(Milan), M Tenconi, G Devoti, P Gardinali (Pavia), G Pagano, G Bruno, E Pisu, F Merletti (Turin); Japan: N Tajima, M Matsushima (Tokyo); Libya: O Kadiki (Benghazi); Mexico: C Robles-Valdes, R Calzada-Leon, N Altamirano-Bustamante (Mexico City); New Zealand: R Elliott (Auckland); Poland: M Rewers (Poznan, currently in Denver, USA); Romania: C Ionescu-Tirgoviste, D Cheta, M Costea (Bucharest); Slovakia: J Vozar (Šamorín); Sweden: G Dahlquist (Umeå); Tanzania: M Makame (Zanzibar); Thailand: V Sridama (Bangkok); United States: T Songer, I Gower, J Dorman, I Libman, E Tull, L Lave, R LaPorte (Pittsburgh); Puerto Rico: T Frazer de Llado (Ponce).

1 Helbach D. A legislative view of driving and legal restriction. *Wis Med J* 1991;90(3):119-20.
2 Laron Z. School, work, driving, and insurance for the diabetic. In: Larkins R, Zimmet P, Chisholm D, eds. *The diabetic in society—living with diabetes.* Amsterdam: Elsevier, 1989:881-6.
3 Havard JDJ. International aspects of driver licensing. *Proceedings of the Royal Society of Medicine* 1977;70:246-9.
4 DCCT Research Group. Diabetes control and complications trial (DCCT): results of feasibility study. *Diabetes Care* 1987;10:1-19.
5 Ward CM, Stewart AW, Cutfield RG. Hypoglycaemia in insulin-dependent diabetic patients attending an outpatients clinic. *N Z Med J* 1990;103: 339-41.
6 Bergada I, Swissa S, Dufrense J, Schiffrin A. Severe hypoglycemia in IDDM children. *Diabetes Care* 1989;12:239-44.
7 Casparie AF, Alving LD. Severe hypoglycemia in diabetic patients: frequency, causes, prevention. *Diabetes Care* 1985;8:141-5.
8 Muhlhauser I, Berger M, Sonnenberg G, Koch J, Jorgens V, Schernthaner G, *et al.* Incidence and management of severe hypoglycemia in 434 adults with IDDM. *Diabetes Care* 1985;8:268-73.
9 Sullivan P. Court, human-rights rulings cause change in CMA advice on diabetic drivers. *Can Med Assoc J* 1991;144(8):1042-3.
10 Department of Transportation, Federal Highway Administration. Qualification of drivers; diabetes; proposed rule. 49 CFR Part 391. *Federal Register* 1990;55(194):41028-37.
11 Ratner RE, Whitehouse FW. Motor vehicles, hypoglycemia, and diabetic drivers. *Diabetes Care* 1989;12:217-22.
12 Department of Transportation, Federal Highway Administration. Qualification of Drivers; waivers; diabetes. 49 CFR Part 391. *Federal Register* 1992;57(204):48011-5.
13 Dutton T. Diabetes and driving, the legal position. London: British Diabetic Association, 1990. (Diabetes Update, Autumn 1990.)
14 WHO DIAMOND Project Group. WHO multinational project for childhood diabetes. *Diabetes Care* 1990;13:1062-8.
15 Evans L. *Traffic safety and the driver.* New York: Van Nostrand Reinhold, 1991.
16 Jamison DT, Mosley WH. Disease control priorities in developing countries: health policy responses to epidemiologic change. *Am J Public Health* 1991;81:15-22.
17 Sturner WQ, Sullivan A. Hypoglycemia as the responsible factor in a truck driver accident fatality. *J Forensic Sci* 1983;28(4):1016-20.
18 Christian MS. Multiple crashes on motorways (letter). *BMJ* 1972;ii:295.
19 Raffle PAB. The contributions of medical surveillance to road safety. *Proceedings of the Royal Society of Medicine* 1977;70:240-3.
20 Jervell J, Nilsson B. *Social rights of diabetic patients in Europe.* Älvsjö: Swedish Diabetic Association, 1986.
21 Ekoé JM, Laberge-Nadeau C, Ghadirian P, Hamet P. L'impact du diabète sucré sur la sécurité routière. *Diabete Metab* 1991;17:61-7.
22 Waller JA. Chronic medical conditions and traffic safety, review of the California experience. *N Engl J Med* 1965;273:1413-20.
23 Songer TJ, LaPorte RE, Dorman JS, Orchard TJ, Cruickshanks KJ, Becker DJ, *et al.* Motor vehicle accidents and IDDM. *Diabetes Care* 1988;11:701-7.
24 Hansotia P, Broste SK. The effect of epilepsy or diabetes mellitus on the risk of automobile accidents. *N Engl J Med* 1991;324:22-6.
25 Eadington DW, Frier BM. Type 1 diabetes and driving experience: an eight year cohort study. *Diabetic Med* 1989;6:137-41.
26 Stevens AB, Roberts M, McKane R, Atkinson AB, Bell PM, Randal Hayes J. Motor vehicle driving among diabetics taking insulin and non-diabetics. *BMJ* 1989;299:591-5.
27 LaPorte RE, Songer TJ, Gower IF, Lave LB, Ekoé JM. *Review of 49 CFR 391.41(b)(3) regarding diabetic commercial motor vehicle drivers.* Washington DC, Federal Highway Administration, US Dept of Transportation, 1992. (Final Report No FHWA/MC-92/004.)
28 Songer TJ, Lave LB, LaPorte RE. The risks of licensing persons with diabetes to drive trucks. *Risk Analysis* 1993;13:319-26.
29 Lave LB, Songer TJ, LaPorte RE. Should persons with diabetes be licensed to drive trucks?—Risk management. *Risk Analysis* 1993;13:327-34.

(Accepted 5 May 1993)

Lesson of the Week

Secondary adrenocortical insufficiency

P Mansell, V L Scott, R F Logan, J P D Reckless

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

Department of Medicine, Royal South Hants Hospital, Southampton SO9 4PE
P Mansell, *senior registrar*

Department of Geriatrics, St Mary's Hospital, Portsmouth
V L Scott, *registrar*
R F Logan, *consultant*

Department of Medicine, Royal United Hospital, Bath
J P D Reckless, *consultant*

Correspondence to:
Dr Mansell.

BMJ 1993;307:253-4

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 $<0{\cdot}3$ nmol/l

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.

1 Burke CW. The pituitary megatest: outdated? *Clin Endocrinol (Oxf)* 1992;**36**: 133-4.
2 Pavord SR, Girach A, Price DE, Absalom SR, Falconer-Smith J, Howlett TA. A retrospective audit of the combined pituitary function test, using the insulin stress test, TRH and GnRH in a district laboratory. *Clin Endocrinol (Oxf)* 1992;**36**:135-9.
3 Stewart PM, Corrie J, Seckl JR, Edwards CRW, Padfield PL. A rational approach for assessing the hypothalamo-pituitary-adrenal axis. *Lancet* 1988;i:1208-10.
4 Harsoulis P, Marshall JC, Kuku SF, Burke CW, London DR, Fraser TR. Combined test for assessment of anterior pituitary function. *BMJ* 1973;iv:326-9.
5 Shah A, Stanhope R, Matthew D. Hazards of pharmacological tests of growth hormone in childhood. *BMJ* 1992;**304**:193-4.
6 Clayton RN. Diagnosis of adrenal insufficiency. *BMJ* 1989;**298**:271-2.
7 Borst GC, Michenfelder HJ, O'Brian JT. Discordant cortisol response to exogenous ACTH and insulin-induced hypoglycaemia in patients with pituitary disease. *N Engl J Med* 1982;**306**:1462-4.
8 Cunningham SK, Moore A, McKenna TJ. Normal cortisol response to corticotrophin in patients with secondary adrenal failure. *Arch Intern Med* 1983;**143**:2276-9.
9 Burke CW. Adrenocortical insufficiency. *Ballières Clin Endocrinol Metab* 1985;**14**:947-76.
10 Park GP, Raggatt P. Diagnosis of adrenal insufficiency. *BMJ* 1989;**298**: 669-70.
11 Lytras N, Grossman A, Perry L, Tomlin S, Wass JAH, Coy DH, *et al.* Corticotrophin releasing factor: responses in normal subjects and patients with disorders of the hypothalamus and pituitary. *Clin Endocrinol (Oxf)* 1984;**20**:71-84.

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.