Reminder of important clinical lesson

Cushing syndrome associated with an adrenal tumour

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Summary

Cushing syndrome (CS) in children is a rare disorder that is most frequently caused by an adrenal tumour or a pituitary corticotrophin-secreting adenoma. The management is challenging and requires an individualised approach and multidisciplinary care. We present the case of a 23-month-old female child with a history of excessive weight gain, growth failure, hirsutism, acne and behavioural difficulties. Investigations revealed elevated serum midnight cortisol and 24 h urinary free cortisol. Overnight dexamethasone suppression testing showed no suppression of cortisol levels. Abdominal imaging revealed a right-sided suprarenal mass. She underwent right adrenalectomy and the histology showed an adrenal cortical carcinoma. There was clinical improvement with catch-up growth and weight normalisation. Despite being rare in clinical practice, in a child with weight gain, hirsutism and growth failure the diagnosis must be considered. The overall prognosis of CS in childhood is good, but challenges remain to ensure normal growth and body composition.

BACKGROUND

Cushing syndrome (CS) is a rare disorder with an incidence of 2–3 cases/million/year, and only 10–20% of cases occur in childhood and adolescence. Unlike adults, where a clear female preponderance is observed, there is no sex predilection in childhood cases.¹ The term Cushing syndrome is used to describe all causes, whereas Cushing disease (CD) is reserved for cases of pituitary-dependent CS.² Paediatric CS can be classified into adrenocorticotrophic hormone (ACTH)-independent and ACTH-dependent causes.³ The two most common aetiologies of endogenous CS are adrenal tumours and pituitary corticotrophin-secreting adenomas.^{1–4} In children, ectopic production of ACTH is extraordinarily rare.^{3–4} Adrenocortical tumours (ACTs) most often occur in childhood (at 4–5 years); in contrast, CD typically presents during adolescence (at 13–15 years). CD accounts for at least 75% of childhood cases of CS.^{1–3} A high index of suspicion is required to make an early diagnosis, and a delay of a few years between onset of disease and diagnosis is well described.¹ The classic presentation is obesity and below-average growth velocity. Catabolic manifestations of hypercortisolism like thin skin, striae, easy bruising, muscle weakness and osteoporosis, though of high discriminatory value, are less common in children than in adolescents. Delayed puberty, pseudoprecocity and signs of hyperandrogenism are also well-described manifestations. Less commonly, CS can present as polycystic ovarian syndrome, type 2 diabetes mellitus, hypertension or osteoporosis.¹

In making a diagnosis, a combination of tests is carried out, first to establish a state of endogenous hypercortisolism, and second to localise its source. Management of CS requires an individualised approach and multidisciplinary care.^{1–2}

ACTs are rare in children. Most ACTs in children are functional tumours and present with virilization, precocious puberty or CS.⁵

CASE PRESENTATION

Female child, 23 months old. No significant history of malignancy or consanguinity in the family. First child, 39 weeks gestation, caesarean delivery, birth weight of 3544 g. Uneventful neonatal period. History of frequent upper respiratory infections since the age of 14 months.

The child presented with a 2-month history of excessive weight gain, growth failure, hirsutism, acne and behavioural difficulties. When examined she had a moon face, buffalo hump, facial and back hirsutism, facial acne, greasy hair, and abdominal distension but without a palpable mass. Her height and weight centiles were 0.4th–2nd and >99.6th, respectively. The blood pressure was 140/100 mm Hg (>99th centile). Her pubertal development showed Tanner stage 2 pubic hair development but no cliteromegaly.

INVESTIGATIONS

Investigations showed a midnight cortisol of 796 nmol/l and ACTH of <5 ng/l; her 24 h cortisol profile demonstrated high cortisol levels throughout with a mean cortisol of 728 nmol/l and loss of circadian rhythm; serum androgens were raised (tables 1 and 2).

Urine steroid profile (USP) and urinary free cortisol (UFC) showed raised outputs of cortisol, androgens and cortisol metabolites on separate occasions, with marked elevation of 11 β -hydroxyandrosterone. There was no hyperglycaemia or glycosuria. Overnight dexamethasone suppression test showed no suppression of cortisol (cortisol predexamethasone 838 nmol/l, postdexamethasone 990 nmol/l). Abdominal ultrasound and MRI revealed a right-sided mixed solid/cystic suprarenal mass, which measured 6.8×6.5 cm in axial dimensions. There was no sign of vascular, hepatic or renal invasion and no metastatic deposits were seen on chest CT.

TREATMENT

The child was referred to the Paediatric Urology Department for laparoscopic surgery. Because

Table 1 Laboratory tests at admission

Glucose (3.9–5.8 mmol/l)	5.2
Plasma sodium (135–145 mmol/l)	140
Plasma potassium (3.5–5.1 mmol/l)	4.3
LH (0.9–1.9 IU/l)	<0.2
FSH (0.7–3.3 IU/l)	0.6
Free T4 (10.8–19 pmol/l)	18.4
TSH (<6 mU/l)	<0.1
17-OHP (0–5 nmol/l)	1
DHEAS (0.2–2.1 µmol/l)	10.7
Androstenedione (<1.1 nmol/l)	22.6
Testosterone (0.2–2.9 nmol/l)	4.33
IGF-1 (51–303 ng/ml)	310
IGFBP-3 (0.8–3.9 mg/l)	2.83
α-Fetoprotein (0–10 kU/l)	5
β-hCG (0–4 IU/l)	<1
Renin (2–60 pg/ml)	10
Aldosterone (280–850 pmol/ml)	170
Urine VMA/creatinine ratio (<12 mg/g)	1

ACTH, adrenocorticotrophic hormone; LH, luteinising hormone; FSH, follicle stimulating hormone; T4, thyroxine; TSH, thyroid-stimulating hormone; 17-OHP, hydroxyprogesterone; DHEAS, dehydroepiandrosterone sulphate; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; HCG, human chorionic gonadotrophin; VMA, vanillylmandelic acid.

preoperatively she maintained high cortisol levels associated with irritability, increased appetite, lethargy and hypertension, she was started on metyrapone with good clinical response. She underwent right adrenalectomy laparoscopically without complications and with complete removal of the tumour with no spillage. She was discharged day 5 postoperatively on maintenance hydrocortisone, as there was evidence of suppression of the left adrenal gland. The blood pressure normalised. Her 24 h cortisol profile on her postoperative day 8 revealed a mean cortisol of 166 nmol/l. Androgen levels were undetectable. Histology showed features suggestive of adrenal cortical carcinoma with complete resection. No genetic cause was identified (11p15 and p53 negative).

OUTCOME AND FOLLOW-UP

After a year of follow-up there was gradual improvement in height and weight, the glucocorticoid supplementation was stopped and follow-up abdominal ultrasound imaging did not show evidence of tumour recurrence. She is followed up by regular abdominal ultrasound and USP (as a tumour marker).

DISCUSSION

The recognition of features which can alert the clinician to the diagnosis of CS is of crucial importance in early diagnosis and treatment. Most children and adolescents have a typical cushingoid appearance.² In this clinical report, poor linear growth and weight gain were present, consistent with other reports.

Given the rarity of CS and the paucity of extensive experience at any given centre, the patients are best managed by a multidisciplinary team. Once CS is suspected on the basis of clinical manifestations, the

diagnostic evaluation involves the administration of multiple tests in a logical sequence.⁴

Overproduction of cortisol is the biochemical hallmark of CS regardless of its cause, which was documented in the first stage of the investigations. In normal subjects, plasma cortisol levels are at their highest first thing in the morning and reach a nadir at around midnight (<50 nmol/l in a non-stressed subject). This circadian rhythm is lost in patients with CS such that in the majority of patients the 9:00 hours plasma cortisol is normal but midnight levels are raised. UFC is an integrated measure of plasma-free cortisol and can be used for subsequent follow-up as a tumour marker. Normal values are less than 220 to 330 nmol/24 h depending upon the assay used. USP is also a useful tumour marker for tumours secreting glucocorticoid and androgen metabolites. Patients should make two or three complete consecutive collections.^{2 4}

The most discriminatory time of day to measure ACTH is between 23:00 and 1:00 when ACTH/cortisol secretion is at a nadir. A midnight ACTH result greater than 22 ng/l in a patient with biochemical hypercortisolism confirms that the disease is ACTH dependent. In patients with adrenal tumours, plasma ACTH is usually undetectable² as in this case.

In normal subjects, the administration of a supraphysiologic dose of glucocorticoid results in suppression of ACTH and cortisol secretion. In CS of whatever cause, there is a failure of this suppression when low doses of the synthetic glucocorticoid dexamethasone are given. Various doses of dexamethasone have been used, but 1 mg of dexamethasone is usually given at midnight. A normal response is a plasma cortisol less than 140 nmol/l between 8:00 and 9:00 the following morning. Sensitivity can be improved by reducing the plasma cortisol cut-off value. In the 48 h low-dose dexamethasone suppression test, failure to suppress confirms hypercortisolism, but does not necessarily provide information about the cause.² In this case, the child initially had ultrasound imaging compatible with an ACTH-independent cause of CS. Consequently, it was not felt necessary to proceed with further investigations such as low- and high-dose dexamethasone suppression, etc. The child was sick and the tumour appeared to be growing rapidly.

Adrenal-directed medical management consists of adrenostatic drugs (ketoconazole, metyrapone), adrenolytic drugs (mitotane) and glucocorticoid receptor antagonist (RU-486). Adrenal-directed drugs may prove useful in pre-operative management to control hypercortisolism and reduce the perioperative risks, which was why one was used in this patient. Metyrapone inhibits 11β-hydroxylase and has been most commonly given. The daily dose has to be determined by measuring either plasma or UFC. The drug is usually given in doses ranging from 250 mg twice daily to 1.5 g every 6 h.^{1 2}

First-line therapy for cortisol-secreting ACTs is complete surgical excision. Glucocorticoid replacement is required

Table 2 24 h cortisol profile (nmol/l)

Time	22:00	00:00	02:00	04:00	07:00	09:00	11:00	13:00	15:00	17:00	19:00	21:00
Cortisol	698	588	814	888	606	789	786	739	659	712	817	640

postoperatively because of suppression of the contralateral adrenal.³ Adrenocortical carcinoma is referred in the literature as the most common type, being more frequent in females.⁵

Predisposing genetic factors can be found in certain patients with ACTs. Both Beckwith-Wiedemann and Li-Fraumeni syndrome have been commonly associated with ACTs with known associated chromosomal mutations, 11p15 and p53, respectively.⁵ In this child these mutations were not found and there was no suggestive family history.

Monitoring improvement in growth impairment, reduced bone mineral density and altered body composition, plus continued surveillance for evidence of any recurrence, are critical concerns after presumptive curative therapy.¹

Learning points

- ▶ Cushing syndrome in children is a rare disorder that is most frequently caused by an adrenal tumour or a pituitary corticotrophin-secreting adenoma.
- ▶ The management is challenging and requires an individualised approach and multidisciplinary care.
- ▶ In a child with excessive weight gain, hirsutism and growth failure the diagnosis must be considered.

Competing interests None.

Patient consent Obtained.

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