CASE REPORT

Addison's disease and its associations

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SUMMARY

Addison's disease is a relatively rare endocrine condition resulting from adrenal insufficiency due to various causes. Weight loss is a common feature; however, patients may be seen by a variety of specialists, even requiring acute admission before the diagnosis is made. Addison's disease is commonly associated with other autoimmune diseases. In some cases such as autoimmune polyendocrine syndromes (APS) types 1 and 2, these associations are more commonly found. We present a case of one such patient who presented to the acute medical team having been referred to the gastrointestinal services in the previous year for persistent vomiting and weight loss. On review of history, the cause of vomiting and weight loss was questioned and combined with subsequent biochemical testing a diagnosis of Addison's disease was made. The patient was also noted to have other associated endocrine and autoimmune conditions.

BACKGROUND

Addison's disease is not as common as other endocrine conditions such as diabetes or thyroid disease. However, it is an important consideration in acute admissions due to the associated significant morbidity and mortality.¹ It can be very difficult to diagnose due to its varied presentation and often referrals to various specialties occur before a diagnosis is made. Many patients are only diagnosed once acutely admitted in Addison's crisis, which makes prompt diagnosis all the more important. Crisis can also be triggered by sepsis which can also mask symptoms and make the diagnosis difficult. Addison's disease is known to have associations with other conditions; therefore, knowledge of this can lead to prompt diagnosis and earlier management once this diagnosis is made.

CASE PRESENTATION

A 20-year-old female patient was admitted in October with a 3-month history of persistent vomiting between 5 and 15 times a day and weight loss. She was dehydrated and unable to tolerate oral intake due to nausea and vomiting. Her bowel motions were normal; she had no problems with micturition or symptoms of infection, however had noticed significant weight loss in the preceding few months.

She had known hypothyroidism and had previously been referred directly to the gastroenterologists for persistent vomiting. She underwent an oesophagogastroduodenoscopy (OGD) which showed gastritis and therefore, she was started on proton pump inhibitor therapy. A blood test showed negative tissue transglutaminase antibodies,

positive gastric parietal cell antibodies and she was scheduled for a CT enterograph.

Given this history she was treated as ongoing gastritis with vomiting secondary to the above. She had a sodium level of 133 mmol/L and low blood pressure and this was felt to be secondary to dehydration. This was treated with intravenous fluids and she was subsequently discharged on antiemetics.

The patient presented again 4 months later with persistent vomiting with some fresh blood at the end due to a Mallory-Weiss tear. She mentioned ongoing weight loss from 50 kg in August to 41 kg currently and ongoing lethargy. She described some right-sided abdominal pain and a pregnancy test was negative. She denied thyroxine abuse or forced vomiting. The patient was unsure about any relevant family history. She was a social smoker and denied any alcohol intake.

On examination she was very thin, hypotensive and tachycardic. She was clinically dehydrated and was noted to have some mild skin pigmentation.

INVESTIGATIONS

Her sodium levels were 129 mmol/L (normal 133–146 mmol/L), potassium levels normal at 4.9 mmol/L (3.4–5.3 mmol/L), C reactive protein (CRP) 16 (<5), haemoglobin 12.4 g/dL (12.5–16 g/dL), white cell count (WCC) 11.6 ($4\text{--}11 \times 10^9/\text{L}$) and she had a mild eosinophilia. Given the history and findings a random cortisol was requested which came back at 2 nmol/L (102–535 nmol/L). Liver and renal function tests were normal. Thyroid stimulating hormone (TSH) was 33 mU/L (0.27–4.2 mU/L) and blood glucose was 4.5 mmol/L (4–6 mmol/L).

DIFFERENTIAL DIAGNOSIS

On the basis of the history and investigation results, the patient was diagnosed with Addison's disease. Given her history of hypothyroidism, Addison's disease and positive gastric parietal cell antibodies; the possibility of autoimmune polyendocrine syndrome was raised.

TREATMENT

The patient was started on intravenous hydrocortisone 100 mg four times a day and fluids resulting in subsequent improvement.

OUTCOME AND FOLLOW-UP

A hormone profile revealed normal leutinising hormone (LH), follicle stimulating hormone (FSH), oestradiol, progesterone and prolactin with a low insulin-like growth factor (IGF). A pituitary MRI and an abdominal CT were normal with no adrenal changes.

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The patient was discharged home on oral hydrocortisone and fludrocortisone tablets and educated about the importance of compliance. Unfortunately she was readmitted within the next 6 months with a further episode of Addison's crisis due to poor compliance.

DISCUSSION

The above case highlights the importance of reviewing previous admissions and to think of other differential diagnoses especially when the presenting symptom is similar. The patient had been initially referred to the gastroenterologists; therefore, subsequent admissions were put down to a gastrointestinal cause despite there being limited improvement in symptoms. However given the ongoing weight loss despite no underlying cause on previous investigations, it was important to rule out other diagnoses and eventually the diagnosis of Addison's disease was made almost 1 year after symptoms presented.

Addison's disease is a relatively rare condition with an annual incidence of 4 million in the western population.² It can be very difficult to diagnose and easily missed due to its presentation with non-specific symptoms.³

The delay in diagnosis is not uncommon and patients can be seen by various healthcare professionals including gastroenterologists or psychiatrists before being correctly diagnosed.^{4 5}

The wide variety in symptoms means that the diagnosis can be attributed to other conditions and the more cardinal features such as skin or mucous membrane pigmentation may be missed although these may not always be present.⁶

Anorexia or hypotension may be relevant however are again non-specific as they be explained by alternative diagnoses such as an underlying infection.

Investigations can provide many clues to the clinician to make them suspect Addison's disease. On routine blood tests the patient may have hyponatraemia and/or hyperkalaemia, hypoglycaemia, eosinophilia.⁷

Raised TSH may be a feature and sometimes Addison's disease can be worsened by starting thyroxine.⁸

A clinician may then suspect the diagnosis and consider a random cortisol level. However, this can be inaccurate due to the circadian rhythm of cortisol production with peak levels in the morning and low levels at midnight and also an increase in production in times of stress.⁹ An unusually low cortisol in the presence of clinical features of Addison's disease should prompt a diagnosis and this may be confirmed by a trial of hydrocortisone.

The key test for diagnosis is a short synacthen test however this can be difficult in the crisis scenario as intravenous hydrocortisone should be started immediately. Cortisol and adrenocorticotrophic hormone (ACTH) levels should also be taken prior to steroid administration.

In the non-acute setting, Synacthen or synthetic ACTH (also called tetracosactrin) can be administered either intravenously or

intramuscularly. A typical test involves baseline cortisol levels taken (0 min) followed by administration of 250 µg tetracosactrin and then repeat cortisol levels taken at 30 min (and 60 min in some cases). The level suggesting intact adrenal gland function has varied from between 400 and 550 nmol/L but the generally agreed level is 525 nmol/L.^{10 11}

About half of the patients with Addison's disease are diagnosed only after an acute adrenal crisis. It is a medical emergency often precipitated by an infection or other forms of stress in an undiagnosed or inadequately treated patient with Addison's disease. In this condition, patients present acutely unwell with severe dehydration, hypotension or circulatory shock.⁴

There are known autoimmune associations with Addison's disease. Thomas Addison described the presence of pernicious anaemia and vitiligo when describing his eponymous condition.¹² Fifty per cent of patients with Addison's disease have an associated autoimmune disease with the most common being thyroid disease.¹³

Addison's disease can be associated with other autoimmunity therefore if a past medical history reveals conditions such as vitiligo, thyroid disease, coeliac disease or atrophic gastritis then this raises the suspicion of another autoimmune diagnosis. The above patient had hypothyroidism and positive gastric cell antibodies. This also suggested the possibility of autoimmune polyendocrine syndrome (APS).

Autoimmune polyendocrine syndrome

APS refers to multiple endocrine gland insufficiency associated with autoimmune disease¹⁴; however, it is also used to describe syndromes characterised by the association of two or more organ specific disorders.¹⁵

There is also the presence of genetic inheritance such as autoimmune regulator (AIRE) gene in APS type I or polygenic inheritance in APS type II.¹⁶ Neufeld and Blizzard¹⁷ further classified this syndrome into four main types based on clinical findings, however the main two syndromes are APS types I and II.

APS type I is an autosomal recessive condition and is characterised by the associations including mainly Addison's disease, hypoparathyroidism and chronic candidiasis. However, other associated features include pernicious anaemia, atrophic gastritis, hepatitis, vitiligo and type 1 diabetes mellitus.¹⁸

APS type II (AKA Schmidt's syndrome) is more common than type I and is associated with conditions including Addison's disease, insulin dependant diabetes mellitus and autoimmune thyroid disease. It is associated with human leucocyte antigen (HLA)—HLA DR3 and HLA DR4.

Pernicious anaemia is also found but is more common in APS type I.^{7 15}

Table 1 below summarises the key associations with Addison's disease and APS.^{7 12–18}

Table 1 Table showing the conditions associated with Addison's disease and autoimmune polyendocrine syndromes (APS) types 1 and 2

Addison's disease	APS type 1	APS type 2
Conditions associated		
Thyroid disease, coeliac disease, pernicious anaemia, type 1 diabetes mellitus, gonadal failure, vitiligo, alopecia, myasthenia gravis	<i>Main:</i> Addison's disease, hypoparathyroidism, chronic candidiasis (mucocutaneous) <i>Other:</i> gonadal failure, hepatitis, atrophic gastritis, pernicious anaemia, malabsorption, alopecia, type 1 diabetes, autoimmune thyroid disease, diabetes insipidus, hypopituitarism	<i>Main:</i> Addison's disease, type I diabetes mellitus, autoimmune thyroid disease <i>Other:</i> gonadal failure, vitiligo, pernicious anaemia, alopecia, myasthenia gravis, arthritis (seronegative/rheumatoid), diabetes insipidus

Learning points

- ▶ Addison's disease is one differential to be excluded in patients with unexplained weight loss with or without persistent vomiting.
- ▶ It is sometimes important to question previous diagnoses and management especially if symptoms persist and to look for other causes of symptoms.
- ▶ The diagnosis of Addison's involves simple blood tests however, in the acute setting; a random cortisol can sometimes provide sufficient information. If in doubt, intravenous steroids can be given if there is a high index of suspicion without blood tests.
- ▶ If left untreated Addison's disease can be potentially fatal and prompt diagnosis can avoid unnecessary hospital admissions with a crisis.
- ▶ Owing to the association between autoimmune conditions, think of associated conditions in patient's diagnosed with Addison's disease including autoimmune polyendocrine syndromes (APS).

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