Cushing's Syndrome: Don't let A Pituitary Adenoma Fool You!

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Abstract

We present the case of a young male admitted with Cushing's syndrome and a pituitary microadenoma for trans-sphenoidal surgery. An equivocal ACTH level and incomplete work up for the hypercortisolism prompted postponement of the surgery in favour of further investigation which revealed an adrenal adenoma. He finally underwent a laparoscopic left adrenalectomy which proved curative.

Background

The adrenal gland is composed of the adrenal cortex and medulla, which arise from distinct embryological origins. The cortex is responsible for producing aldosterone, cortisol and androgens, whereas the medulla produces catecholamines. The clinical presentations of adrenal tumours vary accordingly to the hormones secreted. The rarely encountered mixed corticomedullary tumour (MCMT) is distinguished as a single tumour mass of the adrenal gland composed of intermixed cortex and medullary cells.[1]

Cushing's syndrome results from chronic excess cortisol production. Causes may be classified as ACTH - dependent (pituitary or ectopic origin) and ACTH-independent (adrenal origin). Adrenal tumours causing Cushing's syndrome are commoner in females. The peak incidence is in the fourth and fifth decade.[2]

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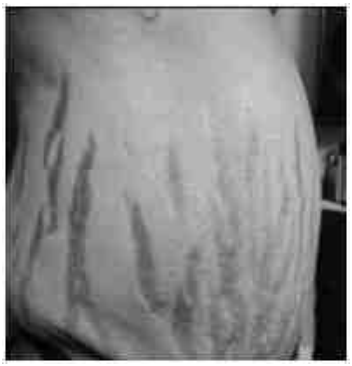
Causes and relative frequency of Cushing's syndrome in adults:

Pituitary adenoma 68 % (Cushing's Disease)
Ectopic ACTH syndrome 12%
Ectopic CRH secretion <1%
Adrenal adenoma 10 %
Adrenal carcinoma 2%
Bilateral micronodular adrenal hyperplasia <1%
Bilateral macronodular hyperplasia <1%
Exogenous steroid use.

Case Report

Our patient, was a 26 year old male, admitted in the general ward with complaints of a 5 kg weight gain in one year, polyuria, nocturia, and vision difficulty since 3-4 months. Prior to admission he had been seen by an endocrinologist and diagnosed with hypertension for which he was on triple drug therapy including an ACE inhibitor, CCB and a β-Blocker. He had overt cushingoid features and was found to have a mildly elevated serum cortisol- 21.3 ug/dl (normal 6-19 ug/dl), and a random ACTH value of 17 ug/dl. Blood sugars

were normal.



MRI of the sella with contrast had revealed a pituitary microadenoma in the right half of adenohypophysis measuring 6 mm x 6.7 mm

Based on these tests, a diagnosis of pituitary Cushing's was made by the outside endocrinologist and he was admitted under neurosurgery for trans-sphenoidal surgery scheduled for the following day. An Endocrine Consult was given to us for peri-operative hormonal management. Given the equivocal biochemistry results and severe hypokalaemia on admission, we decided to investigate step by step, and the neurosurgeon agreed to hold off surgery.

The lab parameters were as follows:

24 hour urinary cortisol - 1228 ug/day (55-403)

Sr. ACTH (8 am) - 21.4 ug/dl

Post LDDST (low dose dexamethasone suppression test) Sr cortisol- 20.24 ug/dl-Unsuppressed, confirmatory for the diagnosis of Cushing's syndrome

Post HDDST (High dose dexamethasone suppression test) Sr cortisol - 21.18 ug/dl-unsuppressed, suggesting an adrenal/ectopic source of cortisol; note: dexamethasone would be expected to suppress cortisol more than 50% if arising from a pituitary source

Sr. Potassium- 2.7 mmol/l; Sr. Na-138 mmol/l

Sr. testosterone- 1.21 nmol/l

Prolactin - 14 ng/ml

LH- 6.87 iu/l

FSH- 8.34 iu/l

TFT -Normal

HBA_{1C}-5.5%

DHEAS normal (rule out mixed corticomedullary tumour of adrenal)

A PET-CT was done and it revealed an intensely FDG -avid, homogenous, well defined left adrenal mass (3.5 cm x 2.9 cm x 3.2cm) making the left adrenal adenoma as source of hypercortisolism more likely. There was no FDG pick up in the pituitary region. No FDG avid uptake elsewhere ruled out an ectopic ACTH producing lesion as well. Adrenal venous sampling, although ideal, was not performed due to lack of facilities and finances. Plasma free metanephrines level was checked after withholding the necessary anti-hypertensive agents to rule out phaeochromocytoma.

Laparoscopic left adrenalectomy was finally done after correction of hypokalaemia and under perioperative cover of hydrocortisone. The surgery was uneventful. Histopathology confirmed a benign left adrenal adenoma. Post-operatively after two days of intravenous steroids, he was started on oral Hydrocortisone 10 mg at 8 am and 5 mg at 4 pm. He was discharged with well controlled blood pressure on tapered doses of β-Blocker and ACE inhibitor.

Post operative (2 weeks after left

adrenalectomy)-

24 hour urinary cortisol- 14.74 ug/day (55-403), urine volume -2200

8 am Sr. cortisol- 0.714 ug/dl (6.2-19.4 ug/dl) (off steroids for 24 hours prior test)

Sr potassium- 5.1 mmol/l

Sr Na- 141 mmol/l

4 months post surgery, he had lost 3 kg and was normotensive without any antihypertensive agents. Bone density was normal. He continued to need hydrocortisone replacement.

Discussion

Cushing syndrome (CS) is an uncommon endocrine disorder with incidence of 2-3 cases per million of population per year in most countries. A step by step work up is imperative to arrive at the right diagnosis and manage accordingly.

This commences with careful history taking and physical examination. Exogenous steroid use must be kept in mind and ruled out. The first step is to confirm hypercortisolism with a midnight salivary cortisol and/or the 1 mg overnight or low-dose dexamethasone suppression tests. Next measure ACTH in order to differentiate adrenocorticotrophin (ACTH)-dependent from ACTH-independent CS. With an elevated ACTH, the next step is to differentiate pituitary-dependent from ectopic ACTH-dependent CS.[4,5] Many dynamic tests such as the HDDST (high dose dexamethasone suppression test) may be considered, although ideally bilateral inferior petrosal sinus sampling (BIPSS) should be performed in almost all patients with ACTH-dependent CS, except for patients with a pituitary macroadenoma.[6] Imaging follows biochemical testing and should include MRI of the pituitary, and CT scanning of the chest and abdomen to look for an ectopic source. Whenever an adrenal source is suspected on the basis of a low to normal ACTH, CT scanning of adrenals help to localise the source which can be further confirmed by adrenal venous sampling whenever the facility is available. Confirmation of the diagnosis of CS and accurate localisation of its source are essential to optimise therapy for this complex disorder[3] or one might turn up operating at the wrong site!

Serum cortisol should be performed only after stopping oral exogenous oestrogens, oral contraceptive pills, hormone replacement therapy at least a month prior.

Conclusion

The presence of a pituitary tumour, in a case of Cushing's syndrome can sometimes lead to a hasty and incorrect diagnosis of a central cause, resulting in unnecessary pituitary surgery that can have drastic consequences to the extent of permanent panhypopituitarism. A detailed history followed by a step by step biochemical evaluation though tedious, is imperative and the first step prior to imaging studies.

Adrenal venous sampling or petrosal sinus sampling also are of immense value in confirming the source, but remain underutilised.

Non-functioning pituitary microadenomas do not mandate surgical intervention; a timed follow up with a

repeat pituitary MRI and anterior pituitary hormonal evaluation is sufficient.[7]

Post-operative temporary adrenal insufficiency ensues because of long term suppression of ACTH often requiring glucocorticoid replacement for up to 2 years.

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