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'Great tan but I feel awful'

Case study – Andrew

'Everyone says I look great but I feel awful. I've lost weight, I feel sick all the time, I don't have any energy and I struggle just to get through the day'.

Andrew is lean and tanned, but he has lost 8 kg since his last visit 3 months ago. He seems a bit flat in mood and listless in manner. He doesn't have a temperature, his blood pressure (BP) is 105/65, and examination of his chest and abdomen is normal. When the results of Andrew's tests come back the following day you are surprised to see abnormalities in his electrolytes (*Table 1*).

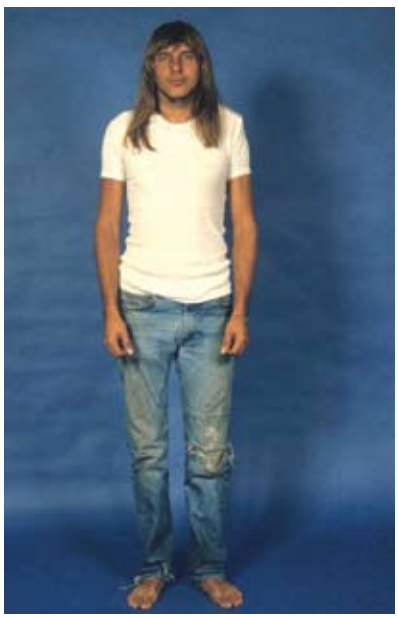


Table 1. Results of Andrew's tests

Sodium	131 mmol/L	(normal range 137–145)
Potassium	5.6 mmol/L	(normal range 3.5–5.9)
Chloride	103 mmol/L	(normal range 100–109)
Bicarbonate	22 mmol/L	(normal range 22–32)
Urea	6.1 mmol/L	(normal range 2.7–8.0)
Creatinine	0.02 mmol/L	(normal range 0.05–0.12)
Glucose	3.1 mmol/L	(normal range fasting 3.8–5.5)

Question 1

What endocrine condition(s) could be responsible?

Question 2

How would you investigate further?

Question 3

What therapy is indicated?

Question 4

What other conditions are Andrew and his family prone to?

Answer 1

Andrew is likely to have the unusual but potentially dangerous endocrine problem, Addison disease (primary hypoadrenalism). He has several classic signs and symptoms:

- clinical – weight loss, postural hypotension, nausea, vomiting or diarrhoea; hyperpigmentation if chronic, and
- biochemical – hyponatremia, hyperkalaemia, hypoglycaemia.

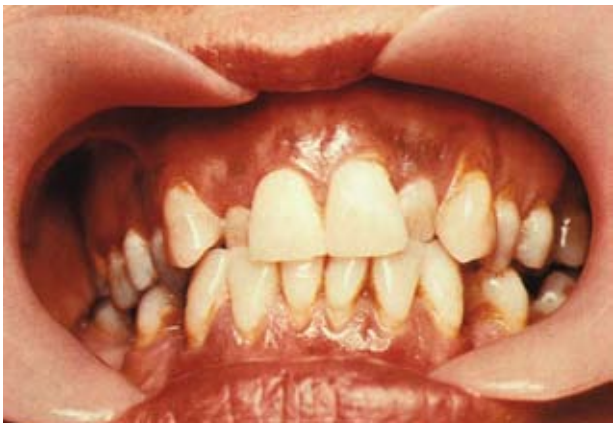
People are often misled by the 'healthy' tan associated with high adrenocorticotrophic hormone (ACTH) levels from the pituitary in response to low cortisol levels. As ACTH is derived from the same precursor protein as melanocyte stimulating hormone, the pituitary's increased secretion of ACTH in response to the low cortisol secretion from a failing adrenal gland stimulates melanocytes and produces a 'great tan'. Increased ACTH also increases pigmentation in other areas – mucosal surfaces, scars and skin creases, which can alert you to the diagnosis (*Figure 1*).

Primary hypoadrenalism reduces the secretion of all adrenal cortical hormones (cortisol, aldosterone and androgen) but not the medullary hormones (catecholamines: adrenaline, noradrenaline).

The lack of cortisol has widespread effects including hypotension, the risk of cardiovascular collapse (Andrew's seated BP is low; standing BP lower at 80/45), hypoglycaemia (Andrew's blood glucose is 3.1 mmol/L). In addition, the loss of aldosterone affects on water, sodium, potassium and acid base metabolism reduces the ability to excrete water, retain sodium, and excrete potassium and acid. Loss of adrenal androgens generally doesn't have significant clinical effects.

Causes of primary hypoadrenalism are listed in *Table 2*.[1]

Figure 1. Andrew's gums



Answer 2

Because normal endocrine glands respond to changes in the internal and external environment, endocrine function testing is aims to:

- stimulate failing glands, and
- suppress overactive glands

For a failing adrenal this means stimulation with exogenous ACTH (a short synacthen test). Blood is taken before and 30 and 60 minutes after a dose of an ACTH analogue (synacthen 0.25 mg intramuscularly). Cortisol levels should exceed 500 nmol/L. Blood is taken to confirm a low cortisol and high ACTH. In an emergency, cortisol replacement can start immediately. A short synacthen test can be organised later when glucocorticoid replacement can be temporarily changed to dexamethasone, which doesn't interfere with the laboratory cortisol assay.

Answer 3

Both primary (adrenal) and secondary (pituitary) hypoadrenalism affect cortisol secretion. However, in secondary hypoadrenalism the renin angiotensin system continues to control aldosterone secretion. Both gluco- and mineralo-corticoid replacement are needed in primary hypoadrenalism whereas only glucocorticoid replacement is required in secondary (pituitary) hypoadrenalism.

Usually there is a diurnal pattern to cortisol secretion that is difficult to mimic – low cortisol at night rising in the early hours and decreasing later in the day. Hydrocortisone or cortisone is given to provide day and night coverage (eg. 20 and 10 mg of hydrocortisone in the morning and evening, or three doses of 10, 4 and 4 mg before breakfast, lunch and the evening meal).

Table 2. Causes of primary hypoadrenalism

- Autoimmune adrenalitis
- Infection (tuberculosis, fungal, HIV, syphilis)
- Neoplasia (secondary lung, breast or colon cancer; lymphoma)
- Medications (ketoconazole, rifampicin, phenytoin)*

* This list is not comprehensive but includes the common causative medications

Table 3. The autoimmune endocrine cluster*

- Thyroid disease – hypo- and hyper-thyroidism, goitre
- Gonadal failure (ovarian, testicular)
- Type 1 diabetes
- Hypoparathyroidism
- Pernicious anaemia

* Formally known as polyglandular autoimmune syndrome type 2

Mineralocorticoid replacement is with fludrocortisone (50–100 µ/day) and is guided by BP and potassium levels.

Patients and their health professionals need to be aware that at times of stress glucocorticoid replacement needs to increase (but not mineralocorticoid). Double the dose and if necessary give glucocorticoid parenterally. Patients who don't have access to emergency services should have a supply of syringes and injectable hydrocortisone (within its expiry date) and should be shown how to draw up and give an intramuscular injection. Clear written instructions should be provided.

Replacement is monitored by the patient's wellbeing and by lack of symptoms and signs of over replacement. There is no laboratory test to monitor glucocorticoid replacement.

Patients may wish to share experiences with others who have hypoadrenalism through the Australian Addison's Disease Association Inc. (www.addisons.org.au). Doctors may also wish to visit this website for patient education material.

Answer 4

If Andrew is confirmed as having autoimmune primary hypoadrenalism, he may also have or develop other autoimmune conditions. The most common cluster is shown in *Table 3*. Approximately 50% of those with primary hypoadrenalism will have, or will develop, one or more of these conditions.

The cluster affects other family members in approximately 50% of cases. Different family members can develop different sequences of the individual components (eg. for Andrew primary hypoadrenalism followed by hypothyroidism and for Andrea, his sister, type 1 diabetes followed by hypoadrenalism).

Other autoimmune disorders can also occur such as vitiligo, rheumatoid arthritis, Sjögren syndrome, myasthenia gravis, antiphospholipid syndrome or serositis.

Conflict of interest: none declared.

Reference

1. Therapeutic Guidelines. Endocrinology. Version 3. North Melbourne: Therapeutic Guidelines Ltd, 2004.

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