

# Work-up and management of paediatric Cushing's syndrome

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## Purpose of review

Paediatric Cushing's syndrome presents a diagnostic and therapeutic challenge. Most paediatric endocrinologists have limited experience in managing children or adolescents with Cushing's syndrome and thus benefit from close consultation with adult colleagues. A protocol for investigation of the child with suspected Cushing's syndrome is presented followed by principles of management.

## Recent findings

Cushing's syndrome is rare in childhood, but causes serious morbidity. Investigations have evolved and now include new genetic and imaging techniques as well as classical endocrine studies. In Cushing's disease trans-sphenoidal surgery has transformed management, although only a few surgeons have experience in children. Pituitary radiotherapy is effective second-line therapy.

## Summary

Early diagnosis and treatment of Cushing's syndrome is vital for long-term outcome. The overall prognosis for Cushing's syndrome is good but challenges remain to ensure normal postcure growth and body composition.

## Keywords

Cushing's disease, Cushing's syndrome, paediatrics, pituitary radiotherapy, pituitary surgery

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## Introduction

Cushing's syndrome in childhood and adolescence may present difficult diagnostic and therapeutic challenges for the clinician [1,2\*\*]. We will discuss clinical assessment, investigation and advances in treatment. We will emphasise that very few, if any, paediatric endocrinology units have sufficient experience to manage Cushing's syndrome in isolation and that consultation and joint decision-making with more experienced adult endocrinology units will benefit the care of the patient.

## Classification and epidemiology of paediatric Cushing's syndrome

Paediatric Cushing's syndrome can be classified into adrenocorticotrophic hormone (ACTH)-independent and ACTH-dependent causes. The classification of paediatric Cushing's syndrome can be shown as follows:

- (1) ACTH-independent
  - (a) exogenous glucocorticoid administration
    - (i) tablets, nose drops, nasal spray, skin cream
  - (b) adrenocortical tumour (ACT)
    - (i) adenoma or carcinoma
  - (c) primary adrenocortical hyperplasia
    - (i) primary pigmented adrenocortical disease (PPNAD)

- (ii) macronodular adrenal hyperplasia (AIMAH)
    - (iii) McCune–Albright syndrome (MAS).
  - (2) ACTH-dependent
    - (a) Cushing's disease (ACTH-secreting pituitary adenoma)
    - (b) ectopic ACTH syndrome (EAS).

Cushing's syndrome may occur throughout childhood and adolescence, but certain causes present more frequently at certain ages (Fig. 1).

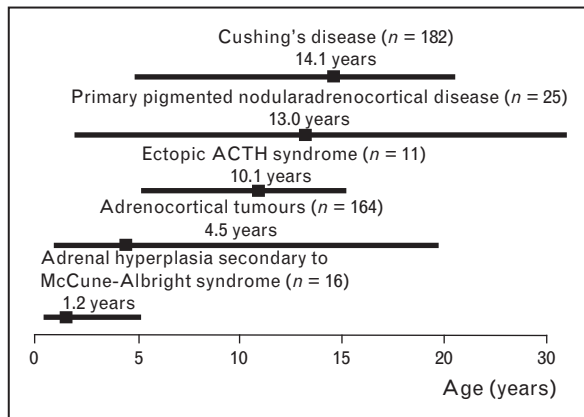
## McCune–Albright syndrome

Cushing's syndrome in infancy is usually associated with MAS caused by activating mutations of arginine 201 in the guanine-nucleotide-binding protein (G protein)  $\alpha$ -subunit [3]. In infancy, MAS, occurring predominantly in females, may present with Cushing's syndrome, often with additional endocrine dysfunction such as hyperthyroidism and precocious puberty [4]. Cushing's syndrome is usually severe and potentially life threatening and requires bilateral adrenalectomy. Histological appearance shows nodular adrenocortical hyperplasia [5].

## Adrenocortical tumours

ACTs comprise 0.3–0.4% of neoplasms in children and are an important cause of paediatric Cushing's syndrome

**Figure 1** Different causes of paediatric Cushing's syndrome from the literature ( $n = 398$  cases) shown at ages of peak incidence (boxes)



ACTH, adrenocorticotrophic hormone.

[6]. Much has been learnt from experience in Southern Brazil where the incidence of is 3.4–4.2 per million children, that is 10–15 times higher than in other geographical areas [7,8]. Adrenocortical carcinoma is also associated with Li–Fraumeni syndrome and germ-line point mutations of the p53 tumour suppressor gene (*TP53*) encoding an R337H amino acid substitution [7]. The genetics of adrenal tumours has recently been reviewed [9<sup>••</sup>]. In the Brazilian series ACT occurred most commonly under 4 years of age and was usually associated with virilization (56%) or mixed hormone secretion, including cortisol (29.2%), with pure cortisol-secreting ACT making up 5.5 and 3% of patients in two series [8].

#### Ectopic adrenocorticotrophic hormone syndrome

EAS is extremely rare occurring much less frequently than its 15% prevalence in adult ACTH-dependent Cushing's syndrome [10]. However, paediatric EAS is well documented [2<sup>••</sup>,10,11]. Carcinoid tumours predominate as causes of paediatric EAS and most are bronchial or thymic, but renal oncocyctic carcinoid, duodenal carcinoid and clear cell sarcoma have been reported, as have neuroendocrine tumours of the pancreas and Wilms' tumour [2<sup>••</sup>].

#### Primary nodular adrenal hyperplasia

Primary bilateral adrenocortical hyperplasia is a rare but important cause of paediatric Cushing's syndrome [12]. PPNAD is usually associated with the multiple endocrine neoplasia (MEN) syndrome; Carney complex. Carney complex [CNC; Mendelian Inheritance in Man (MIM) 160980] [13] is an autosomal dominant syndrome characterized by lentigines, cardiac myxomas, endocrine and nonendocrine tumours, and PPNAD is its most frequent presentation in children and young adults [13].

PPNAD typically occurs in adolescence or early adulthood [13]. The adrenal lesion shows multiple, small, pigmented, adrenocortical nodules surrounded by cortical atrophy [12]. The hypercortisolemia of PPNAD may rarely be subclinical or cyclical [14], and it has been suggested that classical Cushing's syndrome may be absent in childhood. In our series of seven cases all patients displayed typical features of Cushing's syndrome including hypertension and virilization [15].

#### Cushing's disease

Paediatric pituitary-dependent Cushing's disease, caused by an ACTH-secreting corticotroph adenoma, accounts for 75–80% of Cushing's syndrome and is almost always caused by a pituitary microadenoma [1,2<sup>••</sup>,16]. We have seen only one macroadenoma in 34 paediatric cases [2<sup>••</sup>]. The commonest age of presentation of paediatric Cushing's disease is during adolescence (Fig. 1), and our youngest patient was aged 6.2 years.

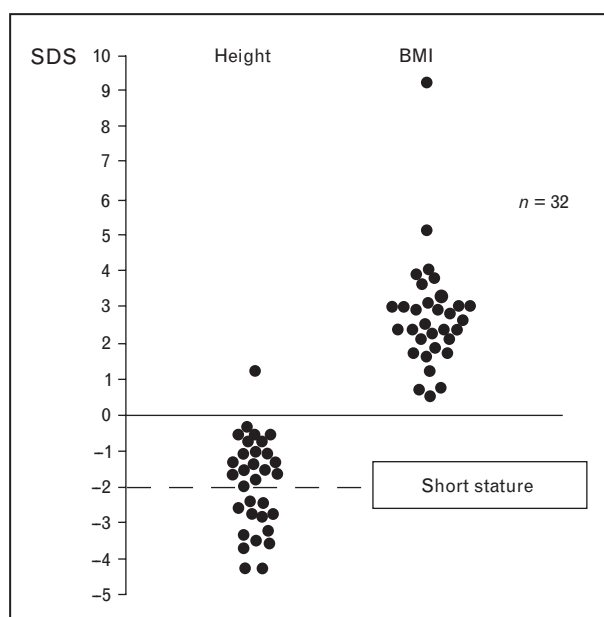
In adults, Cushing's disease has a female preponderance [17] but in 50 Cushing's disease patients aged 6–30 years and found a strong predominance of males in the prepubertal patients [18]. There were similar incidences of males and females during puberty and an increasing predominance of females in the postpubertal patients. Our report was the first to describe this male predominance in young children; however, the large series from the National Institutes of Health (NIH) [16] shows the same phenomenon.

#### Clinical assessment of the child with suspected Cushing's syndrome

The recognition of features that can alert the clinician to the diagnosis of Cushing's syndrome is of crucial importance. Most cases have a typical cushingoid appearance. However, this is frequently not recognized and the mean length of symptoms prior to diagnosis in our series was more than 2 years. Facial appearance was always altered and all patients complained of weight gain. However, the young child can present with obesity and poor growth without the classical features of plethora, hirsutism, acne and striae.

#### Linear growth

Short stature was present in half of our Cushing's disease patients and growth velocity when available was subnormal. Height standard deviation score (SDS) was almost always below the mean, and BMI SDS was consistently above it (Fig. 2). Comparison of height and BMI SDS values in 29 paediatric Cushing's disease patients and 44 age-matched participants with simple obesity showed a significant difference in the ratio of these two variables between the two groups [19], height being increased in simple obesity and decreased in Cushing's disease. Bone

**Figure 2 Height and BMI standard deviation score values in 32 pediatric patients with Cushing's disease**

The dotted line indicates the standard deviation score (SDS) value below which patients are significantly shorter than average. These data are from our unit at the William Harvey Research Institute.

age at diagnosis in 17 Cushing's disease patients was delayed by a mean of 2.0 'years' and correlated negatively with height SDS, duration of symptoms and age at diagnosis [20].

### Puberty development

There are a few detailed reports of puberty in Cushing's disease, although virilizations with pseudo-precocious puberty are important features [1,2<sup>\*\*</sup>,16]. We analysed clinical pubertal development in 27 Cushing's disease patients and identified abnormal virilization in 12 [21<sup>•</sup>]. In these patients serum androstenedione, dehydroepiandrosterone sulphate (DHEAS) and testosterone SDS were higher than in participants without abnormal virilization, and sex hormone-binding globulin (SHBG) SDS values were lower ( $P = 0.006$ ). Gonadotropin levels were suppressed.

### Investigation of Cushing's syndrome

Investigation protocols of Cushing's syndrome has been extensively reviewed [2<sup>\*\*</sup>,22,23<sup>\*\*</sup>]. We will highlight aspects that we have found helpful during the management of 49 paediatric Cushing's syndrome patients over the past 25 years. Investigations in children should be based on those performed in adults [22]. The protocol consists initially of confirmation or exclusion of the diagnosis of Cushing's syndrome followed by definition

of cause. Scheme of investigation for patients with suspected Cushing's syndrome is shown below:

- (1) Confirmation or exclusion of Cushing's syndrome
  - (a) urinary free cortisol excretion (24 h urine collection) daily for three times
  - (b) serum cortisol circadian rhythm study (09.00 h, 18.00 h, midnight [sleeping])
  - (c) low-dose dexamethasone suppression test (LDDST)
    - (i) dose: 0.5 mg 6 hourly [09.00 h, 15.00 h, 21.00 h, 03.00 h]  $\times$  48 h
    - (ii) dose for patients weighing less than 40 kg: 30  $\mu$ g/kg/day
    - (iii) serum cortisol measured at 0 and 48 h.
- (2) Definition of cause of Cushing's syndrome
  - (a) plasma ACTH (09.00 h)
  - (b) corticotropin-releasing hormone (CRH) test [1.0  $\mu$ g/kg intravenous (i.v.)]
  - (c) analysis of change in serum cortisol during LDDST
  - (d) adrenal or pituitary MRI scan
  - (e) bilateral inferior petrosal sinus sampling (BIPSS) for ACTH (with CRH).

### Confirmation or exclusion of Cushing's syndrome

We first perform three consecutive 24 h urine collections for urinary free cortisol (UFC) followed by measurement of serum cortisol at three time-points [09.00 h, 18.00 h and midnight (sleeping)] to assess circadian rhythm. Midnight cortisol should be less than 50 nmol/l, although young children may reach their cortisol nadir earlier than midnight. Elevation of midnight sleeping serum cortisol has the greatest sensitivity of all tests for Cushing's syndrome in children [23<sup>\*\*</sup>]. Precannulation is essential, so as not to wake the child.

We then perform a LDDST, using 0.5 mg 6 hourly (at 09.00, 15.00, 21.00 and 03.00 h) for 48 h, unless the child weighs less than 40 kg, when we use the NIH-recommended dose of 30  $\mu$ g/kg/day [16]. In the LDDST, blood is taken for serum cortisol at 0 and at 48 h, when it should be undetectable ( $<50$  nmol/l). These tests individually, and in combination, have a high sensitivity for Cushing's syndrome and an even higher specificity for the exclusion of this diagnosis.

### Definition of the cause of Cushing's syndrome

Having confirmed the presence of Cushing's syndrome, ACTH-dependent or ACTH-independent disease needs to be established. Determination of 09.00 h plasma ACTH showed that all our patients with an ACT or nodular adrenal hyperplasia ( $n = 8$ ) had undetectable ACTH [15], which is a clear indication for adrenal MRI. Conversely, in all of our 34 patients with Cushing's

disease, ACTH was detectable, ranging from 12 to 128 ng/l (normal range 10–50 ng/l).

We routinely perform a CRH test (1.0 µg/kg i.v.) and in 27 Cushing's disease patients' serum cortisol increased by more than 20% (range: 106–554%) [24]. Although it is arguable that the rarity of EAS in children does not justify the CRH test, we find an increased response contributes to the diagnosis of Cushing's disease. We have discontinued the high-dose dexamethasone suppression test (HDDST) because in 24 patients with Cushing's disease, mean baseline serum cortisol values of  $590.7 \pm 168.8$  nmol/l decreased to  $337.4 \pm 104.0$  nmol/l at 48 h during LDDST showing that cortisol suppression during LDDST strongly supports the diagnosis of Cushing's disease [25].

#### **Biochemical features in nodular adrenal hyperplasia**

In our series, all patients with PPNAD had typical primary adrenal Cushing's syndrome with raised UFC levels, failure of cortisol to suppress on LDDST and HDDST, undetectable plasma ACTH and absent cortisol response during a CRH test [15]. In addition, a paradoxical increase of UFC and/or 17-hydroxy-corticosteroids is reported in the second phase of a HDDST, which can be diagnostic for PPNAD [12].

#### **Genetics of nodular adrenal hyperplasia**

PPNAD may occur in association with Carney complex and linkage studies have suggested two predominant genetic loci. The 2p16 locus (CNC2) was identified first but the gene responsible remains unknown [26]. Recently, inactivating mutations of the regulatory subunit type 1-α of the protein kinase A (PRKAR1A) have been reported at the second genetic locus (17q22-24) [13]. Mutations are found most frequently in exons 4B, 2 and 6 of the *PRKAR1A* gene resulting in a premature stop codon. To date, *PRKAR1A* gene mutations have been observed in 40–50% of families with CNC [27,28] and more recently a third locus has been suggested in at least one large family [29]. The genetic features of Carney complex and PPNAD have recently been reviewed extensively [30••].

#### **Adrenal imaging**

Adrenal imaging is an essential part of the investigation of primary adrenal Cushing's syndrome. The differential diagnosis is between ACT and primary nodular adrenal hyperplasia. Most adrenal tumours are visible on MRI scan. In PPNAD, the adrenals are usually of normal size [15]. Although the adrenocortical nodules are small (often <6 mm), they may be visualized on computed tomography or MR scanning. Unilateral or bilateral macronodules may be visible and can be quite large (10–30 mm) [15].

#### **Pituitary imaging**

Pituitary MR imaging is an important step towards the successful treatment of Cushing's disease by

trans-sphenoidal surgery (TSS). Most paediatric ACTH-secreting pituitary tumours are microadenomas with diameters less than 5 mm [31]. These have a hypointense signal, which fails to enhance with gadolinium [22]. In the NIH series, approximately 50% of microadenomas were visible on pituitary MRI [16]. In our series, pituitary imaging was relatively unhelpful, showing a normal appearance in over half of the patients, with a low predictive value of the position of the adenoma, as identified at surgery [32].

#### **Bilateral inferior petrosal sinus sampling for adrenocorticotrophic hormone**

BIPSS was developed mainly at the NIH and is now performed in paediatric patients [16,33]. Because of the rarity of EAS, the aim of BIPSS is primarily to demonstrate lateralization of ACTH secretion. The first paediatric data reported a predictive value of lateralization of 75–80% [1]. In our experience, ACTH sampling gave a better prediction of the site of the microadenoma than pituitary imaging [32,33].

BIPSS is a specialized technique and in our unit is performed by the same radiologist who studies adult patients. We do not use general anaesthesia to avoid potential alteration of ACTH secretion. The youngest patient we studied without general anaesthesia was aged 8.4 years. We have now performed BIPSS in 26 paediatric Cushing's disease patients, without complications, and have shown lateralization (interpetrosal sinus ACTH ratio of >1.4 after CRH) in 77% of patients [32]. A more recent study [34] from the NIH described BIPSS in 94 paediatric patients and reported localization of ACTH secretion concurring with the site of the adenoma at surgery in 58% of cases, concluding that the technique was not essential in the paediatric investigation protocol. The percentage of lateralization, however, increased to 70% (51/73) after exclusion of 18 centrally located and four bilateral lesions.

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#### **Treatment of Cushing's syndrome**

Treatment will be described for primary adrenal and then pituitary-dependent Cushing's syndrome.

#### **Primary adrenal lesions**

First-line therapy for cortisol-secreting ACTs is surgical excision. Glucocorticoid replacement is required preoperatively and postoperatively because of suppression of the contra-lateral adrenal. The definitive treatment of PPNAD is open or laparoscopic bilateral adrenalectomy [2••,15]. This therapy is not only to treat the Cushing's syndrome but also to prevent the secondary complications of hypercortisolemia and the risk of development of adrenocortical neoplasia. We give preoperative metyrapone therapy to normalize cortisol levels preoperatively.

After cure by surgery, patients will require long-term steroid replacement and life-long endocrine follow-up with regular screening for features of CNC, especially if a *PRKARIA* mutation is identified.

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### Cushing's disease

Cushing's disease requires prompt and expert treatment, which should be curative. The approach to treatment has evolved over the years. Initially, bilateral adrenalectomy was widely practised and, when effective, the pituitary adenoma remained *in situ* and there was a risk of Nelson's syndrome [35]. In the management of 34 cases, we have performed adrenalectomy twice, when the patients were critically ill and unfit for pituitary surgery. In one of these patients, hypercortisolaemia could only be controlled by i.v. etomidate prior to adrenalectomy [36].

### Trans-sphenoidal surgery

Trans-sphenoidal pituitary surgery, consisting of selective removal of the adenoma, is now considered first-line therapy for paediatric Cushing's disease. TSS is considered a well tolerated and effective procedure in children [37,38]. Adult Cushing's disease studies show variable surgical success rates depending on which definition of cure is adopted. Our adult endocrine unit has taken undetectable postoperative serum cortisol (<50 nmol/l) as the criterion for cure. We use the same definition. Following cure by TSS in 21 patients, we have not seen recurrence of Cushing's disease.

Selective microadenectomy is technically very difficult in children. The microadenomas may be very small [31] and an appreciable rate of failure, in terms of definite cure, exists even in the most experienced hands. We have recently analysed our experience over the past 25 years and considered the factors that contributed to successful surgical therapy [32]. The overall cure rate from TSS in 34 paediatric patients from 1982 to 2007 was 62% and in 26 who treated since preoperative BIPSS was introduced, the cure rate was 77% [2<sup>••</sup>,32]. We, therefore, feel that the ability of BIPSS to identify the lateral or central position of the adenoma has contributed to an increased rate of surgical success. Other paediatric series report cure rates varying from 45 to 78% [2<sup>••</sup>,16].

Successful TSS consists of removal of the microadenoma with retention normal pituitary tissue, which is vital for the child's future development. Postoperative hypopituitarism is, therefore, a potential complication. An important potential hormone deficiency for future growth is that of growth hormone (GH) (see below).

### Pituitary radiotherapy

Pituitary radiotherapy has been a therapeutic option for paediatric Cushing's disease for many years. Children

with Cushing's disease respond more rapidly than adults [39]. In our centre, external beam radiotherapy is used as a second-line therapy, following unsuccessful TSS. Our practice is to make a decision to proceed to radiotherapy, usually within 2–4 weeks of TSS, when it is clear from cortisol levels that removal of the adenoma has been incomplete [40]. We deliver 45 Gy in 25 fractions over 35 days [40]. We have treated 13 patients during the past 25 years with a successful cure rate of 85%, which occurred at a mean interval of 0.8 years (range: 0.3–2.9). We analysed long-term pituitary function in six patients showed that GH deficiency was frequent but may recover [41]. Gonadotropin secretion was generally preserved with normal, or early puberty, and thyroid-stimulating hormone (TSH) and ACTH deficiency was minimal [41].

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### Postcure growth and development

Most patients with Cushing's syndrome have subnormal growth and short stature [1,2<sup>••</sup>,15]. A key article [42] from the NIH described abnormalities of height and GH secretion in Cushing's disease together with a rather pessimistic view of posttreatment catch-up growth and adult height. We attribute poor catch-up growth to continuing GH deficiency, occurring either from TSS or from pituitary radiotherapy [43]. In Cushing's disease, we test for GH deficiency 3 months after TSS or completion of radiotherapy. If GH therapy is demonstrated, GH therapy is started possibly with a gonadotropin-releasing hormone (GnRH) analogue. Catch-up growth usually occurs and adult height within range of target height is achieved in most patients [45]. Normal body composition is more difficult to achieve. Many patients remain obese and BMI SDS was elevated ( $P < 0.01$ ) at a mean interval of 3.9 years after cure in 14 patients [44]. In a long-term follow-up study [45], total body fat and the ratio of visceral to subcutaneous fat were abnormally high.

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### Conclusion

In paediatric Cushing's syndrome, early diagnosis remains a challenge because of the frequent lack of appreciation of the nature of the disorder by parents and general practitioners. Once suspected, investigation requires a formal protocol and the choice and interpretation of tests is productively discussed with an adult endocrinologist. Cushing's disease presents the most difficult challenge in terms of effective therapy. Ideally, a centre that combines paediatric and adult endocrinology, TSS and pituitary radiotherapy would be optimal. The choice of neurosurgeon experienced in TSS in children is likely to improve significantly the chance of cure. Posttreatment management presents challenges for normalization of growth, puberty and body composition.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 394–395).

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