Allgrove syndrome: when a recognisable paediatric disorder occurs in adulthood

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We report a man with longstanding undiagnosed adrenal insufficiency. At 37, our patient is the oldest reported case. Although most cases of Allgrove syndrome are diagnosed during childhood, awareness of this condition when undiagnosed in adults is crucial, as it is life threatening, and can severely affect neurological, sexual and psychological function. ***(MJA 2004; 180: 74-75)***

ALLGROVE SYNDROME was first described in 1978.[1] It is an autosomal recessive condition associated with adrenal insufficiency due to adrenocorticotrophic hormone (ACTH) resistance, alacrima, and achalasia of the oesophageal cardia.[1,2] Affected patients usually present as children, with achalasia and alacrima,[3] but clinical features may be heterogeneous, sometimes including neurological involvement, and they present over a variable time course.[4] The disease gene, *ALADIN*, localises to 12q13,[5] with mainly nonsense mutations, resulting in expression of a truncated protein.[3]

Case report

A 37-year-old man with known achalasia was admitted for investigation of an 18-month history of extreme tiredness, recurrent cough, and weight loss of 10 kg.

Previous history

One year before admission, he had a 2-day history of lethargy, dizziness, and collapse with hypotension. On admission to an intensive care unit, he required crystalloid resuscitation, with inotropes for blood pressure maintenance for 2 days, after which he recovered slowly. Serotonin syndrome was proposed as a diagnosis, because he had recently started taking paroxetine for management of presumed psychogenic impotence.

At age 31 he had begun to experience progressive generalised weakness, with soreness of lower limbs. A neurological report described mixed motor neurone abnormalities, with symmetrical four-limb weakness, predominantly distal muscle wasting, bilateral pes cavus, symmetrical hyperreflexia and positive Babinski reflexes. Bulbar involvement and optic atrophy were observed. Computed tomography (CT) scanning and magnetic resonance imaging of his brain showed no abnormality. No clear diagnosis was reached.

Over several years he had sought professional help for erectile dysfunction and ejaculatory failure, from urologists, sexual counsellors, psychiatrists and neurologists, without success. Marital separation followed this difficult period.

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Twenty years before these events the patient had developed swallowing difficulties. Achalasia was diagnosed on radiological and endoscopic findings, with symptomatic improvement following pneumatic dilatation.

His family history was unremarkable and did not include consanguinity. Muscle weakness and clumsiness was recognised from age 4 years, but he had always participated in sports activities. Growth and puberty occurred normally.

Current admission

An endocrinological consultation was sought because of increasing lethargy, weakness and reported testicular atrophy. Examination showed minimal pigmentation of skin and palmar creases, severe generalised weakness, proximal and distal myopathy and hypotension (95/50 mmHg) with a postural drop to 60 mmHg systolic on standing. Testicular volume was 25 mL (adult normal range, 12–25 mL) with normal virilisation and no gynaecomastia. Extremely indistinct "bulbar" speech was noted, with nasal escape rendering speech almost incomprehensible.

Direct questioning confirmed alacrima, the patient stating that he never produced tears at any age. He also reported extreme difficulties with swallowing, taking an hour to eat a meal, constant cough, poor saliva control and accompanying inhalation of food.

A diagnosis of Allgrove syndrome was made clinically, and adrenal insufficiency was confirmed with the discovery of elevated ACTH and low basal cortisol levels (see Box). An intramuscular injection of hydrocortisone (100 mg) resulted in rapid improvement of blood pressure and muscle strength, so that he could stand and walk without dizziness. There was significant improvement in his speech, cessation of cough and reported normalisation of eating habits. Replacement therapy with hydrocortisone (20 mg/m^2 daily) was initiated. Plasma renin activity was normal. Fludrocortisone was not required as the patient's blood pressure had returned to normal with no postural drop after glucocorticoid replacement, confirming intact mineralocorticoid function.

After discharge from hospital 3 days after the diagnosis was made, he reported ongoing marked improvement in strength and coordination and returned to full-time manual trade work.

Discussion

This patient with Allgrove syndrome, who developed symptoms of severe life-threatening adrenal insufficiency at age

1: Patient's blood test results before diagnosis

Investigation	Results	Reference values
Sodium	139 mmol/L	135–145 mmol/L
Potassium	3.8 mmol/L	3.5–5.0 mmol/L
Chloride	102 mmol/L	95–107 mmol/L
Bicarbonate	25 mmol/L	23–32 mmol/L
Urea	3.4 mmol/L	3.2–7.3 mmol/L
Creatinine	57 μmol/L	40–130 μmol/L
Cortisol (08:00 h)	43 nmol/L	200–750 nmol/L
Adrenocorticotrophic hormone	864 pmol/L	< 20 pmol/L
Plasma renin activity	1.0 ng/mL/h	0.3–1.4 ng/mL/h

2: Clues to recognising the syndrome

- Clinical suspicion of adrenal insufficiency in the presence of achalasia in any patient, children or adults
- Alacrima — ascertaining this usually depends on direct questioning about tear production.
- Neurological dysfunction — not universal, but the combination of achalasia and neurological dysfunction should prompt specific questions about symptoms of adrenal insufficiency.
- Elevated adrenocorticotrophic hormone and low basal cortisol levels confirm the diagnosis.

36, but retained normal mineralocorticoid function, is the oldest reported case surviving with undiagnosed adrenal insufficiency.

In cases reported previously, adrenal insufficiency was usually diagnosed in the first decade[6] (with a few exceptions[2,7,8]), accompanied by hypoglycaemia and increased skin pigmentation.[5] Most patients had normal mineralocorticoid function, but deficiency has been reported.[5,9] Achalasia is usually diagnosed at the same time or after the diagnosis of adrenal insufficiency.[5] In our patient, achalasia preceded the diagnosis of adrenal insufficiency by 20 years. Such a late diagnosis emphasises the need for assessment of adrenal function in any young person with achalasia or alacrima.

The gene is defined for this rare autosomal recessive disorder (*ALADIN* at 12q13); fewer than 100 cases have been reported, usually in family clusters. Our patient had no family history of the disorder, indicating that he was likely to be the first (index) case with the mutated gene.

Diagnosing adrenal insufficiency: Diagnosis of hypocortisolism is frequently delayed for patients with adrenal insufficiency, because of the subtle nature of clinical complaints (weakness, tiredness, dizziness and slow weight loss). When mineralocorticoid function is intact, postural hypotension and electrolyte disturbance, with an acute medical emergency presentation, is less likely. ACTH insensitivity due to adrenocortical atrophy is the resultant clinical picture. Skin pigmentation varies, and is often missed unless a careful search for buccal, crease and scar pigmentary change is sought.

A diagnosis of primary adrenal insufficiency usually includes consideration of an autoimmune basis where adrenal antibody status should be tested (with or without other pointers to polyautoimmune endocrinopathy), infective causes (tuberculosis, viruses and mycoses) and, in older patients, malignant infiltration. These problems usually result in extensive adrenal destruction and associated mineralocorticoid deficiency, often with a more dramatic presentation of ill health and electrolyte imbalance.

Neurological features: Peripheral motor and sensory neuropathy are common,[10] and may be subtle in childhood.[5] Impotence is infrequently reported with Allgrove syndrome[5,7,8] perhaps because of underreporting, or a diagnosis of psychogenic impotence. Erectile dysfunction in our patient was neurological in origin, and so it is not surprising that it failed to respond to usual therapies. The differential diagnosis includes adrenoleukodystrophy (ALD) in childhood or adolescence, with either neurological abnormality or adrenal insufficiency as the first presentation. Adrenomyelodystrophy occurs when patients with this progressive demyelinating disorder first present in adulthood. As our patient's first neurological complaint occurred when he was 4 years of age, ALD could be excluded. Similarly, the gene for Duchenne muscular dystrophy is located adjacent to the *DAX-1* gene, producing neurological deterioration and adrenal insufficiency, but is generally diagnosed earlier.

Although neurological disorder constitutes part of the condition, the severe and progressive muscle weakness of long-term undiagnosed adrenal insufficiency makes a major contribution to reduced motor function and quality of life, as seen in our patient. Unlike other neurological disorders associated with adrenal insufficiency, neurological change with Allgrove syndrome is extremely slow. With adequate cortisol replacement, monitoring of ACTH levels and education to ensure appropriate increases in corticosteroid treatment during intercurrent illness or anaesthesia, the prognosis for health and quality of life is improved.

Competing interests

None identified.

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