Anomalous responses to stimulation and suppression tests in Cushing's syndrome due to a calcified adrenal adenoma

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Summary

A case of Cushing's syndrome, due to an adrenal adenoma, which responded to dexamethasone with a rise in plasma urinary steroids is described. Further unusual features were radiologically visible calcification and a response to ACTH stimulation.

Introduction

The differential diagnosis of the various forms of Cushing's syndrome rests mainly on the response of the adrenal glands to stimulation and suppression. Usually Cushing's syndrome due to adrenal hyperplasia is suppressed by dexamethasone in sufficient doses and stimulated by ACTH and metapyrone. Tumours either benign or malignant are usually non-responsive to stimulation or suppression by these agents. Adrenal venography may also help differentiate between tumour or hyperplasia. The results of these findings are important in that they determine the management of the disease. There have been previous reports of anomalous responses to metapyrone and dexamethasone in that tumours also may show suppression or stimulation, i.e. non-autonomy. It is, however, uncommon for any cause for Cushing's syndrome to be stimulated by dexamethasone. We wish to report a patient who had Cushing's syndrome due to a proven adrenocortical adenoma which was not only stimulated by dexamethasone but was also responsive to ACTH stimulation. Another unusual feature was the presence of radiologically visible calcification in the adenoma.

Case report

In 1970 the patient, a white female then aged 31 years, developed thyrotoxicosis which was treated by subtotal thyroidectomy. She was seen in Groote Schuur Hospital in May 1972 when she gave an 18-month history of increasing weight, facial hirsutes, easy bruising and depression. She also complained of low back pain and generalized weakness.

Her periods had been irregular since the menarche but 3 years previously she had been started on norethisterone which had temporarily regularized them. However, for the past 6 months her periods had once again become irregular in spite of the norethisterone.

On systematic enquiry her only other complaint was of occasional ankle swelling. Her thyroxine had been stopped 4 months previously but she continued to take norethisterone daily throughout her investigation.

On examination the striking clinical feature was a round, full face, plethora and minimal hirsutes. A small buffalo hump, centripetal obesity and occasional pink striae were also evident. The thyroidec-tomy scar was well healed and the patient was clinically euthyroid. She was slightly hypertensive with a BP of 145/90 mmHg but physical examination was otherwise normal.

Methods

Plasma fluorogenic corticoids were measured by method of Mattingly (1962), urinary steroids were measured by the Zimmermann reaction using the method of Dreker *et al.* (1952) for the 17 oxosteroids and that of Few (1961) for the 17 oxogenic steroids.

Investigation

Hb 16.7 g/100 ml, WBC 12,500/mm³, differential count: neutrophils 85%, lymphocytes 12%, eosinophils 0%. Creatinine clearance 101 ml/min. Blood urea 26 mg/100 ml, sodium 143 mEq/l, potassium 3.8 mEq/l. Blood glucose 73 mg/100 ml. T₃ resin 44%, T₄ 6.3 µg/100 ml, TSH 3.0 µU/ml.

X-ray of skull and tomography of pituitary fossa—normal. X-ray abdomen and IVP demonstrated punctate calcification in the left adrenal (Fig. 1) and a normal upper urinary tract. Adrenal venography confirmed the presence of a mass approximately 2.5 cm in diameter in the left adrenal (Fig. 2) and a normal venous pattern on the right.

FIG. 1. Plain radiograph of left adrenal showing punctate calcification.

The effect of adrenal suppression and stimulation tests are shown on Table 1.

It can be seen from these results that the patient had relatively normal levels of plasma cortisol but there was a loss of diurnal variation. Following the administration of dexamethasone, 8 mg daily, a striking rise occurred in both urinary and plasma steroids and during this time the patient became markedly more Cushingoid and developed ankle oedema. Further rise did not occur when the dexamethasone was increased to 16 mg daily but no suppression was seen during this time. There was no response to lysine vasopressin but a marked rise occurred in plasma cortisol following synthetic ACTH stimulation.

In view of the radiological findings it was felt that the patient had an adrenocortical tumour and she was therefore referred for surgery. At operation the left adrenal gland was occupied by a bright yellow tumour 2.7×3×2 cm in size which was removed along with the remainder of the left adrenal. The

FIG. 2. Selective left adrenal venogram demonstrating the tumour in the upper pole of the adrenal.

right adrenal gland was not visualized. Histology showed an adrenocortical tumour with areas of necrosis and calcification. The nuclei of the cells were mainly uniform but a few hyperchromatic cells were present. No mitotic figures were seen. Tumour cells were seen within the capsule but there was no evidence of invasion of blood vessels. It was concluded that this was probably an adenoma although certain features suspicious of malignancy were present.

The patient had an uneventful post-operative course. The results of adrenal function tests 2 weeks after the operation are shown in Table 2.

Discussion

This patient demonstrated several features not usually encountered in Cushing's Syndrome due to an adrenal adenoma.

The first was a paradoxical rise in both plasma and urinary steroids following dexamethasone. This has been reported in both adrenal hyperplasia (Brookes *et al.*, 1966; James, Landon & Wynn 1965; Hardon & Forrest, 1964) and adenoma (James *et al.*, 1965; Liddle, 1960; Ross, Marshall-Jones & Friedman, 1966).

TABLE 1. Pre-operation

Plasma cortisol ($\mu\text{g}/100\text{ ml}$)		Urinary steroids ($\text{mg}/24\text{ hr}$)		Dexamethasone
9.00	24.00	17 Oxo-	17 Oxogenic	
19	12	4.2	23.0	2 mg at 24.00 0.5 mg 6 hourly 0.5 mg 6 hourly 2 mg 6 hourly 2 mg 6 hourly 4 mg 6 hourly 4 mg 6 hourly
24	15	—	—	
19	—	—	—	
—	13	6.0	28	
40	—	—	—	
39	37	8.6	38	
—	20	—	—	
26	20	7.0	—	
Tetracosactrin test (plasma cortisol $\mu\text{g}/100\text{ ml}$)		Lysine vasopressin test (plasma cortisol $\mu\text{g}/100\text{ ml}$)		
0 min	18	0 min	25	
0.25 mg tetracosactrin given i.m.		10 PU lysine vasopressin given i.m.		
30 min	41	30 min	26	
60 min	47	60 min	28	
Blood from left adrenal vein—plasma cortisol 336 $\mu\text{g}/100\text{ ml}$.				

TABLE 2. Post-operation

	Urinary steroids ($\text{mg}/24\text{ hr}$)	
	17 Oxo-	17 Oxogenic
Dexamethasone 0.5 mg b.d.	2.3	0.9
Dexamethasone 0.5 mg b.d.	1.9	0.2
Tetracosactrin test (while on dexamethasone 0.5 mg b.d.) (plasma cortisol $\mu\text{g}/100\text{ ml}$)		
0 min	1	
1.0 mg depot tetracosactrin given i.m.		
30 min	2	
60 min	3	
6 hr	3	
24 hr	3	
30 hr	3	

The reasons for this increase are not clear, but have been attributed to direct stimulation of the adrenals by administered steroid, an alteration in extra-adrenal steroid metabolism or a positive feed-back effect on ACTH caused by dexamethasone (French *et al.*, 1969).

Adrenal tumours are typically ACTH unresponsive although responsive adenomata have been described (Martin & Hamman, 1966; Ross *et al.*, 1966). James & Landon (1968), however, suggested that there was no reason why the contralateral adrenal gland should not respond to ACTH if it had not been fully suppressed. In this case, however, the response to synthetic ACTH seen before operation (Table 1) was absent post-operatively (Table 2), showing that the ACTH responsive tissue was situated either in the tumour itself or in the uninvolved portion of the left adrenal gland.

The failure of the plasma cortisol to increase following lysine vasopressin (Table 1) is in keeping with the assertion that this response is absent in an adenoma, but present in bilateral hyperplasia (Bethge *et al.*, 1971). However, recent reports of lysine vasopressin responsive adenomata (Demura *et al.*, 1972) indicate that this test cannot be relied on to distinguish tumour from hyperplasia.

Another striking feature was that of radiologically evident calcification in the left adrenal (Fig. 1). Although such calcification is present in 31% of adrenal carcinomas, in a recent review Vermess, Schour & Jaffe (1972) were only able to find two other cases of calcification in an adenoma apart from their own. Venograms revealed disordered vasculature in the region of the left adrenal but this was of little help in distinguishing between adenoma and carcinoma, although it excluded hyperplasia.

Histologically, the tumour was thought to be benign although capsular invasion was present. Clinically, the lack of virilization, the normal electrolytes, relatively low levels of plasma cortisol and urinary ketosteroids would favour an adenoma.

It is not clear why the patient developed ankle oedema only at the time of the paradoxical rise in plasma cortisol during the dexamethasone suppression test. This may have been related to the release of mineralocorticoids, but even excess cortisol *per se* can be responsible for sodium retention in man (Dingman *et al.*, 1958). The oedema was self-limiting and disappeared shortly thereafter.

The increasing number of anomalous responses to both stimulation and suppression tests in the various types of Cushing's syndrome would seem to indicate that while dexamethasone suppression is still useful in making the initial diagnosis, measurement of

plasma ACTH together with radiological visualization of the adrenal glands will have to be relied upon to place the lesion primarily in the hypothalamic-pituitary axis or in the adrenal.

Acknowledgments

We would like to thank Dr A. Swanepoel for referring the patient, Professor J. H. Louw who performed the operation and the Department of Chemical Pathology, University of Cape Town, for the steroid estimations.

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Postgraduate Medical Journal (December 1973) 49, 926-928.

Acute renal failure complicating McArdle's syndrome

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Summary

A case of McArdle's syndrome is described in which an epileptiform seizure was followed by acute reversible renal failure with hypercalcaemia in the diuretic phase.

Introduction

McArdle's syndrome is a rare disorder of muscle metabolism which presents in early life with pains and stiffness in the muscles during exercise. The disorder is known to be due to muscle phosphorylase deficiency (Schmid & Mahler, 1959) and behaves as

an autosomal recessive. Myoglobinuria is known to occur during attacks, but acute oliguric renal failure has been reported in only two patients (Grünfeld *et al.*, 1972). We report a further case of renal failure associated with McArdle's syndrome with the added complication of hypercalcaemia occurring during the diuretic phase.

Case report

The patient, R.G., previously reported in a family study of McArdle's syndrome (Salter,