diabetes, primary hypogonadism, autoimmune hypophysitis, vitiligo, myasthenia gravis, thrombocytopenic purpura, Sjögren's syndrome, rheumatoid arthritis and primary antiphospholipid syndrome.

Over-treatment with glucocorticoids may result in rapid bone loss. In postmenopausal women it is important to establish a baseline bone density and conduct ongoing surveillance, and to initiate management to limit future risk of fracture if osteoporosis is present.

A baseline bone mineral density scan showed osteopenia at the left femoral neck (Table 4). Investigation of ongoing lethargy identifies borderline low vitamin B_{12} levels with positive antibodies to intrinsic factor and gastric parietal cells, indicating pernicious anaemia.

Glenda has been well to date. Her weight has increased and her BMI is now 26 kg/m^2. She has not had any Addisonian crises in the two years since diagnosis. She participates in regular clinical teaching sessions to educate medical students on the recognition, diagnosis and management of Addison's disease and adrenal insufficiency. **ET**

COMPETING INTERESTS: None.