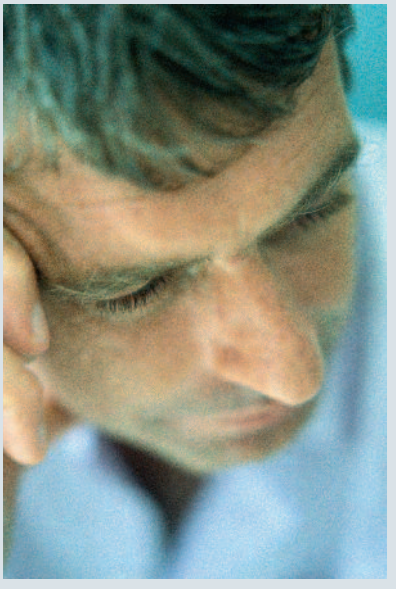
A case of Addison's disease in a 45-year-old man

VIVIENNE MILLER MB BS, FRACGP, DRACOG, DCH, MACPM, MWAME

Bill is a 45-year-old man whom you do not know well, although you have seen his family frequently. He has 'never been ill before' and is taking no medications. His wife has been urging him to see you because he has been unwell for several months. When he finally does see you, he tells you he has lost 5 kg in weight over the past three months, but he has no other symptoms he can think of.



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Dr Miller is a GP in Sydney, NSW.

What questions would you ask him?
Answer: Bill's weight loss needs to be investigated further. Is he nauseated and has he vomited recently? Is he anxious or depressed? Has he been trying to lose weight, skipping meals or increasing exercise? Has he had any bowel changes? How does he feel if he eats – better or worse, and does this change with the food he eats or the amount? Is he drinking normal amounts of water and has he been passing more or less urine than normal? Is he sleeping well? Has he noticed any tremors in his hands or any heat intolerance? Is he feeling the same or worsening with time?

Bill thinks he has lost weight because he does not feel hungry and is not eating as much as normal. If he eats, he feels no better and vaguely nauseated, but he has been craving pretzels and potato chips. He has been very fatigued, which he has put down to skipping meals and working more. His bowels are less regular than normal but otherwise normal. He does not feel depressed or anxious but is beginning to become concerned about the cause of the fatigue, which is worsening.

You examine Bill. The examination is essentially normal apart from a blood pressure of 112/60 mmHg when sitting, dropping to 92/50 mmHg on standing. He is mildly clinically dehydrated. His capillary blood glucose level and urinalysis in the surgery are normal. What investi - gations would you do initially and why?
Answer: Initial investigations would be a full blood count, liver function tests, iron studies and measurement of levels of urea, electrolytes, creatinine, C-reactive protein, thyroid-stimulating hormone, formal blood glucose, vitamin B_{12} and serum corrected calcium. The differential diagnosis is wide but you would be considering a serious malabsorption condition, chronic blood loss (perhaps from a gastrointestinal tumour), thyrotoxicosis, a serious metabolic condition (other than type 1 diabetes, which he clearly does not have) or a chronic infection of some sort.

It is reasonable to request hepatitis serology for hepatitis C, hepatitis A immunoglobulin M and G, and hepatitis B surface antigen (if he is not vaccinated); however, these tests are not indicated initially and could be performed later if the other test results do not suggest an alternative diagnosis. It would also be reasonable to consider measuring the random plasma cortisol level, but this may be difficult to interpret during times of ill health and should only be performed if an adrenal crisis is suspected, in which case the result would be abnormally low.

Bill's electrolyte levels are mildly abnormal, with a serum sodium level of 132 mmol/L (lower range of normal is 135 mmol/L) and a serum chloride level of 91 mmol/L (lower range of normal is 96 mmol/L). His serum potassium level is 5.4 mmol/L (upper range of normal is 5.5 mmol/L). Bill is slightly acidotic with a bicarbonate level of 14 mmol/L (lower range of normal is 16 mmol/L). His blood glucose level is 3.5 mmol/L. The rest of his investigations are normal. What should you do next?
Answer: There is no obvious reason to suspect a diagnosis of hyponatraemia (such as prolonged vomiting or diarrhoea, and this would not also explain the acidosis). It is wise at this point to discuss Bill's condition and his results with an endocrinologist. The clinical picture and test results are consistent with adrenal insufficiency and at this stage the endocrinologist should urgently advise on further investigations and care, or take over Bill's management.

Adrenal insufficiency may be due to primary adrenal failure (Addison's disease) or hypopituitarism. A key feature of Addison's disease is hyperpigmentation, which is due to high levels of adrenocorticotropic hormone (ACTH) and hence only seen in patients with Addison's disease and not in those with pituitary failure.

As autoimmune disease is the most common cause of Addison's disease, some patients may have a personal or family history of autoimmune disorders.

Further urgent investigations for Bill would include urgent measurement of serum cortisol and ACTH levels. A low plasma cortisol level will confirm the diagnosis of Addison's disease (primary adrenal insufficiency). Usually this test is performed early in the morning because this is when ACTH stimulation is greatest and cortisol levels should be highest. The cortisol level is usually lowest at midnight. The ACTH level would be raised in patients with Addison's disease and measurement is often performed as part of the ACTH stimulation test. This test is a quick test that involves the measurement of serum cortisol levels before and after an injection of synthetic ACTH. This will confirm if the adrenal glands are able to produce cortisol. A prolonged ACTH stimulation test may be performed over one to three days if the diagnosis of primary or secondary adrenal insufficiency is unsure.

Serum aldosterone levels are also usually measured in this scenario. If they are low this is more evidence for a diagnosis of Addison's disease and Bill will require pharmacological replacement. Serum renin levels are very high in patients with Addison's disease and serve to separate the various causes of low aldosterone levels, if present.

The endocrinologist arranges for Bill to have further urgent blood tests. His ACTH stimulation test is suggestive of a diagnosis of Addison's disease and his morning serum cortisol level is low. His serum adrenal autoantibodies are positive. A CT scan images the adrenals with difficulty and they appear to be of a smaller size than normal and mildly atrophic. Bill's diagnosis of Addison's disease is confirmed. What are the causes of Addison's disease?

Answer: Autoimmune destruction of the adrenal glands is the most common cause of Addison's disease in developed countries. Iatrogenic causes include the sudden withdrawal of high-dose corticosteroid medication after treatment for at least six days (due to adrenal suppression or, if longer term, adrenal atrophy). Other causes include haemorrhage or infarction of the adrenal glands, adrenal destruction from infection (classically tuberculosis) or metastases, congenital adrenal hyperplasia, rare genetic mutations affecting hormonal receptors, cholesterol or corticosteroid synthesis, X-linked adrenoleukodystrophy (which should be considered in all males with Addison's disease because neurological complications may develop) and amyloidosis.

What is an 'Addisonian' (or 'adrenal') crisis?

Answer: An Addisonian crisis is the life-threatening presentation of severe adrenal insufficiency and most commonly occurs in patients with undiagnosed Addison's disease or in those with the condition who have become acutely unwell (e.g. due to infection or trauma). The symptoms and signs of an Addisonian crisis include severe vomiting and diarrhoea (enough to cause dehydration), hypotension, sudden pain in the abdomen (which may mimic peritonitis), pain elsewhere including the lower back, syncope and profound weakness, fever, confusion and convulsions. Addison's disease may present with hyperpigmentation resulting from stimulation of melanocytes by elevated ACTH, as well as pituitary-derived melanocyte-stimulating hormone. Biochemically, hyponatraemia, hyperkalaemia and, occasionally, hypoglycaemia and hypercalcaemia may be present.

Patients in adrenal crisis need venous access to be established early and cortisol substitution must be started as soon as possible. These patients do not need an ACTH stimulation test; under these circumstances it is sufficient to measure a random cortisol level before starting medication. It should be noted that in the present case Bill presents with a subacute condition. Adrenal crisis needs immediate intervention.

What other conditions are associated with autoimmune Addison's disease?

Answer: Other autoimmune conditions associated with Addison's disease include Graves' disease, chronic Hashimoto's thyroiditis, pernicious anaemia, hypoparathyroidism, myasthenia gravis and dermatitis herpetiformis. Autoimmune polyendocrine syndrome includes the clustering of type 1 diabetes and Hashimoto's thyroiditis.

Among the associated autoimmune diseases, thyroid disease is most common, especially primary hypothyroidism due to Hashimoto's disease. Although most people with Addison's disease will not develop hypothyroidism, it is important in the case of hypothyroidism and Addison's disease to ensure that corticosteroid is replaced before thyroxine is commenced because otherwise excessive metabolic stress may occur.

What does Bill need to know about managing his Addison's disease in future?

Answer: Bill needs to understand that he must take adrenal replacement hormones to replace his levels of cortisol (hydrocortisone or prednisolone most commonly) and aldosterone (fludrocortisone) indefinitely. At times of physiological stress, such as systemic infection, surgery or trauma, he should increase his glucocorticoid levels by, for example, increasing hydrocortisone threefold for three days. If he is unable to take his hormone replacements orally – for example, during a bout of gastroenteritis – he will need parenteral (intramuscular or intravenous) hydrocortisone. Isolated patients should have a supply of hydrocortisone for intramuscular administration and have someone available who can administer this promptly when needed. Bill should purchase a medical alert wrist band and keep some written information about his condition and the dosages of medication in his wallet. He will require periodic blood tests to ensure his condition is well controlled and that he does not develop other associated autoimmune conditions.

Outcome: Bill was initially commenced on hydrocortisone 50 mg four times a day for stabilisation and showed rapid improvement. He was maintained on hydrocortisone 10 mg twice daily and fludrocortisone 100 µg daily. Maintenance can be calculated as 10 to 15 mg/m^2 body surface area per day. He was provided with education about sick-day management, purchased a medical alert wrist band and was educated about the use of injectable hydrocortisone in case of an emergency. He and his family were taught how to administer the injection. Bill was also referred to the Australian Addison's Disease Association (www. addisons.org.au/core.htm) He regained his 5 kg of lost body weight and is being monitored for excessive weight gain, which could indicate an excessive hydrocortisone replacement dose. Bill has improved markedly but has some residual fatigue for which he is seeing his endocrinologist. **ET**