Isolated adrenocorticotrophic hormone (ACTH) deficiency associated with acute adrenal crisis

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Summary: A 37 year old black female presented with congestive cardiac failure, 2 months post-partum. She developed spontaneous hypoglycaemia and symptoms of acute adrenal crisis (hypotension, nausea, abdominal pain and tachycardia with small thready pulse), which responded to i.v. dextrose, sodium chloride and hydrocortisone. Biochemical investigations revealed low serum cortisol and plasma adrenocorticotrophic hormone (ACTH) levels. The patient initially showed an impaired cortisol response to intramuscular aqueous tetracosactrin, but an exuberant response after priming with intramuscular tetracosactrin depot. These findings, together with the normal remaining pituitary function, led us to conclude that this patient had isolated ACTH deficiency associated with congestive cardiac failure and acute adrenal crisis.

Introduction

Isolated ACTH deficiency is an extremely uncommon cause of hypoadrenalism and was first reported by Steinberg *et al.* in 1954. In this condition, the development of adrenal crisis is a rare complication (Stacpoole *et al.*, 1982). A patient with isolated ACTH deficiency and congestive cardiac failure who experienced an acute adrenal crisis is reported in this communication.

Case report

A 37 year old black housewife was admitted to King Edward VIII Hospital in December 1983 with a 2 week history of diarrhoea, nausea, generalized weakness, abdominal pain, dyspnoea on exertion and swelling of the legs. Two months before presentation, she had an uneventful pregnancy culminating in the normal delivery of a live infant. The patient gave no history of taking glucocorticoids or any other medications. On enquiry, there was no history of any past illnesses except for pulmonary tuberculosis, which had been diagnosed 3 years ago and was successfully treated.

On admission, she was asthenic and hypothermic (35.8°C). Her blood pressure was 112/80 mm Hg, pulse rate 120 beats/min; the patient was found to be in cardiac failure. A chest radiograph confirmed the clinical diagnosis of congestive cardiac failure. Electrocardiographic findings of low voltage on limb leads and presence of left ventricular hypertrophy on chest leads were consistent with those found in congestive cardiomyopathy (Chesler, 1974). Stool, blood and urine examination and culture were negative and repeated sputum examination did not demonstrate acid-fast bacilli.

Results of routine biochemical and haematological investigations were within the respective reference ranges, except for a mild acidosis and a normocytic normochromic anaemia. Her condition improved with strict bed rest, and hydrochlorothiazide therapy. However, 2 d later she was found to have impaired consciousness, and was cold and sweating. Her blood pressure was 90/60 mm Hg, the pulse rate was 160 beats/min and of small volume. The blood glucose was 1.5 mmol/l and the patient responded to intravenous dextrose, sodium chloride and hydrocortisone. Because of her clinical features and response to hydrocortisone, a diagnosis of hypoadrenalism was entertained. Hypoadrenalism was confirmed with the finding of a cortisol level of less than 2 µg/dl. Serum cortisol was determined by radioimmunoassay (Clin-

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ical Assays, Travenol Laboratories, Massachusetts). The intra- and interassay coefficients of variation of this assay are 2.4% and 7.7%, respectively. Further serum cortisol levels done on 2 consecutive mornings (at 09.00 h), were also low: less than 2 µg/dl and 2.7 µg/dl, respectively (reference range 6–25 µg/dl); 09.00 h plasma ACTH levels were also found to be persistently low (less than 20 pg/ml, the reference range being 0–80 pg/ml). Venous blood for ACTH measurement was collected, free of haemolysis, in chilled tubes with EDTA, spun immediately in a refrigerated centrifuge and the plasma stored at –20°C. The plasma ACTH was measured within 3 weeks of collection by radioimmunoassay (CIS Radioimmunoassay, Italy). The finding of a low plasma ACTH in the face of a low serum cortisol and the absence of adrenal calcification suggested secondary hypoadrenalism. The patient showed an impaired cortisol response to 0.25 mg i.m. aqueous tetracosactrin (Synacthen-Ciba Geigy), but an exuberant response after 9 d priming with 1 mg/d tetracosactrin depot (Depot Synacthen-Ciba Geigy) (Table I). Furthermore, her 09.00 h serum cortisols showed a sustained rise while on tetracosactrin depot (Figure 1). The fact that 9 d of priming with depot ACTH still resulted in an exuberant cortisol response following aqueous ACTH, suggests that maximum stimulation had not been attained. Further support for this proposition is that the basal plasma cortisol following 9 d of stimulation with tetracosactrin depot (1 mg/d), was only 18 µg/dl (normal range 22–54 µg/dl 24 h after tetracosactrin depot).

These findings are consistent with a diagnosis of secondary hypoadrenalism. Investigation of the other pituitary hormones revealed normal luteinising hormone (LH) and follicle stimulating hormone (FSH) responses to luteinising hormone releasing hormone (LHRH), normal thyroid stimulating hormone (TSH) and prolactin (PRL) responses to thyroid releasing hormone (TRH), and the propranolol augmented L-dopa test (Jialal *et al.*, 1984) done on the following day, elicited an adequate growth hormone (GH) response (Table II), as judged by criteria for normal hormonal

Table I Cortisol response (in µg/dl) to i.m. 0.25 mg aqueous tetracosactrin on day 0 and following 9 days of priming with tetracosactrin depot.

	– 15 min	0 min	30 min	60 min
Day 0	<2	<2	2.3	3.1
Day 9	18.5	15.5	43.3	34.3

Criteria for normal responses:

- (1) Basal plasma cortisol: greater than 5 µg/dl.
- (2) Increment of cortisol at 30 or 60 min: greater than 7 µg/dl.
- (3) Peak cortisol at 30 or 60 min: greater than 18 µg/dl.

Table II Responses of TSH, PRL, LH and FSH to 200 µg TRH i.v. and 100 µg LHRH i.v. and response of GH to 500 mg oral L-dopa and 40 mg oral propranolol, all given at 0 min

	0 min				20 min				60 min			
	– 15 min	0 min	15 min	30 min	60 min	90 min	120 min	150 min	180 min	240 min		
TSH (µU/ml)			1.9		1.5		17.9			15.0		
PRL* (ng/ml)			74.3		57.2		150.0			136.0		
LH† (mIU/ml)			4.5		4.8		31.3			41.8		
FSH (mIU/ml)			23.4		21.8		33.1			44.3		
GH (ng/ml)												
	–	1.9	1.7	2.5	3.0	6.1	8.1	10.9	8.4	1.9		

Basal values (reference range for mature non-lactating females, not in periovulatory period)

TSH (µU/ml) 0–6
PRL* (ng/ml) 5–25
LH† (mIU/ml) 5–30
FSH (mIU/ml) 5–16

* Patient lactating.

† Patient not lactating.

Figure 1 09.00 h cortisol showing elevation of levels after initiation of 1 mg i.m. tetracosactrin depot.

responses (Jialal *et al.*, 1981, 1984). It was concluded that the patient had an isolated ACTH deficiency. In an attempt to ascertain whether the primary lesion was in the hypothalamus or pituitary, the lysine-vasopressin test was carried out (Gwinup, 1965). Lysine-

vasopressin failed to elicit a rise in serum cortisol, suggesting a disorder of pituitary origin. Skull radiographs and pituitary tomograms did not reveal any abnormality of the pituitary fossa.

Discussion

From the clinical findings and investigations it is evident that this patient has secondary hypoadrenalism (low serum cortisol and plasma ACTH levels with failure of cortisol response to aqueous tetracosactrin initially, but substantial response following priming with tetracosactrin depot). Since the assessment of the rest of her pituitary function was normal, this pointed to a diagnosis of isolated ACTH deficiency. Because of the unavailability of corticotrophin releasing factor, the lysine-vasopressin test was undertaken: vasopressin is thought to act directly on the pituitary gland (Yates *et al.*, 1971; Gillies & Lowry, 1979) and the lack of a cortisol response suggests that the lesion is in the pituitary gland. Insulin-induced hypoglycaemia was not used to determine the site of the lesion, because of the fear of precipitating acute crisis (Hall *et al.*, 1980).

Classical adrenal crisis has only rarely been reported in patients with isolated ACTH deficiency and usually followed some precipitating factor, namely, infection (Odell *et al.*, 1960; Woeber & Arky, 1965) or dental extraction (Nicholas *et al.*, 1978). There was no obvious stress precipitating the acute adrenal crisis in our patient, except perhaps associated cardiac failure.

Puerperal cardiomyopathy is a common and distinct entity in Blacks in South Africa (Seftel & Susser, 1961), and has not previously been reported in association with isolated ACTH deficiency.

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