The Investigation of suspected paediatric Cushing's Syndrome (hypercortisolaemia)

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Scope To guide UK paediatric endocrinologists in the investigation and diagnosis of suspected paediatric Cushing's syndrome (hypercortisolaemia).

Introduction:

Cushing's syndrome (CS) is a clinical disorder caused by prolonged excessive, inappropriate, glucocorticoid exposure. CS can be divided into adrenocorticotrophic (ACTH)-dependent and ACTH-independent aetiological categories (1) (Table 1). Endogenous CS is rare in childhood and adolescence. The incidence is approximately 10% of adult cases i.e. ~0.7-2.4 new cases/million/year (2, 3). The most common cause of CS in all ages is iatrogenic, secondary to exogenous glucocorticoid administration e.g. inhaled, oral, parenteral or topical corticosteroids. Therefore, if CS is suspected, it is fundamental to take a thorough medication history to exclude exogenous CS (2). Cushing's disease (CD), caused by an ACTH-secreting pituitary adenoma, is responsible for 75-85% cases of endogenous paediatric CS (4, 5).

Table 1. Simple classification of paediatric Cushing's syndrome (CS)

ACTH-independent

1. Exogenous glucocorticoid administration (tablets, nose drops, inhalers, nasal spray, topical therapies)
2. Adrenocortical tumour (adenoma or carcinoma)
3. Primary adrenocortical hyperplasia
    a. Primary pigmented nodular adrenocortical disease (PPNAD)
    b. Macronodular adrenal hyperplasia (AIMAH)
    c. McCune Albright syndrome

ACTH-dependent

1. Cushing's disease (ACTH-secreting pituitary adenoma)
2. Ectopic ACTH syndrome

Clinical features:

The characteristic features of CS in childhood and adolescence are weight gain, growth failure and classical Cushingoid facial features (plethoric, round face). A reduction in height associated with elevated BMI / weight gain, is a key clinical feature of hypercortisolaemia in children. The presence

of growth failure can also effectively differentiate children with simple obesity from those with Cushing's disease, as simple obesity is usually associated with normal or tall stature (6).

Abnormal virilisation is common in pre-pubertal children with CS and gonadotrophin deficiency is a complication of prolonged hypercortisolaemia (7). Classical features of CS and their frequency in children are shown in Table 2.

Table 2. Clinical features at diagnosis of paediatric Cushing's disease

Major symptoms	Patients (n)	% of total
Facial changes	52	100%
Weight gain	51	98%
Weight loss	1	2%
Growth failure	51	98%
Short stature (height SDS <-2.0)	19	37%
Pre-pubertal virilisation	21/24	88%
Fatigue	33	63%
Emotional lability/depression	30	58%
Hirsutism	33	63%
Headaches	26	50%
Striae	25	48%
Hypertension	24	45%
Acne	22	42%

Data from 52 paediatric patients diagnosed with Cushing's disease at Barts Health NHS Trust (internal audit data and reference 8).

Diagnosis:

If paediatric CS is suspected, it is extremely important to rapidly establish the diagnosis and the aetiology using a formal investigation protocol. Due to the rarity of paediatric CS, it is recommended that children are investigated by paediatric endocrinologists in close liaison with adult endocrinologists who are more experienced in managing CS (8).

Investigation algorithm:

Before embarking on biochemical evaluation exogenous CS secondary to oral, nasal or topical glucocorticoid treatments should first be excluded. A consensus statement recommends only investigating children with obesity and associated slowing of their growth (9). The algorithm for investigating children with suspected CS is based on that performed in adults (10-12). The protocol of investigations consists initially of confirmation or exclusion of CS (hypercortisolaemia) followed by investigations to determine the aetiology (Table 3 and Figure 1).

Table 3. Scheme of investigation for patients with suspected CS

A. Initial testing - confirmation or exclusion of CS (hypercortisolaemia)

1. Urinary free cortisol excretion (24hr urine collection) daily for at least 2, and ideally consecutive 3 days
2. Serum cortisol circadian rhythm study (09.00h, 18.00h, midnight [sleeping]*)
3. 1mg overnight dexamethasone suppression test (DST)**
4. Low-dose dexamethasone suppression test (LDDST)
    a. Dose 0.5mg 6 hourly (09.00, 15.00, 21.00, 03.00h) for 48hrs
    b. Dose for patients weighing <40 kgs; 30µg/kg/day
    c. Serum cortisol measured at 0 and 48hrs

* Late night / midnight salivary cortisol is a less invasive alternative to serum cortisol and avoids stressful venepuncture in children (13). However, normative ranges have not been characterised for different aged children. Elevated sleeping midnight cortisol >50 nmol/L is suggestive of CS.

** There are no specific data regarding the interpretation or performance of overnight DST in the paediatric population. If there is incomplete suppression of serum cortisol following an overnight DST, consider 48hr LDDST. In normal patients, serum cortisol should suppress to <50 or <20 nmol/L – see additional considerations.

B. Confirmation of the aetiology of CS (consider referral to a specialised centre)

1. Plasma ACTH (09.00hr) - to confirm or exclude ACTH-dependence
2. CRH test (1.0 µg/kg IV) - to confirm central ACTH production (Cushing's disease)
3. Adrenal or pituitary MRI scan – when ACTH-independent or ACTH-dependent CS is confirmed, respectively
4. Bilateral simultaneous inferior petrosal sinus sampling (BSIPSS) for ACTH (with CRH) – to confirm central ACTH production (Cushing's disease)*

* Refer to centre with expertise in performing BSIPSS and interpreting BSIPSS results in children

Additional considerations:

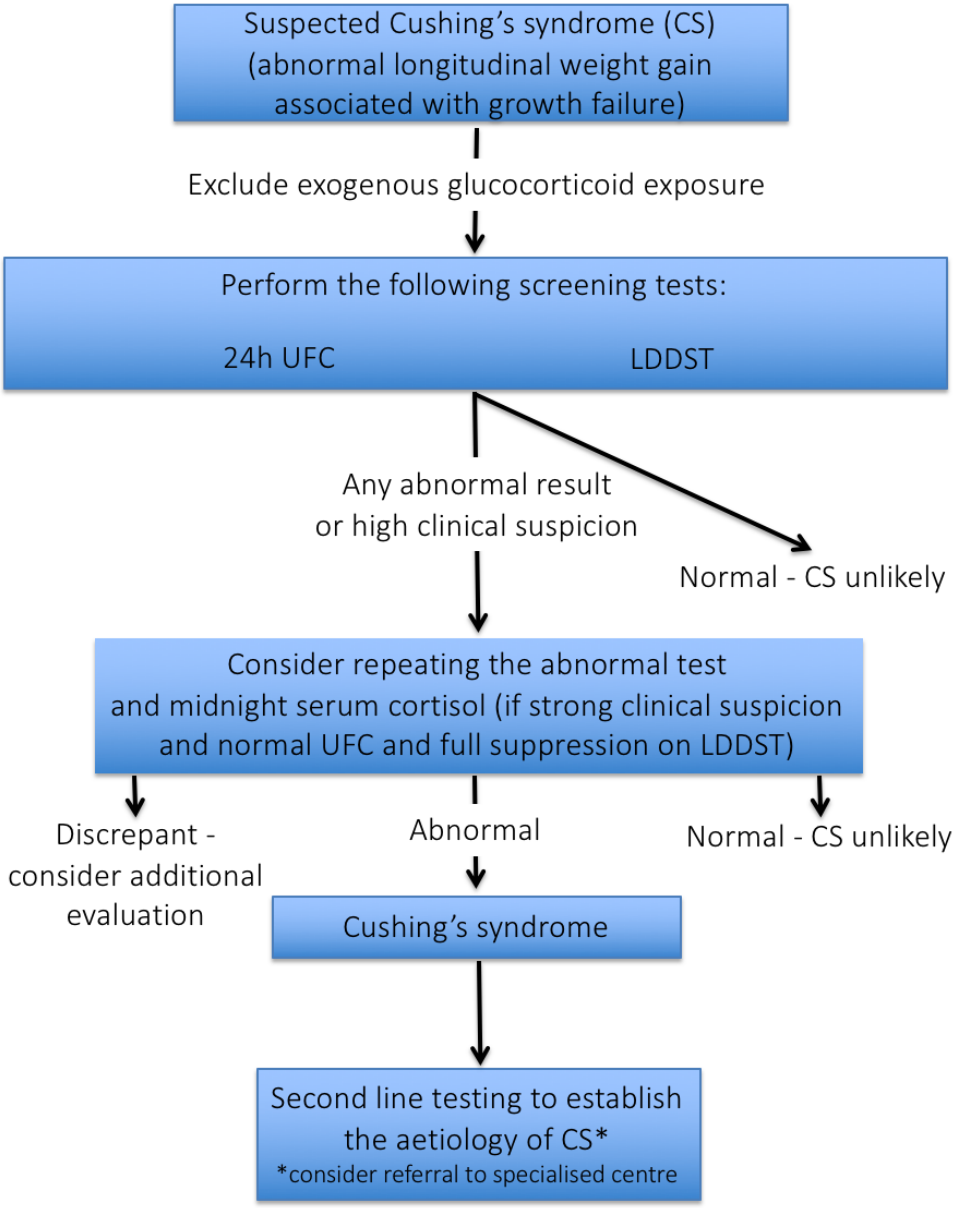
- Suppression of serum cortisol to <50 nmol/L following dexamethasone suppression testing (DST) occurs in a small proportion of patients with Cushing's disease (secondary to a pituitary corticotroph adenoma).
- In cases of suspected periodicity ('cyclical' CS) or mild CS, screening tests should be performed to coincide with clinical symptoms.
- Anticonvulsant therapy e.g. phenytoin, carbamazepine, phenobarbitone induce hepatic clearance of dexamethasone and therefore DST may give false positive results and midnight cortisol is the preferred screening investigation to exclude CS (9, 14).

- Renal impairment may give falsely low UFC level as urine cortisol production is dependent on renal filtration and midnight cortisol is the preferred screening investigation to exclude CS.

- False elevation of UFC can occur with excessively high fluid intake.

- The literature on DST referring to a cut-off of 50 nmol/L largely comes from a time when biochemical autoanalysers did not routinely read down to very low values. Many clinicians experienced in the assessment of suspected CS consider that 'normal' individuals should suppress to <20 nmol/L during a DST and that post DST values of 20-50 nmol/L represent a range of uncertainty.

Figure 1. Algorithm summarising the investigation of children with suspected CS.



UFC, Urinary free cortisol excretion (24hr urine collection) daily for at least 2, and ideally 3 days; LDDST, low dose dexamethasone suppression test.

References:

1. Ferrigno R, Hasenmajer V, Caiulo S, Minnetti M, Mazzotta P, Storr HL, et al. Paediatric Cushing's disease: Epidemiology, pathogenesis, clinical management and outcome. Rev Endocr Metab Disord. 2021.
2. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006;367 (9522):1605-17.
3. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, et al. Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab. 2001;86(1):117-23.
4. Magiakou MA, Chrousos GP. Cushing's syndrome in children and adolescents: current diagnostic and therapeutic strategies. Journal of Clinical Investigation. 2002;25(2):181-94.
5. Weber A, Trainer PJ, Grossman AB, Afshar F, Medbak S, Perry LA, et al. Investigation, management and therapeutic outcome in 12 cases of childhood and adolescent Cushing's syndrome. Clinical Endocrinology. 1995;43:19-28.
6. Greening JE, Storr HL, McKenzie SA, Davies KM, Martin L, Grossman AB, et al. Linear growth and body mass index in pediatric patients with Cushing's disease or simple obesity. J Endocrinol Invest. 2006;29(10):885-7.
7. Dupuis CC, Storr HL, Perry LA, Ho JTF, Ahmed L, Ong KK, et al. Abnormal puberty in paediatric Cushing's disease: relationship with adrenal androgen, sex hormone binding globulin and gonadotrophin concentrations. Clinical Endocrinology. 2007;66(6):838-43.
8. Storr HL, Savage MO. MANAGEMENT OF ENDOCRINE DISEASE: Paediatric Cushing's disease. Eur J Endocrinol. 2015;173(1):R35-45.
9. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The Diagnosis of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology and Metabolism. 2008;93:1526-40.
10. Storr HL, Chan LF, Grossman AB, Savage MO. Paediatric Cushing's syndrome: epidemiology, investigation and therapeutic advances. Trends in Endocrinology and Metabolism. 2007;18(4):167-74.
11. Guaraldi F, Storr HL, Ghizzoni L, Ghigo E, Savage MO. Paediatric pituitary adenomas: a decade of change. Horm Res Paediatr. 2014;81(3):145-55.
12. Newell-Price J, Trainer PJ, Besser GM, Grossman AB. The diagnosis and differential diagnosis of Cushing's and peudo-Cushing's states. Endocrine Reviews. 1999;19(5):647-72.
13. Martinelli CE, Jr., Sader SL, Oliveira EB, Daneluzzi JC, Moreira AC. Salivary cortisol for screening of Cushing's syndrome in children. Clin Endocrinol (Oxf). 1999;51(1):67-71.
14. Ma RC, Chan WB, So WY, Tong PC, Chan JC, Chow CC. Carbamazepine and false positive dexamethasone suppression tests for Cushing's syndrome. BMJ. 2005;330(7486):299-300.

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this guideline.