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Addison's disease:

identification and management in primary care

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INTRODUCTION

Addison's disease (AD), also known as primary adrenal insufficiency, is a deficiency of glucocorticosteroids and mineral corticosteroids.[1] This can result in an insidious, protracted presentation. Therefore, unsurprisingly, the diagnosis is often delayed[2] and 60% of patients have seen two or more clinicians before the diagnosis is considered.[3] Around one-half of patients with AD are diagnosed after an acute adrenal crisis,[4] which can be rapidly fatal.[5] Although tuberculosis is the most common cause of AD worldwide,[1] in the developed world, autoimmune disease is the predominant cause.[3] In the latter context, AD is often linked to other autoimmune diseases, such as, vitiligo.[6]

EPIDEMIOLOGY

Addison's disease is estimated to affect 1 in 10 000 people in the UK,[5] and throughout Europe.[7] The female:male ratio is 1.8 and adults of all ages are affected.[6] Incidence from Norwegian data is 0.44 per 100 000 population per year and there is some evidence of clustering within families.[6] Annually, in the UK, 1–2 consultations per 10 000 people are undertaken for adrenal gland disorders, compared to between 80–125 per 10 000 for acquired hypothyroidism.[8]

At the authors' practice of 11 000 patients, seven are registered with primary or secondary adrenal insufficiency. One such patient presented in Autumn 2013 (see Figures 1 and 2 demonstrating vitiligo of the face and hands). A 4-month delay in diagnosis occurred due to an extended period of primary care investigation for other (gastrointestinal) causes for the presenting symptoms. The diagnosis was made following an acute admission due to features of an Addisonian crisis including hypotension, vomiting, debilitating fatigue, and hyperkalaemia.

CLINICAL FEATURES

A major problem with identifying people with AD is the non-specific nature of many of the presenting symptoms, at least in pre-crisis stages. Common symptoms, signs, and laboratory results are shown in Table 1, and all can be associated with other, often more common, differential diagnoses.

A rapid appraisal of presentations of AD, conducted though MEDLINE® via NHS Evidence, yielded many disparate presenting symptoms. In summary, diagnostic pitfalls to be aware of include a chronic presentation which may be misdiagnosed as one of a number of other problems, often based on a mental health diagnosis, for example anxiety or depression; precipitation into crisis through use of antidepressants (as sodium-depleting) or through use of steroids for a comorbidity; evolution in pregnancy may be mistaken for chloasma and interpretation of serum cortisol measurement is harder in pregnancy, so if AD is suspected referral to endocrinology is essential; and erratic diabetes control, either recurrent hypoglycaemia or diabetic ketoacidosis.

INVESTIGATION

A high index of suspicion is needed as AD crises can be rapidly fatal. If suspected (features of persistent vomiting, muscle weakness, dehydration, hypotension, headache, extreme fatigue, and shock),[5] the patient should be admitted as a medical emergency. Otherwise, consider measuring urea and electrolytes (U&E) as sometimes, although by no means always, a low sodium and high potassium will be found, and a 9 am serum cortisol level. Local reference ranges should be checked but generally, a serum cortisol result >500 nmol/l makes AD very unlikely, <100 nmol/l is definitely abnormally low[9] requiring rapid investigation. Results lying between these values are indeterminate and should prompt a short synacthen test. Additional relevant secondary care tests at the time of diagnosis include plasma adrenocorticotropic hormone and renin, and serum dehydroepiandrosterone sulfate; other hypothalamic-pituitary axis

Figure 1. Patient with Addison's disease on a background of vitiligo (face).

investigation may be warranted if secondary AD is suspected.[7] Further screening for other autoimmune conditions should be considered and are summarised in Box 1.

ONGOING MANAGEMENT

Lifelong oral steroid supplementation is usually initiated and adjusted in secondary care by an endocrinologist and typically includes glucocorticoid (hydrocortisone) and mineralocorticoid (fludrocortisone) replacement. Under-replacement may be indicated by persisting symptoms or signs and over-replacement by hypertension,

Figure 2. Patient with Addison's disease on a background of vitiligo (hands).

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Table 1. Symptoms, clinical signs, and laboratory results associated with Addison's disease

	At diagnosis, %	On treatment, %
Symptoms		
Fatigue, malaise, lassitude	8[a]–95[b]–100[c]	24[b]
Appetite loss	3[a]–67[b]–100[c]	3.6[b]
Salt craving	15[a]–64[b]	24[b]
Nausea, vomiting, abdominal pain	21[a]–62[b]–92[c]	9.5[b]
Postural light headedness, dizziness	11[a]–56[b]	15[b]
Musculoskeletal pain	20[a]–40[b]	21[b]
Diarrhoea	15[a]–23[b]	7.3[b]
Collapse	7[a]	–
Loss of consciousness	20[a]	–
Constipation	10[b]	5.9[b]
Signs		
Increase in pigmentation	74[b]–76[a]–94[c]	16[b]
Weight loss	25[a]–73[b]	3.8[b]
Hypotension	68[b]	12[b]
Anaemia	13[b]	3.8[b]
Vitiligo	8.5[b]	8.5[b]
Shock	5[a]	–
Test results		
Electrolyte disturbance (including hyponatraemia and hyperkalaemia)	35[b]	4[b]
Hypoglycaemia	3[a]	–

[a]*Reference 9.* [b]*Reference 6.* [c]*Reference 10.*

thin skin, striae, easy bruising, glucose intolerance, hyperglycaemia, and electrolyte imbalance. Patients with AD should be informed that they are eligible for free prescriptions in the UK.

Individualised sick day rules need to be highlighted to patients, and flagged on primary care computer systems. Resources to assist with providing this information can be found at http://www.addisons.org.uk/. Self-administered injectable steroids may be provided in situations where rapid access to supportive treatment in a crisis is not guaranteed.[9]

There is no well-established guidance for primary care follow-up of people with AD. We suggest a disease register with annual recall for review with investigations as shown in Box 1.

Box 1. Potentially coexistent autoimmune diseases and a proposed annual surveillance programme for patients with Addison's disease

Condition	Investigation
General Addison's disease management	• U+E, sitting and standing blood pressure measurement
Pernicious anaemia	• FBC, B12
Coeliac disease	• Anti-TTG
Autoimmune liver disease	• LFTs; check liver autoantibodies if LFTs deranged
Autoimmune thyroid disease	• TSH; check free T4 and anti TPO antibodies if TSH outside reference range
Type 1 diabetes	• Fasting glucose/HbA1c
Autoimmune parathyroid disease	• Bone profile — check PTH if low calcium
Vitiligo	• Physical examination only
Alopecia areata	• Physical examination only
Gonadal autoimmune disease	• Consideration should also be made of testing if premature gonadal failure suspected.

Annual surveillance for other autoimmune disorders is recommended. Some authorities recommend annual screening for the autoantibodies listed above,[7] instead of the proposed stepped approach of investigation. Anti-TPO = anti-thyroid peroxidase. Anti TTG = anti tissue transglutaminase. B12 = vitamin B12 level. FBC = full blood count. HbA1c = glycated haemoglobin. LFT = liver function tests. PTH = parathyroid hormone. TSH = thyroid stimulating hormone. T4 = thyroxine. U+E = urea and electrolytes.

CONCLUSION

AD is an infrequently occurring mimic of many other more common conditions encountered in primary care. Despite multiple useful reviews of AD in the literature, we have personal recent experience of delays in diagnosis and there remains a need to raise the clinical profile in primary and secondary care of this highly treatable but life-threatening disease. Research into a formal diagnostic algorithm would be helpful, as would further epidemiological work to examine clustering of cases in time and place.

Further resources

http://cks.nice.org.uk/addisons-disease
https://www.endocrinology.org/policy/docs/11-03_Adrenal%20insufficiency.pdf

Patient consent

The patient gave consent for publication of this article and the images

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