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FUNCTIONAL SIGNIFICANCE OF IDIOPATHIC ADRENAL CALCIFICATION IN THE ADULT

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SUMMARY

Two young adults with idiopathic adrenal calcification are described. In one patient the calcification was probably secondary to adrenal haemorrhage in the neonatal period. Neither patient exhibited clinical features suggestive of adrenal cortical insufficiency, and baseline serum cortisol levels were normal. The corticosteroid responses to ACTH administration and to other provocative tests indicated that both glucocorticoid and mineralocorticoid reserve was normal. One patient showed an appropriate epinephrine response to insulin-induced hypoglycaemia. We conclude that even extensive adrenal calcification may be compatible with completely normal adrenal function. Since, however, little is known of the natural history of this condition, lifelong follow-up of such patients is advised.

A wide variety of disease entities in addition to tuberculosis and other granulomatous diseases can cause calcification of the adrenal glands. Neuroblastomas (McAfee & Balli, 1956) and familial xanthomatosis (Wolman *et al.*, 1961) are commonly associated with adrenal calcification. Such calcification is less frequently seen in Niemann Pick's disease (Alexander, 1946) and has been described in Cushing's syndrome (Price & Farmer, 1969), phaeochromocytoma (Snyder & Vick, 1947), and cytomegalovirus infections (Magnin, 1973). In addition, adrenal cysts (Wagner, 1961) or adenomas (Epstein *et al.*, 1973) may calcify. There is considerable evidence for an association between obstetrical trauma, adrenal haemorrhage and subsequent adrenal calcification in the paediatric literature (Snelling & Erb, 1935; Jarvis & Seaman, 1959; Black & Williams, 1973; Newman *et al.*, 1979), but this problem has received little attention in the endocrine literature pertaining to adults.

In the present report we describe two young men in whom adrenal calcification was discovered as an incidental finding. In one patient the adrenal calcification was probably secondary to obstetric trauma and subsequent haemorrhage into the adrenal; in the other

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patient the cause of the adrenal calcification was not determined. These patients exhibited no clinical evidence of adrenal insufficiency. Detailed biochemical evaluation of all aspects of adrenal function failed to reveal any abnormalities, although both patients had borderline elevations of their ACTH levels.

CASE REPORTS

Patient 1

This 29-year-old white male was in good health until August 1978, when he developed the gradual onset of lethargy, fatigue and malaise. There was no anorexia, weight loss, fever or cough. Upon seeking medical advice, the patient was found to be hypertensive (blood pressure 150/100 right arm sitting) and an intravenous pyelogram was performed. Plain films of the abdomen revealed striking bilateral adrenal calcification (Fig. 1). On physical examination there was no hyperpigmentation, evidence of dehydration or postural hypotension. Electrolytes, blood sugar and blood urea nitrogen were normal. There was no history of tuberculosis, and PPD (intermediate strength) skin tests were negative on repeated testing. Delayed hypersensitivity responses to Candida antigen were positive. Complement fixation tests for coccidiomycosis, histoplasmosis and blastomycosis were negative. Serological screening tests for echinococcus and toxoplasmosis were also negative. The chest X-ray was within normal limits. A rapid sequence intravenous pyelogram was normal. A family history revealed that the patient's father was also mildly hypertensive.

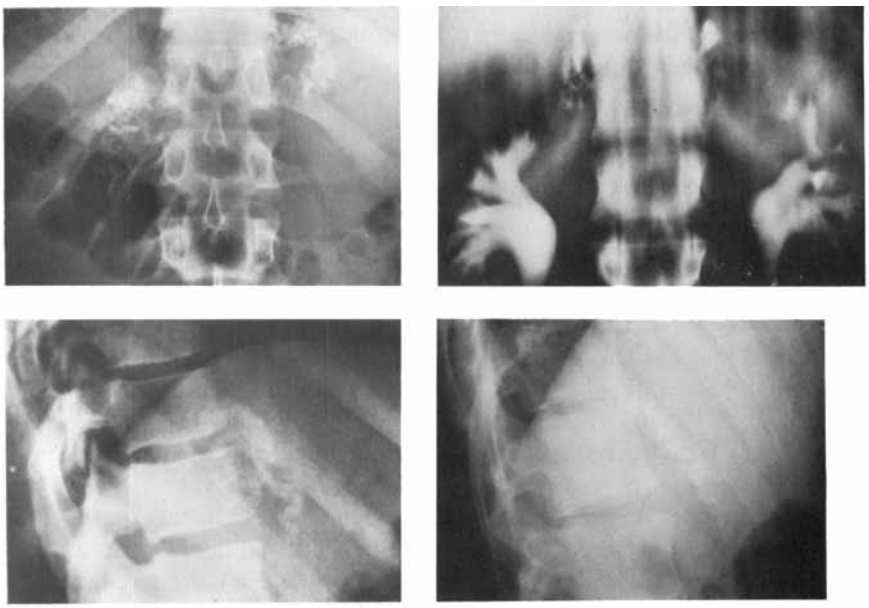

Fig. 1. The X-ray appearance of adrenal calcification in two adult males. Both antero-posterior and lateral films are shown for patient 1 (left) and patient 2 (right). The film for patient 2 was obtained during intravenous pyelography.

Review of past medical history revealed that the patient was born at 34 weeks, weighing 3 pounds, 14 ounces. The third stage of labour was prolonged and the patient's twin brother suffered irreversible, severe brain damage as a result.

He was admitted to the University of Michigan Clinical Research Centre for endocrine evaluation in January 1979. At that time he was on no antihypertensive therapy or other medication.

Patient 2

This 23-year-old American soldier, stationed in Malaysia in 1971, was discovered to have adrenal calcification during evaluation of an injury to his back (Fig. 1). The patient had no signs or symptoms of adrenal insufficiency or hypercortisolism and was in a state of excellent general health. The patient had no history of anorexia, fever or weight loss and his physical examination was completely normal. There were no pulmonary complaints or history of tuberculosis exposure, and the chest X-ray was normal. Birth history was not available. The patient had been given BCG immunization in 1968 before leaving for Malaysia, so a tuberculin skin test was not performed. Urine cultures for acid fast bacilli were negative on three occasions. Blood urea nitrogen, electrolytes, blood sugar, liver function tests and complete blood counts were all normal.

The patient was admitted in 1971 to Princess Margaret Hospital, Christchurch, New Zealand, for evaluation of adrenal cortical function.

METHODS

Patient 1

Plasma cortisol (Dash *et al.*, 1975), ACTH (Vague *et al.*, 1971), plasma renin activity (Haber *et al.*,1969), angiotensin II (Nicholls & Espiner, 1976) and aldosterone in urine (Bayard *et al.*, 1970) and plasma (Antunes *et al.*, 1976) were measured by radioimmunoassay. Plasma epinephrine was assayed by a single isotope radioenzymatic method (Peuler & Johnson, 1977).

Patient 2

Plasma cortisol was measured by a fluorometric method (De Moor *et al.*, 1960) and ACTH by radioimmunoassay (Donald, 1968).

RESULTS

Patient 1

Cortisol levels at 09.00 h ranged between 20 and 24 μg/dl (normal range 7–27 μg/dl), and supine plasma aldosterone (10 mEq/day sodium diet) on separate determinations were 21·1 and 36·1 ng/dl (normal range 17–33 ng/dl). Both cortisol and aldosterone levels rose briskly following the intravenous administration of Cortrosyn® 0·25 mg (Table 1). Plasma ACTH at 09.00 h was 95·1 pg/ml (normal range 35–95 pg/ml). Plasma renin activity, angiotensin II and plasma aldosterone levels all increased rapidly after the ingestion of a 10 mEq sodium diet combined with upright posture (Table 2). The observed levels of angiotensin II and aldosterone were within normal limits, but plasma renin

Table 1. Cortisol and aldosterone response to ACTH stimulation*

Minutes after 0·25 mg Cortrosyn i.v.	Patient 1		Patient 2
	Serum cortisol (μg/dl)	Plasma aldosterone (ng/dl)	Serum cortisol (μg/dl)
0	23·7	36·1	7·0
30	32·6	58·4	
60	37·8	61·8	
120	38·1	40·9	27·4

* In patient 1 ACTH was administered intravenously as a bolus, and in patient 2 was given as an intramuscular injection. Patient 1 was studied while receiving a low sodium diet (10 mEq/day).

activity was higher than expected (Table 2). Following the administration of intravenous insulin (0·15 unit/kg) the patient's blood glucose dropped to 19 mg/dl and an appropriate rise in circulating epinephrine and cortisol resulted (Fig. 2).

The patient was discharged from the hospital on no therapy with the diagnoses of idiopathic adrenal calcification and mild essential hypertension. His presenting symptoms of lethargy, fatigue and malaise were transient and no underlying cause was found.

Table 2. The effect of dietary sodium intake and upright posture on the renin-angiotensin system in patient 1

	160 mEq Na Diet	10 mEq Na Diet
Plasma renin activity		
08.00 h supine	3·79 ng/ml/h (0–1·6)	6·77 ng/ml/h (1·5–7·9)
10.00 h upright	9·90 ng/ml/h (0·3–3·4)	29·71 ng/ml/h (3·3–15·5)
Serum angiotensin II		
08.00 h supine	9·0 pg/ml (8–25)	42·0 pg/ml (18–55)
10.00 h upright	57·0 pg/ml (15–50)	113·0 pg/ml (35–115)
Plasma aldosterone		
08.00 h supine	16·2 ng/dl (6·5–17·5)	21·1 ng/dl (17–33)
10.00 h upright	25·4 ng/dl (11–27)	79·7 ng/dl (40–90)
Urinary aldosterone/24 h	10·3 μg (5–12)	26·9 μg (10–25)

The results were obtained on the fourth day of both diets. The numbers in parentheses represent the normal ranges under the stated experimental conditions. For plasma renin activity and plasma aldosterone this range includes two standard deviations from the mean.

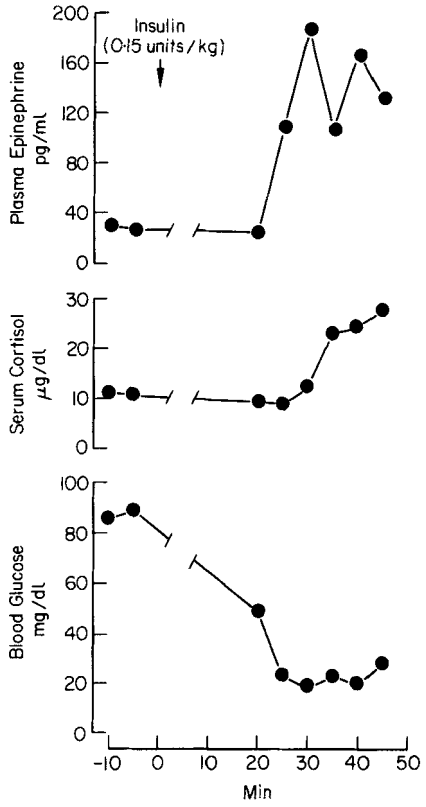

Fig. 2. Epinephrine, cortisol and glucose responses to insulin (0·15 u/kg regular insulin) given as a single intravenous bolus in patient 1. After baseline sampling, no blood was drawn until 20 min after insulin administration (discontinuous line).

Patient 2

Cortisol levels drawn at 08.00 h ranged between 7 and 12 μg/dl (normal range 7–20 μg/dl) and rose briskly following Cortrosyn® 0·25 IM (Table 1). Plasma ACTH at 08.00 h on two separate determinations was 100 pg/ml and 123 pg/ml (normal range 5–95). Cortisol secretion rate was 30 mg/24 h (normal range 12–30 mg/24 h). Aldosterone secretion was tested indirectly by measuring the urine and serum electrolyte responses to severe sodium restriction. On the fifth day of a 10 mEq/day sodium and 60 mEq/day potassium diet, urinary sodium excretion was 9·5 mEq/24 h and potassium excretion was 75·6 mEq/24 h. Serum sodium at that time was 137 mEq/l and potassium was 4·25 mEq/l.

DISCUSSION

Numerous children with idiopathic adrenal calcification have been described (Jarvis & Seaman, 1959; Black & Williams, 1973) and only rarely do these patients exhibit clinical features of adrenal cortisol insufficiency. Many of the cases, however, were reported prior to the development of sensitive assay procedures, so adrenal reserve could not be fully assessed. Our two patients were studied in order to see whether their adrenal calcification

was associated with subtle or subclinical adrenal insufficiency. This consideration is of practical importance, since it is possible that these patients may be at risk of developing adrenal insufficiency under stressful circumstances such as surgery, major trauma or severe illness. Such patients with adrenal calcification may be at risk from developing adrenal insufficiency in adulthood, even though the vast majority of them apparently do not do so as children (Jarvis & Seaman, 1959).

Present data indicate that our two patients had normal mineralocorticoid and glucocorticoid levels and adequate adrenocortical reserve. For patient 1, aldosterone levels in plasma and urine were normal and they responded appropriately to sodium restriction, postural change and ACTH (Tables 1 and 2). Whereas the elevated plasma renin values in this patient might be taken to indicate early mineralocorticoid deficiency, concomitant angiotensin II levels were within normal limits, and as noted aldosterone responsiveness to sodium restriction and to ACTH stimulation were brisk, indicating normal aldosterone reserve. The reason for the raised plasma renin levels is not readily apparent. Patient 2 was studied prior to the widespread availability of aldosterone radioimmunoassays, but his ability to conserve urinary sodium and maintain normal serum electrolytes on a sodium restricted diet strongly suggests normal aldosterone reserve. His cortisol secretion rate was 30 mg/24 h, and both patients had normal serum cortisol levels as well as brisk cortisol responses to ACTH (Table 1). In addition, the cortisol increment during hypoglycaemic stimulation was normal in patient 1.

Another young adult with non-tuberculous adrenal calcification and a history of birth trauma has recently been described, and this patient's cortisol rise following ACTH administration was also normal (Cohen *et al.*, 1978). The borderline elevation of ACTH in our two patients is thus the only indication of a possible disorder of glucocorticoid secretion resulting from their adrenal calcification. Only long-term follow-up will determine whether or not their mild elevations of ACTH are indicative of a propensity to the eventual development of glucocorticoid insufficiency.

Studies of adrenal medullary function were performed on patient 1 since, in children, adrenal calcification has been associated with defective epinephrine responses to insulin-induced hypoglycaemia (Jacobsen *et al.*, 1975; Ploier *et al.*, 1978). These latter patients were reported to have normal adrenal cortical function. Patient 1 had no history of hypoglycaemia and his epinephrine response to insulin-induced hypoglycaemia was vigorous (Fig. 2).

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