Case report

Thomas Addison’s disease after 154 years: modern diagnostic perspectives on an old condition

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Summary

Thomas Addison was first to describe adrenocortical failure in 1855. Despite advances in the treatment of this condition, the diagnosis is still often delayed and sometimes missed with potentially fatal consequences. From the same institution where Thomas Addison performed his original autopsy studies, we present four recent cases highlighting the wide clinical spectrum and discuss how modern biochemical and immunological tests could be utilized in early diagnosis and aetiological classification.

Introduction

During his remarkable career as a physician and scientist at Guy’s Hospital in London,1 Thomas Addison described several important diseases that were hitherto unknown to mankind. In 1855, in a publication titled ‘On the Constitutional and Local Effects of Disease of the Suprarenal Capsules’, he described, in the following paragraph the clinical presentation and behaviour of 10 patients who died of adrenal failure.2

For a long period I had from time to time met with a very remarkable form of general anaemia, occurring without any discoverable cause whatever. The disease presented in every instance the same general character, pursued a similar course, and, with scarcely a single exception, was followed, after a variable period, by the same fatal result. The appetite is impaired or entirely lost; the whites of the eyes become pearly; the pulse small and feeble. The body wastes, slight pain or uneasiness is from time to time referred to the region of the stomach, and there is occasionally actual vomiting, which in one instance was both urgent and distressing; Neither the most diligent inquiry, nor the most careful physical examination, tends to throw the slightest gleam of light upon the precise nature of the patient’s malady; But with a more or less manifestation of the symptoms already enumerated, we discover a most remarkable, and, so far as I know, characteristic discoloration taking place in the skin (Figure 1).

Addison performed his original autopsy studies, we present four recent cases highlighting the wide clinical spectrum and discuss how modern biochemical and immunological tests could be utilized in early diagnosis and aetiological classification.

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modern biochemical and serological tests can be utilized for the diagnosis and management of this rare yet important disease.

Case presentations

Patient 1

A 28-year-old female presented to hospital feeling generally unwell with nausea, vomiting and a productive cough of 9 days duration. She had been commenced on antibiotics by her GP with no benefit. She collapsed at home prior to admission but did not lose consciousness. There was a history of primary hypothyroidism and the patient had been diagnosed with sero-negative rheumatoid arthritis (RA) 2 years previously when she presented with joint pains and constitutional symptoms. She was on 4 weekly infusions of Golimumab (an anti-TNF agent) for RA. Thyroxine had been taken rather intermittently. There was no history of corticosteroid treatment. On questioning she also admitted to the development of skin ‘freckles’ and tendency to ‘tan’ easily. The blood pressure (BP) was 84/59 mmHG with a low volume pulse of 96/min. She had epigastric tenderness but the rest of the examination was unremarkable.

Investigations summarized in Table 1 showed hyponatraemia, low serum basal and stimulated cortisol levels. ACTH was markedly raised and the adrenal androgen levels were very low.

The patient was initially treated with IV fluids and broad spectrum antibiotics. On Day 2 a diagnosis of Addison’s disease was suspected and hydrocortisone and fludrocortisone were commenced. On Day 5 the serum sodium was 140 mmol/l and she felt much better. The thyroxine was withheld until she was adequately replaced with gluco- and mineralocorticoids.3 Three months after diagnosis she remains well. The previous label of RA is being re-evaluated.

Patient 2

A 34-year-old female was admitted to hospital as an emergency feeling unwell, with nausea and vomiting. She had lost 12 kg over the preceding year and the BMI was 16 kg/m². She also complained of feeling anxious, with dizziness on standing, worsening fatigue and increased generalized pigmentation over this period. The patient had completed 6 weeks of counselling for ‘anxiety’ prior to hospital admission but no improvement was noted. BP lying was 94/58 mmHg and standing 86/55 mmHg, with a low volume pulse 74/min. There were patches of vitiligo on the elbows and ankles.

Investigation findings were similar to Case 2 and are summarized in Table 1.

A diagnosis of Addison’s disease was made and treatment was administered (IV hydrocortisone, oral fludrocortisone and IV fluids). The sodium on Day 5 was 138 mmol/l. Six weeks later the patient reported improvement in her general health on oral hydrocortisone and fludrocortisone. The thyroid function was normal with TSH 2.2 mU/l (0.27–4.2).

Patient 3

A 49-year-old man was referred by his GP with a 10 month history of increased skin pigmentation, reduced appetite, reduced energy levels, occasional dizziness and light-headedness. He had a past history of rectal carcinoma, which had been successfully treated with surgery and chemotherapy in 2004. One week prior to referral he had been commenced on diclofenec for acute back pain. Examination showed deep generalized pigmentation and pigmented scars in forearms, abdomen and elbows (Figure 2). The BP was 110/72 mmHg (lying) and 106/60 mmHg (standing). There was no goitre and rest of the examination was unremarkable.

Investigation findings are shown in Table 1.

He was in acute renal failure, which responded to cessation of the NSAID and increased oral fluid intake. He was commenced on oral hydrocortisone and fludrocortisone followed by thyroxine and 2 months later his general symptoms had improved and there was less pigmentation.

Figure 1. A drawing from Addison’s original autopsy series showing pigmentation and co-existent vitiligo.
A 55-year-old man with a previously unremarkable medical history saw his family physician with fever, headaches, general aches and pains and ‘weakness’. The BP was 90/60 mmHG and blood tests showed a mild hyperkalemia at 5.4 mmol/l but normal sodium at 138 mmol/l. No diagnosis was reached and 8 months later during an episode of tonsillitis the potassium level was 5.7 mmol/l with serum sodium 125 mmol/l. Several further visits were made with the family physician over the next 12 months and the patient’s wife noted that ‘he would often be unwell and complained of feeling weak and that when he suffered such episodes he would just lie around’. Four years later patient underwent removal of wisdom teeth under general anaesthetic. Post-operatively the BP was 93/56 mmHG. He was discharged the same day and felt ill in the car on the way home. He started vomiting that evening and this continued over the next 48 h accompanied by epigastric pain. The family medical practice was contacted but the patient was advised to seek help from the emergency dental service. Three days after the tooth extraction the patient was found dead at home. The post-mortem showed that both adrenal glands were small with little obvious cortical lipid. Their combined weight was 1.5 g (adrenal glands normally weigh around 5 g each). A post-mortem diagnosis of Addison’s disease was made.

**Discussion**

Addison’s disease is a rare disease with an estimated prevalence of 110–140 cases per million inhabitants of Western Europe. Autoimmune adrenal failure can occur early in life as part of autoimmune
polyendocrine syndrome type 1 (APS type 1) which is due to a mutation in the autoimmune suppressor gene (AIRE) located on chromosome 21q22.3, or in adults in isolation or as genetically more complex autoimmune polyendocrine syndrome type 2 (APS type 2). About 80% of patients with APS type 1 develop Addison’s disease and other characteristic disease associations include mucocutaneous candidiasis and hypoparathyroidism. About 18% develop type 1 diabetes mellitus.6

In contrast, APS type 2 is polygenic syndrome associated polymorphism of HLA system.7 In particular, genotypes HLA–DR3/DQ2 and DR4/DQ8 haplotypes seems to confer increased risk. Associated conditions classically include thyroid disease and type 1 diabetes but many other autoimmune diseases such as pernicious anemia, vitiligo, alopecia, celiac disease8 and gonadal insufficiency has been described. Vigilance and early testing for adrenocortical failure should be undertaken in these groups even without classic symptoms. In addition Addison’s disease is also associated with a mutated allele (5.1) of a non-classical HLA molecule MHC class I chain related A (MICA) gene which appears to be independent of the DR or DQ gene polymorphism.

The clinical features and treatment of the condition are well established.9–12 However, the diagnosis is still often delayed or missed with potentially serious consequences.13 It is not uncommon for these patients to be misdiagnosed with other conditions such as chronic fatigue, thyroid disease (often co-existent), depression14 and rheumatological conditions. Retrospective population based studies from Sweden has shown that even patients who are appropriately diagnosed and treated with current steroid replacement regimes have increased standardized mortality ratios (SMR) compared with general population.15,16 In a recent publication16 involving 3299 patients with primary adrenal failure more than 2-fold increased mortality risk was observed in both women (SMR 2.9, 95% CI 2.7–3.0) and men (SMR 2.5, 95% CI 2.3–2.7). Highest risks were observed in patients diagnosed in childhood. SMR was higher in APS1 patients (SMR 4.6, 95% CI 3.5–6.0) compared with patients with APS2 (SMR 2.1, 95% CI 1.9–2.4).

Introduced in 1960s the ‘short synacthen test’ remains the gold standard test for the biochemical diagnosis of Addison’s disease.15 This test involves the parenteral administration of a large dose of synthetic ACTH (Cosyntropin) in order to maximally stimulate the adrenal cortex. The response is assessed by measurement of serum cortisol levels.16 This classical test is, however, open to misinterpretation particularly in the early stages of adrenocortical destruction or if it is performed after patients have already started glucocorticoid therapy. Other biochemical tests can also be useful in identifying primary adrenal failure. Classical endocrine feedback regulates the secretion of adrenal cortical hormones and, analogous to the rise in TSH seen in primary hypothyroidism, ACTH levels start to rise in early primary adrenal failure. Reliable ACTH assays are now widely available and should be utilized to help confirm the diagnosis. ACTH levels in this context are usually hugely elevated (Table 1) and partial homology between ACTH and melanocyte stimulating hormone (MSH) results in the classical pigmentation seen in primary adrenal failure.19

Production of the adrenal androgens DHEAS and Androstenedione are also stimulated by ACTH. The low serum levels of DHEAS and Androstenedione in the presence of very high levels of ACTH as illustrated in our cases are a strong indication of adrenal cortical destruction.

Aldosterone production from the zona glomerulosa of the adrenal cortex is under the control of renin angiotensin system. Lack of aldosterone leads to salt wasting and elevated renin levels. In fact raised renin levels are one of the earliest changes seen in this condition. Renin and aldosterone measurements are now more robust and available and should therefore also be considered as an adjunct to diagnosis. Modest elevation of Serum TSH level is common in untreated glucocorticoid deficiency.20 This is thought to be due to a direct effect of glucocorticoid deficiency and reverses with replacement therapy (Patient 2). Persistent elevation of TSH after adequate replacement therapy or markedly raised TSH level at presentation in association with positive thyroid autoantibodies, however, suggests concomitant autoimmune thyroid disease (Patients 1 and 3). Autoimmune adrenal failure occurs due to T-cell mediated adrenal cortical destruction but reliable assays for measurement of autoimmune T cells are not widely available. Instead clinicians rely on autoantibodies as surrogate markers to detect disease activity. Adrenocortical antibodies (ACA) measured using indirect immunofluorescence techniques on cryostatic sections of adrenal gland tissue can be found between 60% and 80% patients with Addison’s disease at diagnosis.7 Recognition of the enzyme steroid 21 hydroxylase as the major adrenocortical autoantigen has resulted in development of sensitive assays and antibodies against 21 hydroxylase (21OHaB) can be found in high proportion (80–90%) of patients with Addison’s disease at diagnosis. Results from a study in 222 patients with primary adrenal failure suggested that presence of both ACA and 21OHaB was unequivocally associated...
with autoimmune aetiology. Therefore assessment of the patient with possible primary adrenal failure should include measurement of electrolytes, ACTH, cortisol, renin, aldosterone, androstenedione and DHEAS in addition to anti-adrenal cortex antibody. In cases where adrenal antibodies are negative alternative causes for adrenal failure (such as infection or infiltration) should be sought and cross sectional imaging (CT or MRI scan) of the adrenals should be performed.

Once the diagnosis is suspected, the patient should be started on hydrocortisone replacement therapy without further delay, ideally after obtaining a blood sample for above tests but treatment should not be delayed pending biochemical confirmation. The SST remains an important part of the confirmation of primary adrenal failure but this could be done at a later date after withdrawing hydrocortisone for 24 h.

The dose of the hydrocortisone is dictated by patient’s clinical condition. Patients who are acutely unwell should be treated with large doses (50–100 mg/6 h) of intravenous hydrocortisone. At such high dosage hydrocortisone will have sufficient mineralocorticoid activity to warrant monotherapy. Patients who are not acutely unwell should be started on oral hydrocortisone (suitable dose would be 15–10 mg on waking and 5–10 mg late afternoon/early evening) together with 100 mcg of oral Fludrocortisone and referred to secondary care for the confirmation of the diagnosis.

Summary
Addison’s disease can present with non-specific clinical features to a variety of medical practitioners. We present four cases of recently diagnosed Addison’s disease, which illustrate the varied clinical presentation and illustrate how the measurement of adrenal cortical hormones and their respective feedback hormones can help confirm the diagnosis. Once the diagnosis is suspected patients should be started on hydrocortisone and fludrocortisone replacement and referred to an endocrinologist for confirmation of the diagnosis and optimal long-term management.

Conflict of interest: None declared.

References