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Lesson of the Week

Secondary adrenocortical insufficiency

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Patients presenting with unexplained hyponatraemia should be assessed for pituitary disease to implicate a diagnosis of secondary adrenocortical insufficiency, even if the short tetracosactrin (synacthen) test has normal results

Adrenocortical insufficiency may be due either to primary adrenal failure or to hypopituitarism. An adequate response of cortisol in the short tetracosactrin (synacthen) test reliably excludes primary disease and also, it has been proposed, secondary disease.¹⁻³ In common with other screening procedures, however, the short tetracosactrin test is not infallible and should be interpreted along with other clinical evidence. We report two elderly patients presenting with hyponatraemia in whom the correct diagnosis of adrenocortical insufficiency was considered but initially rejected because of overreliance on a normal short tetracosactrin test, despite other features of hypopituitarism being present.

Case reports

CASE 1

In 1985 a 63 year old man was referred to the diabetic clinic. Chlorpropamide treatment was thought to account for his hyponatraemia of 127 mmol/l (reference range 133-145 mmol/l); serum potassium and urea concentrations were normal. He was also taking thyroxine 200 µg daily for longstanding hypothyroidism; results of thyroid function tests before treatment are not available. He had a mild normochromic normocytic anaemia (haemoglobin concentration 128 (135-170) g/l) with normal serum ferritin, vitamin B-12, and red cell folate concentrations. In 1988 insulin treatment was instituted for poor control of glycaemia.

In 1989 he was admitted with a fractured neck of left femur. His serum sodium concentration fell from 131

to 108 mmol/l after surgery with a high spot urinary sodium concentration of 88 mmol/l, and he was managed with fluid restriction and hydrocortisone. The short tetracosactrin test (undertaken before exogenous steroids were given and at a serum sodium concentration of 114 mmol/l) gave serum cortisol concentrations of 275, 663, and 843 nmol/l at 0, 30, and 60 minutes after intramuscular injection of tetracosactrin 250 µg. Local reference values for serum cortisol in this test are basal >200 nmol/l, with increment >200 nmol/l and peak >580 nmol/l. He was therefore thought not to have adrenocortical insufficiency, and steroids were withdrawn. His hyponatraemia was attributed to perioperative overhydration with intravenous 5% dextrose and a possible syndrome of inappropriate antidiuretic hormone secretion.

He remained well when taking thyroxine and just 8-12 U of insulin daily until 1991, when he was admitted with drowsiness and vomiting after fracturing his right wrist. His serum sodium concentration fell to a nadir of 108 mmol/l and he was managed with fluid restriction and demeclocycline. His serum sodium concentration had risen to 128 mmol/l when he again fell, sustaining a head injury and a fracture of the right hip. After surgery he became hypotensive, confused, and drowsy. An emergency computed tomography brain scan showed a large calcified lesion in the region of the pituitary gland with expansion of the pituitary fossa. A presumptive diagnosis of hypopituitarism was made, supported by clinical evidence of testicular atrophy and loss of body hair and by subsequent biochemical data. The random serum cortisol concentration was 256 nmol/l with testosterone <0.3 nmol/l

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and luteinising hormone and follicle stimulating hormone concentrations inappropriately low at <0.5 mU/l and 2.1 mU/l respectively; serum prolactin concentration was 8602 (<400) mU/l. Thyroid stimulating hormone concentration was also low at <0.13 (0.5-5.5) mU/l with total thyroxine 81 (54-142) nmol/l and free triiodothyronine <1.0 (2.9-9.0) pmol/l (he had been unable to take thyroxine for several days). He was treated with corticosteroids and made a full recovery.

At the time of writing he was taking hydrocortisone 20 mg in the morning and 10 mg in the evening, thyroxine 150 µg daily, and Mixtard insulin 26 U in the morning and 16 U in the evening. Serum sodium concentrations have remained within normal limits; his weight has increased from 71 kg to 95 kg, and he was in better health than for several years.

CASE 2

In 1987 a 78 year old woman was admitted with a four week history of anorexia, lethargy, and restlessness. Her haemoglobin concentration was 118 (115-165) g/l with serum sodium 113 (135-146) mmol/l, urea 2.7 (3-7.6) mmol/l, and potassium 4.5 (3.5-5.0) mmol/l. Serum osmolality was 239 (285-295) mmol/kg, with urine osmolality 503 mmol/kg and a spot urinary sodium concentration of 103 mmol/l. A provisional diagnosis of syndrome of inappropriate antidiuretic hormone secretion was made. She was managed with fluid restriction and sodium supplementation; her serum sodium concentration rose to 132 mmol/l and her clinical condition improved.

On review as an outpatient she was well, her serum sodium having remained at about 130 mmol/l. Subsequent investigations showed a serum thyroxine concentration of 82 (70-140) nmol/l, with thyroid stimulating hormone 1.1 (0.3-3.8) mU/l, prolactin 1249 (50-350) mU/l, luteinising hormone <0.5 mU/l, and follicle stimulating hormone 2.2 mU/l. A short tetracosactrin test showed a basal serum cortisol concentration of 457 nmol/l, rising to 729 nmol/l at 30 minutes. This was interpreted as excluding adrenocortical insufficiency even though a computed tomography brain scan indicated a pituitary adenoma with suprasellar extension. Chronic fluid restriction continued and sodium supplements were withdrawn.

On review in 1992, a repeat short tetracosactrin test showed a basal serum cortisol concentration of only 91 nmol/l, rising to a maximum of 251 nmol/l. The correct diagnosis of adrenocortical insufficiency secondary to hypopituitarism was now made. She was given oral hydrocortisone 20 mg in the morning and 10 mg in the evening, and wellbeing improved rapidly; serum sodium concentration increased to 137 mmol/l and was maintained without fluid restriction.

Discussion

In these two cases hyponatraemia was the predominant presenting feature of adrenocortical insufficiency secondary to hypopituitarism, but the cortisol response in the short tetracosactrin test seemed adequate. This led to delays in diagnosis, with many months of poor health in both patients and a life threatening illness in one.

The traditional test of the hypothalamic-pituitary-adrenal axis is the cortisol response to hypoglycaemia induced in an insulin stress test.⁴ This test can, however, be difficult, time consuming, and hazardous,⁵ with ischaemic heart disease, epilepsy, and (as in our patients) advancing years being contraindications.⁶ Instead, cases of adrenocortical insufficiency, whether

due to adrenal failure or secondary to hypopituitarism, can generally,^{1,2,3,6} although not invariably,^{7,8} be diagnosed by eliciting an inadequate cortisol response in the short tetracosactrin test. An increasing cortisol response to repeated injections of tetracosactrin then distinguishes adrenal atrophy secondary to hypopituitarism from primary adrenal failure.⁹

The short tetracosactrin test should be undertaken only after correction of fluid volume and electrolytes, including the short term use of corticosteroids if necessary. If a severely stressed, volume depleted, or hyponatraemic patient, such as case 1, is tested the extreme endogenous stimulation of the hypothalamic-pituitary-adrenal axis may lead to misleadingly "normal" responses in secondary adrenocortical insufficiency.^{6,10}

When interpreted rigidly and in isolation, therefore, the short tetracosactrin test can be unreliable. Other tests of adrenal reserve such as the cortisol response to insulin induced hypoglycaemia and to synthetic corticotrophin releasing hormone also have problems.¹¹ How then may the clinician make the diagnosis of secondary adrenocortical insufficiency in cases such as these? In practice, the correct diagnosis may be made by seeking and recognising other clinical, biochemical, and radiological evidence of pituitary insufficiency and destruction. Clinical clues may include fatigue, anorexia, weight loss, anaemia, features of hypothyroidism or of hypogonadism, reduced insulin requirements in diabetic patients and, in particular, a poor stress response with worsening hyponatraemia and hypotension. Investigations should include testing for inappropriately low thyrotrophin and gonadotrophin concentrations, and consideration should be given to computed tomography or magnetic resonance imaging to look for evidence of a pituitary lesion. The cases above illustrate many of these points.

In patients presenting with hyponatraemia of undetermined cause, the diagnosis of secondary adrenocortical insufficiency should therefore be entertained and clinical, biochemical, and structural evidence of pituitary disease sought and evaluated, even if results of the short tetracosactrin test seem normal.

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Correction

ABC of one to seven: Bronchial asthma

An author's error occurred in this article by H B Valman (19 June, pp 1676-81). The table listing drugs and delivery systems (p 1679) is incorrect: sodium cromoglycate is not available in the Autohaler device, but beclomethasone dipropionate is.