Paediatric Cushing's Disease

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Abstract

Cushing's disease (CD) is the commonest form of ACTH-dependent Cushing's syndrome (CS) and is a rare clinical diagnosis in paediatric and adolescent patients. CD is caused by an ACTH-secreting pituitary corticotroph adenoma and is associated with significant morbidity in children; so early diagnosis and treatment are critical for optimal therapeutic outcome. This review highlights the key clinical and biochemical features of paediatric CD and appraises current practices in diagnosis and management. A close liaison with adult endocrinology colleagues particularly for interpretation of investigations and definition of therapeutic strategy is strongly advised.

Introduction

Endogenous Cushing's syndrome (CS) is a rare life-threatening disorder caused by prolonged exposure to excess glucocorticoid hormone concentrations. CS can be divided into ACTH-dependent and ACTH-independent aetiological categories. Approximately 10% of new CS cases each year occur in the paediatric age range up to 18 years, and Cushing's disease (CD), caused by an ACTH-secreting pituitary adenoma, is responsible for 75–80% of cases. Once CS is suspected, the paediatric patient requires investigation using a formal protocol to ensure an accurate diagnosis and definition of the aetiology. Once CD has been diagnosed, the primary aim of treatment is rapid normalisation of serum cortisol, which is particularly important in children due to the adverse effects of prolonged hypercortisolaemia on growth and development. Once remission of the CD has been established, post-treatment

management also presents challenges for optimisation of growth, pubertal development and body composition.

We will discuss epidemiology, pathogenesis, clinical features, investigations and treatment of paediatric CD. The recommendations in this review are based on published data and our experience from the management of 47 cases of paediatric CD at St Bartholomew's and the Royal London Hospitals during the past 30 years.

Epidemiology

Cushing's disease (CD) is the commonest cause of CS in children over 5 years of age [1-3] accounting for 75-80% of paediatric CS cases compared to 49-71% of adult cases [1, 4]. ACTH-secreting corticotroph adenomas in childhood account for 54.8% of all pituitary adenomas from age 0 to 11 years and 29.4% from 12 to 17 years [5]. Therefore, CD is the commonest cause of CS after the pre-school years, accounting for more than half of pituitary adenomas under the age of 11 years. Cushing's disease accounts for approximately 75% of all cases of CS in children over 5 years. In children under 5 years, primary adrenal causes (adenoma, carcinoma, or bilateral adrenal hyperplasia) are the most common causes of CS [6].

In 182 cases of paediatric CD taken from the literature, the median age of presentation was 14.1 years [7]. The mean age at presentation in our own series was slightly younger at 12.3 ± 3.5 years (range 5.7–17.8) [8]. In adults, CD has a female preponderance, however male predominance is now established in prepubertal subjects, [3, 9] with an overall prevalence of males (63%) compared to females (79%) in paediatric and adult series, respectively [8]. The incidence in males and females during puberty was equal,

with an increasing predominance of females in post-pubertal patients [9]. No clear explanation for this phenomenon exists. Additionally, male paediatric patients may have more aggressive disease with elevated BMI, shorter height and higher ACTH levels compared to females [10]. The basis for this possible gender-dependent biological difference is currently unclear.

Pathogenesis

Pituitary microadenomas, frequently with diameter <5 mm [11, 12] are the commonest cause of CD in children. At surgery corticotroph adenomas are frequently observed to have a diameter of 2 mm or less [5]. Pituitary macroadenomas (defined as >1cm in maximal diameter) account for approximately 10% of adult onset CD but are extremely rare in children. Two cases of a corticotroph macroadenomas have been identified in our series of 47 paediatric cases (4%) [8, 13].

Molecular pathogenesis

The majority of patients with paediatric CD do not have causative germline genetic defects [14]. However, somatic mutations of the *USP8* deubiquitinase gene in corticotroph adenomas have recently been implicated in the molecular pathogenesis of CD [15]. The molecular genetic processes leading to CD are poorly understood but an association with several rare hereditary conditions has been noted. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder characterised by endocrine tumours including anterior pituitary adenomas and MEN1-associated ACTH-producing adenomas have been reported in several young patients [16]. Pituitary macroadenomas have also been reported to be an early manifestation of MEN1 [17].

Mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene predispose to familial pituitary adenomas [18]. However, only 1 out of 73 (1.4%) paediatric CD subjects were found to have an *AIP* mutation [19]. Therefore genetic defects are extremely rare in sporadic, isolated paediatric CD. However, careful family history for features of MEN1 and familial pituitary adenomas is warranted in children presenting with CD and genetic testing should be performed in cases with a positive family history.

Clinical Features

The rarity of paediatric CS in clinical practice underlies the fact that this diagnosis may be overlooked. However, early recognition of the salient features of CD is crucial to allow prompt diagnosis and effective treatment. The features of paediatric CD are well documented [7] and have shown some interesting differences compared with adult patients [8] (Table 1). Key presenting features in children include weight gain, a change in facial appearance and growth failure. In our series of paediatric CD patients, all but one child had evidence of weight gain (mean BMI SDS at diagnosis 2.7 ± 1.6; range 0.0-9.2) and all patients had a change in facial appearance [8]. Although there is a spectrum, most children and adolescents have a typical Cushingoid appearance. Subtle or sub-clinical presentation or even cyclical features appear to be uncommon. The disease onset is often insidious and parents and family doctors may fail to recognise the pathological nature of the change in the child's appearance, significantly delaying diagnosis. The mean length of symptoms prior to diagnosis in 43 paediatric CD patients was 2.5 ± 1.7 years (range 0.3-6.6 years) [8].

Growth failure, traditionally recognised as a key clinical feature of hypercortisolaemia in children, may be less obvious. In our series, only 37% of 52 children with CS due to a range of aetiologies, actually had short stature (height ≤-2 SD) at diagnosis but growth velocity when available was subnormal in all patients (Figure 1) (H. Storr 2014, unpublished observations). However, at presentation, over 95% of subjects demonstrated a striking contrast between height SDS, which was almost always below 0, and BMI SDS which was usually elevated above 1.5 SDS [7]. This auxological feature distinguishes CS from subjects with simple obesity, where most children are tall [20].

A further important aspect of the physical assessment in paediatric patients with CD is examination of secondary sexual development. The majority of children show signs of abnormal virilisation with advanced pubic hair and genital growth in boys in association with pre-pubertal testicular volumes or pubic hair growth in girls with pre-pubertal breast development. These features indicate abnormal exposure to adrenal androgens combined with gonadotrophin deficiency [21].

Striae and acne were present in 49% and 44% of patients respectively and were commoner in older patients (mean age 14.2 ± 2.6 yrs and 13.9 ± 2.2). The young child with CD may present with obesity and growth failure alone, without other classical features such as plethora, hirsutism, acne and striae. Additional features commonly reported in our cohort included emotional lability (60%), fatigue (60%) and hypertension (49%). Muscle weakness and easy bruising were rare symptoms (Table 1) [8].

Therefore five key features, namely a change in facial appearance, weight gain, height SDS around or below 0 SD, elevation of BMI and the presence of genital virilisation should alert the clinician to the possibility of CD and initiate laboratory evaluation.

Diagnostic guidelines

Biochemical evaluation

Prior to embarking on biochemical evaluation to confirm a diagnosis of CD, it is important to exclude other causes of CS such as excess glucocorticoid use (oral, nasal, inhaled, nasal spray and topical treatments), as exogenous CS is much more common than the endogenous form. The investigation of patients with suspected paediatric and adult CD has been extensively reviewed [1], [22, 23]. A consensus statement advised that only those obese children who demonstrated slowing of their growth velocity should be investigated, as a combined reduction in height velocity and increased weight had a high sensitivity and specificity for CD [24, 25].

The algorithm for investigations in children should be based on that performed in adults [22], and consists initially of confirmation or exclusion of the diagnosis of CS followed by investigations to determine the aetiology. The diagnosis of an ACTH-secreting pituitary adenoma follows from the investigation of suspected CS and the demonstration of ACTH-dependent hypercortisolaemia. Our published protocol for diagnosis of CD, in which the initial screening tests have a high sensitivity, is shown in Table 2 [7, 26].

Confirmation or exclusion of hypercortisolaemia

Key biochemical features of hypercortisolaemia are increased 24h urinary-free cortisol (UFC) excretion, loss of serum cortisol circadian rhythm with detectable cortisol at midnight and failure of suppression of cortisol during the low-dose dexamethasone suppression test. UFC measurements in children with hypercortisolaemia have a reported sensitivity of 88% and specificity 90% [27] suggesting that UFC alone may not be an ideal screening test. If there is doubt about the interpretation of these values, we recommend hospitalisation for measurement of serum cortisol at 3 time-points (09.00 h, 18.00 h and midnight [sleeping]) to assess circadian rhythm. Determination of midnight cortisol in the sleeping child gives the highest sensitivity and specificity for the diagnosis of hypercortisolaemia (99 and 100%, respectively using a cut-off of ≥121 nmol/L, ≥4.4 μg/dl,) [27]. Late night salivary cortisol has also been evaluated in the paediatric obese population and a high sensitivity and specificity for hypercortisolaemia (95.2 and 100%, respectively) has been reported [28], however, the influence of age has not been characterised. Following assessment of midnight cortisol, a low-dose dexamethasone suppression test (LDDST) is performed, using the adult dose regimen of 0.5 mg every six hours (at 09.00, 15.00, 21.00 and 03.00 h) for 48 hrs, unless the child weighs <40 kg when the NIH-recommended dose is 30 micrograms/kg/day [29]. The LDDST also has a high sensitivity (>90%) for CS due to multiple causes and is therefore a useful screening test for paediatric patients in an out-patient setting [22, 24]. The 1 mg overnight dexamethasone test has also been used in children but there are no available data on its interpretation or reliability [24].

Confirmation of CD

Following confirmation of hypercortisolism, the priority is to determine its cause. CD is most easily confirmed by determination of basal plasma ACTH. In all patients with

CD, ACTH is detectable and using a cut-off value of 29 ng/L, sensitivity and specificity are reported as 70 and 100% respectively [27]. In ACTH-independent CS, ACTH is always low and usually undetectable.

A CRH test using human sequence CRH (1 microgram/kg IV) is also recommended and in 36 of 39 (92%) CD patients serum cortisol increased by >20% (range of cortisol increase from baseline 2-454%) [8]. Ectopic ACTH syndrome is so rare in children that the need for a CRH test is questionable, however, an increased cortisol response contributes to the diagnosis of CD. Additionally, high sensitivity and specificity (97.5 and 100% respectively) are reported for a cortisol increase of >20% following CRH administration [30].

Radiological imaging

MRI has superseded previous techniques for pituitary visualisation. MRI scanners currently use 3-tesla magnetic field strengths to improve signal-to-noise ratios, therefore further improving image quality [12, 31-33]. T2- weighted imaging offers additional identification of cystic components, with post-contrast sequences improving the conspicuity of small lesions, 2- to 3-mm-thin imaging slices being optimal for their detection. Pituitary adenomas are generally hypointense compared to the adjacent gland and take up contrast less avidly and in a more delayed fashion, and therefore fail to enhance with gadolinium (Figure 2). On pituitary post-contrast MR scanning, 63 and 55% of the corticotroph adenomas were identified in two large paediatric series [8, 34]. This relatively poor visualisation rate in children could be explained by the limited spatial resolution of MRI, i.e. small lesions within a small pituitary gland are less conspicuous. Therefore, pituitary MRI imaging alone cannot

be relied upon to predict the adenoma position or to confirm the diagnosis of paediatric CD.

Bilateral inferior petrosal sinus sampling (BSIPSS)

BIPSS was initially piloted in adults at the NIH [35] to enable distinction between CD and ectopic ACTH syndrome and also to provide a method of identifying a lateral versus central source of ACTH secretion within the pituitary [22]. It has now become routine in adult practice unless the MRI unequivocally shows a pituitary adenoma. In children, ectopic ACTH secretion is extremely rare and so the primary aim of BIPSS is to contribute to the localisation of the microadenoma by demonstrating lateral or midline ACTH secretion. The first paediatric data were reported in the large NIH series where a predictive value of lateralisation was 75-80% [1, 29].

BIPSS is a highly specialised technique and should be performed by the same radiologist who regularly studies adult patients. In the majority of cases, general anaesthesia (GA) is not required so that potential alteration of ACTH secretion is avoided. However in young children GA may be necessary. In our centre, BIPSS has been performed in 35 paediatric CD patients without complications. The results suggest that ACTH sampling gives a better prediction of the site of the microadenoma than pituitary MR imaging [8, 36]. A more recent study from the NIH described their further experience of BIPSS in 94 paediatric patients and reported that localisation of ACTH secretion concurred with the site of the adenoma at surgery in 58% of cases, concluding that the technique was not an essential part of a paediatric investigation protocol [37]. The percentage of predictive lateralisation, however, increased to 70% (51/73) after exclusion of 18 centrally located and 4 bilateral lesions.

Treatment

Paediatric and Adult Co-operation

As mentioned above, CD is extremely rare in the paediatric age range and even an experienced paediatric endocrine unit may only see a handful of cases during a 20-year period. Consequently, paediatric endocrinologists may not acquire the experience to manage these patients with expertise. For this reason, collaboration with a specialised adult endocrinology unit with experience of CS is essential. The combined expertise in medical management, pituitary surgery and pituitary radiotherapy (RT) will greatly benefit the patient.

Pituitary Surgery: Selective Microadenomectomy.

Transsphenoidal surgery (TSS) is regarded as a safe and effective procedure in children [38-41] and is now considered first-line therapy as it involves selective removal of the adenoma, maximising the potential for normal pituitary tissue to remain *in situ*. The small size of ACTH-secreting adenomas and the pituitary fossa in children in association with absent aeration of the sphenoid bone in young patients adds to the technical difficulty of TSS. The outcome of TSS depends on the definition of post-operative 'cure' or remission (Table 3). In a recent report of 200 cases of paediatric CD, 98% were in remission post-surgery [12] and 97% of the subjects who were in biochemical remission had hypocortisolaemia. In all the published series where 'remission' is described, recurrences of post-TSS hypercortisolaemia have occurred which were treated either by pituitary re-operation or by pituitary radiotherapy (RT). In the two paediatric series where 'cure' was defined as post-operative serum cortisol of <1 μg/dl (28 nmol/l) [3] or <1.8 μg/dl (50 nmol/l) [8] 'cure' rates were 100 and 69%, respectively. Follow-up data suggest that recurrence rates of CD in these patients

were very low [8, 34]. Initial post-operative remission in children was associated with identification of the adenoma at surgery and long-term remission correlated with younger age, smaller adenoma and morning serum cortisol of <1 μg/dl (28 nmol/l) after surgery [12]. Lasting remission in children is observed in those patients with younger age, smaller tumour size and absence of cavernous sinus or dural invasion [12]. However recurrence of CD in adults has been reported up to 15 years after apparent surgical cure, even in individuals who had very low or undetectable post-operative cortisol levels [42]. Therefore lifelong follow-up for children treated for CD is essential.

Endoscopic pituitary surgery

More recently the less invasive technique of endonasal endoscopic transsphenoidal pituitary surgery (ETES) has been used in some centres and in adult patients has shown equivalent rates of complete tumour resection, shorter hospital stays, decreased patient discomfort and reduced or equivalent surgical complications [43, 44]. In children, ETES may be preferable as the first-line treatment and for recurrent lesions, being potentially advantageous in terms of efficacy and safety with reduction of surgical trauma, pain perception, paediatric intensive care unit admissions, need for blood transfusions, anterior pituitary deficiencies and incidence of diabetes insipidus [13, 45, 46]. Although paediatric experience with endonasal ETES is limited, preliminary results in children with CD have recently been reported and showed an excellent outcome [13]. With more experience, ETES could become the standard surgical approach in children, as is now practised in adults.

Pituitary radiotherapy

A proportion of paediatric patients who undergo TSS for CD do not achieve postoperative cure or remission [47-49]. The options for second- line therapy are repeat

TSS, pituitary radiotherapy (RT), long-term medical therapy to control hypercortisolaemia and bilateral adrenalectomy. External pituitary RT is known to be effective in children with CD with a more rapid mode of action than in adult patients. Stereotactic radiotherapy and gamma knife approaches are now available and utilised in adult CD, however experience is limited, particularly in children. Centres using RT have administered irradiation from a 4- to 15-MeV linear accelerator, via a three-field technique (two lateral, one frontal) to deliver a total dose of 45 Gy in 25 fractions over 35 days [48]. The effectiveness and rapid onset of this therapy was confirmed in 3 small series. In the first, 7 children were treated and all were cured with a mean interval from RT to cure of 0.94 years (range 0.25–2.86) [48]. In the second series, 8 subjects were treated and 4 were cured in 9–18 months after RT [47]. In the third series, a total of 12 out of 15 patients were cured within 18 months of radiotherapy and 10 of these were cured within 9 months of treatment [50]. In a further series, 8 children were treated with stereotactic external RT using 60 Co gamma radiation. Seven of the 8 subjects were cured during the first year after completion of therapy [51].

Anterior pituitary function after RT was studied and GH deficiency was present in 5 out of 6 subjects tested with peak GH <6 ng/ml at a mean interval after RT of 1.0 years (range 0.11–2.54) [52]. On retesting at an interval of 9.3 years (range 7.6–11.3) in 3 out of 4 subjects, GH secretion had recovered (peak GH 6.4–16.5 ng/ml). Thyroid function, PRL and testicular volume were normal. GH deficiency and hypogonadism were also documented in 7 children successfully treated with higher doses of 50-70 Gy [47, 51]. Children receiving pituitary RT for CD require regular assessment of anterior pituitary function post-therapy.

Medical Therapy and Bilateral Adrenalectomy

Definitive treatments such as surgery and/or radiotherapy, rather than long-term medical therapies are currently recommended for the management of paediatric CD. Medical therapies for paediatric CD are currently limited [49] and not well studied but can be used to urgently lower cortisol levels in very sick patients, to normalise the hypercortisolemia in preparation for surgery or whilst awaiting the effects of radiotherapy. Adrenal steroidogenesis inhibitors such as metyrapone and ketoconazole are well tolerated and can be highly effective at reducing cortisol levels either alone or in combination [6]. However control may be lost due to the corticotropin oversecretion not effective for long term treatment Intravenous administration of etomidate has successfully controlled hypercortisolaemia in children with CD who were either too unwell for TSS or presented with acute unmanageable symptoms such as respiratory failure or severe psychosis [53, 54]. Bilateral adrenalectomy remains a therapeutic option for CD in life-threatening situations or where TSS is not possible or available. Although Nelson's syndrome, a potentially life-threatening complication, appears to be more frequent in children than adults and often requires pituitary surgery or RT [55].

Post-cure growth and development and pituitary function

Growth failure is almost always seen at diagnosis in paediatric patients with CD [1, 56]. Virilisation may lead to acceleration of bone age and may further compromise growth potential [57]. A key article from the NIH described the abnormalities of height and GH secretion [58] together with a poor outcome for post-treatment catch-up growth and adult height [59]. Disappointing post-cure catch-up was also reported, attributed to continuing GH deficiency, occurring either from TSS, pituitary RT or the long-standing effects of chronic hypercortisolaemia on pituitary and growth plate

physiology [56]. The challenge is to reverse these problems and maximise growth potential so as to achieve acceptable adult height and body composition.

In the absence of catch-up growth, we recommend that GH deficiency is investigated at 3 to 6 months after TSS or completion of RT. If required, GH therapy should be initiated without delay and GnRH analogue therapy may be added to delay puberty and epiphyseal closure. Results demonstrate that this regime usually enables adequate catch-up growth and adult height within range of target height for the majority of patients [60]. Combined treatment with GH and aromatase inhibitors may also be a therapeutic alternative in pubertal patients [61].

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 [60]. A long-term follow-up study of childhood and adolescent CD showed that total body fat and the ratio of visceral to subcutaneous fat remained abnormally high in the majority of patients studied 7 years after cure [62]. The implications of chronic excess visceral fat in terms of risk for adult metabolic syndrome deserve future study. Bone mineral density (BMD) was closer to normal together with some patients having normal BMD at diagnosis [63].

A summary of reported long term pituitary deficiencies following first-line TSS in children with CD is shown in Table 3. Pituitary function was analysed in 6 patients at intervals of 6.6 to 16.5 years after receiving RT and have shown that although GH deficiency was frequent initially, some recovery occurred in adult life [52]. Gonadotrophin secretion was generally preserved with normal or early puberty; the latter being a well-recognised complication of cranial radiotherapy [64]. TSH and

ACTH deficiency was minimal [52]. It is important to note that the risk of hypopituitarism may continue to increase in the years after radiation.

Studies of adult CS patients have reported brain atrophy, cognitive impairment and psychopathology, most commonly depression, associated with excess endogenous circulating glucocorticoids [65]. A study from the NIH [66] also found significant cerebral atrophy in children with CD at diagnosis, however, there was no difference in IQ scores between patients and controls. Interestingly, this study also reported an almost complete reversal of the cerebral atrophy as has been observed in association with hypercortisolaemia-induced severe psychosis [53]. However in the former study, a significant decline in cognitive function 1 year after cure by TSS was noted despite reversal of the radiological abnormalities. This is in contrast to adult studies, which report reversible cognitive impairment and reversible loss of brain volume associated with eucortisolaemia [66, 67]. More recently, the NIH group reported that children with CD have impaired health related quality of life (HRQL) which does not fully resolve one year post treatment [68].

Conclusions and future perspectives

Cushing's syndrome rarely occurs in children and thus the paediatrician may be relatively unprepared in terms of diagnosis and management. A close liaison with adult endocrinology colleagues with more experience is strongly advised and will directly enhance the clinical care of these challenging patients. Paediatric CD manifests a number of characteristic features distinct from adult CD, most notably the significant impact on linear growth and pubertal development. Early diagnosis remains a major challenge because of the frequent lack of appreciation of the nature of the pathology by parents and family doctors.

Once suspected, the patient requires investigation using a formal protocol and the choice and interpretation of tests should be discussed with an adult specialist with experience of CD. Referral should be considered to a centre combining paediatric and adult endocrinology, BIPSS, TSS and pituitary RT. A specialised multidisciplinary approach to define the optimal therapeutic strategy is essential. Additionally, choosing a neurosurgeon experienced in TSS in children is likely to significantly improve the chance of effective and curative therapy. The less invasive technique of endonasal endoscopic transsphenoidal pituitary surgery provides an alternative to conventional transsphenoidal microscopic surgery in managing paediatric CD.

In experienced hands, the prognosis for cure is good in the majority of children and adolescents with CD and full recovery of the hypothalamic-pituitary-adrenal axis is possible. However post-treatment management frequently presents challenges for optimisation of growth, puberty and body composition and deserves further investigation. Longitudinal studies are also needed to formally assess potential long-term cognitive impairment and psychopathology after cure of childhood CD. Additionally, further studies are warranted to identify novel genetic defects associated with pituitary corticotroph cell tumourigenesis and to assess the efficacy of new medical therapies and surgical approaches.

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References

1. Magiakou MA & Chrousos GP. Cushing's syndrome in children and adolescents: current diagnostic and therapeutic strategies. *J Endocrinol Invest* 2002 **25** 181-194.
2. Savage MO & Besser GM. Cushing's disease in childhood. *Trends Endocrinol Metab* 1996 **7** 213-216.
3. Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler GB, Nieman LK & Chrousos GP. Cushing's syndrome in children and adolescents, presentation, diagnosis and therapy. *New England Journal of Medicine* 1994 **331** 629-636.
4. Weber A, Trainer PJ, Grossman AB, Afshar F, Medbak S, Perry LA, Plowman PN, Rees LH, Besser GM & Savage MO. Investigation, management and therapeutic outcome in 12 cases of childhood and adolescent Cushing's syndrome. *Clin Endocrinol (Oxf)* 1995 **43** 19-28.
5. Kunwar S & Wilson CB. Pediatric pituitary adenomas. *J Clin Endocrinol Metab* 1999 **84** 4385-4389.
6. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ, Klibanski A, Lacroix A, Lindsay JR, Newell-Price J, Nieman LK, Petersenn S, Sonino N, Stalla GK, Swearingen B, Vance ML, Wass JAH & Boscaro M. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 2454-2462.
7. Storr HL, Chan LF, Grossman AB & Savage MO. Paediatric Cushing's syndrome: epidemiology, investigation and therapeutic advances. *Trends in Endocrinology and Metabolism* 2007 **18** 167-174.

8. Storr HL, Alexandraki KI, Martin L, Isidori AM, Kaltsas GA, Monson JP, Besser GM, Matson M, Evanson J, Afshar F, Sabin I, Savage MO & Grossman AB. Comparisons in the epidemiology, diagnostic features and cure rate by transsphenoidal surgery between paediatric and adult-onset Cushing's disease. *Eur J Endocrinol* 2011 **164** 667-674.

9. Storr HL, Isidori AM, Monson JP, Besser GM, Grossman AB & Savage MO. Pre-pubertal Cushing's disease is more common in males, but there is no increase in severity at diagnosis *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3818-3820.

10. Libuit LG, Karageorgiadis AS, Sina N, 2nd, Nguyen May NM, Keil MF, Lodish MB & Stratakis CA. A gender-dependent analysis of Cushing's disease in childhood: pre- and post-operative follow-up. *Clin Endocrinol (Oxf)* 2014.

11. Fahlbusch R, Savage MO, Bourguignon JP, Grossman AB. Neurosurgical management of Cushing's disease in children; in *Frontiers of Paediatric Neuroendocrinolog. Oxford, Blackwell Scientific* 1995 68-72.

12. Lonser RR, Wind JJ, Nieman LK, Weil RJ, DeVroom HL & Oldfield EH. Outcome of surgical treatment of 200 children with Cushing's disease. *The Journal of clinical endocrinology and metabolism* 2013 **98** 892-901.

13. Storr HL, Drake WM, Evanson J, Matson M, Berney DM, Grossman AB, Akker SA, Monson JP, Alusi G, Savage MO & Sabin I. Endonasal endoscopic transsphenoidal pituitary surgery: early experience and outcome in paediatric Cushing's disease. *Clin Endocrinol (Oxf)* 2013 **80** 270-276.

14. Cuny T, Pertuit M, Sahnoun-Fathallah M, Daly A, Occhi G, Odou MF, Tabarin A, Nunes ML, Delemer B, Rohmer V, Desailloud R, Kerlan V, Chabre O, Sadoul JL, Cogne M, Caron P, Cortet-Rudelli C, Lienhardt A, Raingeard I, Guedj AM, Brue T, Beckers A, Weryha G, Enjalbert A & Barlier

A. Genetic analysis in young patients with sporadic pituitary macroadenomas: besides AIP don't forget MEN1 genetic analysis. *Eur J Endocrinol* **168** 533-541.

15. Reincke M, Sbiera S, Hayakawa A, Theodoropoulou M, Osswald A, Beuschlein F, Meitinger T, Mizuno-Yamasaki E, Kawaguchi K, Saeki Y, Tanaka K, Wieland T, Graf E, Saeger W, Ronchi CL, Allolio B, Buchfelder M, Strom TM, Fassnacht M & Komada M. Mutations in the deubiquitinase gene USP8 cause Cushing's disease. *Nat Genet* 2015 **47** 31-38.

16. Rix M, Hertel NT, Nielsen FC, Jacobsen BB, Hoejberg AS, Brixen K, Hangaard J & Kroustrup JP. Cushing's disease in childhood as the first manifestation of multiple endocrine neoplasia syndrome type 1. *Eur J Endocrinol* 2004 **151** 709-715.

17. Stratakis CA, Schussheim DH, Freedman SM, Keil MF, Pack SD, Agarwal SK, Skarulis MC, Weil RJ, Lubensky IA, Zhuang Z, Oldfield EH & Marx SJ. Pituitary macroadenoma in a 5-year-old: an early expression of multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2000 **85** 4776-4780.

18. Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, Tuppurainen K, Ebeling TM, Salmela PI, Paschke R, Gundogdu S, De Menis E, Makinen MJ, Launonen V, Karhu A & Aaltonen LA. Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* 2006 **312** 1228-1230.

19. Stratakis CA, Tichomirowa MA, Boikos S, Azevedo MF, Lodish M, Martari M, Verma S, Daly AF, Raygada M, Keil MF, Papademetriou J, Drori-Herishanu L, Horvath A, Tsang KM, Nesterova M, Franklin S, Vanbellinghen JF, Bours V, Salvatori R & Beckers A. The role of germline AIP, MEN1, PRKAR1A, CDKN1B and CDKN2C mutations in causing pituitary adenomas

in a large cohort of children, adolescents, and patients with genetic syndromes. *Clin Genet* 2010 **78** 457-463.

20. Greening JE, Storr HL, McKenzie SA, Davies KM, Martin L, Grossman AB & Savage MO. Linear growth and body mass index in pediatric patients with Cushing's disease or simple obesity. *J Endocrinol Invest* 2006 **29** 885-887.

21. Dupuis CC, Storr HL, Perry LA, Ho JTF, Ahmed L, Ong KK, Dunger DB, Monson JP, Grossman AB, Besser GM & Savage MO. Abnormal puberty in paediatric Cushing's disease: relationship with adrenal androgen, sex hormone binding globulin and gonadotrophin concentrations. *Clinical Endocrinology* 2007 **66** 838-843.

22. Newell-Price J, Trainer P, Besser M & Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev* 1998 **19** 647-672.

23. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A & Boscaro M. Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003 **88** 5593-5602.

24. Nieman L, Biller B, Findling J, Newell-Price J, Savage M, Stewart P & Montori VM. The diagnosis of Cushing's syndrome: an endocrine society clinical practice guideline. *Eur J Endocrinol* 2009.

25. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM & Montori V. The Diagnosis of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1526-1540.

26. Guaraldi F, Storr HL, Ghizzoni L, Ghigo E & Savage MO. Paediatric pituitary adenomas: a decade of change. *Hormone research in paediatrics* **81** 145-155.

27. Batista DL, Riar J, Keil M & Stratakis CA. Diagnostic tests for children who are referred for the investigation of Cushing syndrome. *Pediatrics* 2007 **120** e575-586.

28. 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** 67-71.

29. Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler GB, Jr., Nieman LK & Chrousos GP. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. *N Engl J Med* 1994 **331** 629-636.

30. Batista D, Riar J, Keil M & Stratakis CA. Diagnostic tests for children who are referred for the investigation of Cushing syndrome. *Pediatrics* 2007 **120** 575-586.

31. Keil MF & Stratakis CA. Pituitary tumors in childhood: update of diagnosis, treatment and molecular genetics. *Expert review of neurotherapeutics* 2008 **8** 563-574.

32. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML & McCutcheon IE. The prevalence of pituitary adenomas: a systematic review. *Cancer* 2004 **101** 613-619.

33. Lucas JW & Zada G. Imaging of the pituitary and parasellar region. *Seminars in neurology* 2012 **32** 320-331.

34. Batista DL, Oldfield EH, Keil MF & Stratakis CA. Postoperative testing to predict recurrent Cushing disease in children. *J Clin Endocrinol Metab* 2009 **94** 2757-2765.

35. Oldfield EH, Doppman JL, Nieman LK, Chrousos GP, Miller DL, Katz DA, Cutler GB, Jr. & Loriaux DL. Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. *N Engl J Med* 1991 **325** 897-905.

36. Storr HL, Afshar F, Matson M, Sabin I, Davies KM, Evanson J, Plowman PN, Besser GM, Monson JP, Grossman AB & Savage MO. Factors influencing cure by transsphenoidal selective adenomectomy in paediatric Cushing's disease. *Eur J Endocrinol* 2005 **152** 825-833.

37. Batista D, Gennari M, Riar J, Chang R, Keil MF, Oldfield EH & Stratakis CA. An assessment of petrosal sinus sampling for localization of pituitary microadenomas in children with Cushing disease. *J Clin Endocrinol Metab* 2006 **91** 221-224.

38. Massoud AF, Powell M, Williams RA, Hindmarsh PC & Brook CG. Transsphenoidal surgery for pituitary tumours. *Arch Dis Child* 1997 **76** 398-404.

39. Knappe UJ & Ludecke DK. Transnasal microsurgery in children and adolescents with cushing's disease. *Neurosurgery* 1996 **39** 484-493.

40. Kanter AS, Diallo AO, Jane JA, Jr., Sheehan JP, Asthagiri AR, Oskouian RJ, Okonkwo DO, Sansur CA, Vance ML, Rogol AD & Laws ER, Jr. Single-center experience with pediatric Cushing's disease. *J Neurosurg* 2005 **103** 413-420.

41. Joshi SM, Hewitt RJ, Storr HL, Rezajooi K, Ellamushi H, Grossman AB, Savage MO & Afshar F. Cushing's disease in children and adolescents: 20 years of experience in a single neurosurgical center. *Neurosurgery* 2005 **57** 281-285; discussion 281-285.

592 42. Alexandraki KI, Kaltsas GA, Isidori AM, Storr HL, Afshar F, Sabin I, Akker
593 SA, Chew SL, Drake WM, Monson JP, Besser GM & Grossman AB. Long-
594 term remission and recurrence rates in Cushing's disease: predictive factors in
595 a single-centre study. *European journal of endocrinology / European*
596 *Federation of Endocrine Societies* 2013 **168** 639-648.
597 43. Goudakos JK, Markou KD & Georgalas C. Endoscopic versus microscopic
598 trans-sphenoidal pituitary surgery: a systematic review and meta-analysis.
599 *Clinical otolaryngology : official journal of ENT-UK ; official journal of*
600 *Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery*
601 2011 **36** 212-220.
602 44. DeKlotz TR, Chia SH, Lu W, Makambi KH, Aulisi E & Deeb Z. Meta-
603 analysis of endoscopic versus sublabial pituitary surgery. *The Laryngoscope*
604 2012 **122** 511-518.
605 45. Massimi L, Rigante M, D'Angelo L, Paternoster G, Leonardi P, Paludetti G &
606 Di Rocco C. Quality of postoperative course in children: endoscopic
607 endonasal surgery versus sublabial microsurgery. *Acta neurochirurgica* 2011
608 **153** 843-849.
609 46. Chivukula S, Koutourousiou M, Snyderman CH, Fernandez-Miranda JC,
610 Gardner PA & Tyler-Kabara EC. Endoscopic endonasal skull base surgery in
611 the pediatric population. *J Neurosurg Pediatr* 2013 **11** 227-241.
612 47. Acharya SV, Gopal RA, Goerge J, Menon PS, Bandgar TR & Shah NS.
613 Radiotherapy in paediatric Cushing's disease: efficacy and long term follow up
614 of pituitary function. *Pituitary* 2010 **13** 293-297.
615 48. Storr HL, Plowman PN, Carroll PV, Francois I, Krassas GE, Afshar F, Besser
616 GM & Grossman AB. Clinical and endocrine responses to pituitary

radiotherapy in pediatric Cushing's disase: an effective second line treatment. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 34-37.

49. Stratakis CA. Cushing syndrome in pediatrics. *Endocrinol Metab Clin North Am* 2012 **41** 793-803.

50. Jennings AS, Liddle GW & Orth DN. Results of treating childhood Cushing's disease with pituitary irradiation. *New England Journal of Medicine* 1977 **297** 957-962.

51. Thoren M, Rahn T, Hallengren B, Kaad PH, Nilsson KO, Ravn H, Ritzen M, Petersen KE & Aarskog D. Treatment of Cushing's disease in childhood and adolescence by stereotactic pituitary irradiation. *Acta Paediatr Scand* 1986 **75** 388-395.

52. Chan LF, Storr HL, Plowman PN, Perry LA, Besser GM, Grossman AB & Savage MO. Long-term anterior pituitary function in patients with paediatric Cushing's disease treated with pituitary radiotherapy. *Eur J Endocrinol* 2007 **156** 477-482.

53. Chan LF, Vaidya M, Westphal B, Allgrove J, Martin L, Afshar F, Hindmarsh PC, Savage MO, Grossman AB & Storr HL. Use of intravenous etomidate to control acute psychosis induced by the hypercortisolaemia in severe paediatric Cushing's disease. *Hormone research in paediatrics* 2011 **75** 441-446.

54. Greening JE, Brain CE, Perry LA, Mushtaq I, Sales Marques J, Grossman AB & Savage MO. Efficient short-term control of hypercortisolaemia by low-dose etomidate in severe paediatric Cushing's disease. *Horm Res* 2005 **64** 140-143.

55. Barber TM, Adams E, Ansorge O, Byrne JV, Karavitaki N & Wass JA. Nelson's syndrome. *Eur J Endocrinol* 2010 **163** 495-507.

641 56. Lebrethon MC, Grossman AB, Afshar F, Plowman PN, Besser GM & Savage
642 MO. Linear growth and final height after treatment for Cushing's disease in
643 childhood. *J Clin Endocrinol Metab* 2000 **85** 3262-3265.
644 57. Hayles AB, Hahn HB, Jr., Sprague RG, Bahn RC & Priestley JT. Hormone-
645 secreting tumors of the adrenal cortex in children. *Pediatrics* 1966 **37** 19-25.
646 58. Magiakou MA, Mastorakos G, Gomez MT, Rose SR & Chrousos GP.
647 Suppressed spontaneous and stimulated growth hormone secretion in patients
648 with Cushing's disease before and after surgical cure. *J Clin Endocrinol Metab*
649 1994 **78** 131-137.
650 59. Magiakou MA, Mastorakos G & Chrousos GP. Final stature in patients with
651 endogenous Cushing's syndrome. *J Clin Endocrinol Metab* 1994 **79** 1082-
652 1085.
653 60. Davies JH, Storr HL, Davies K, Monson JP, Besser GM, Afshar F, Plowman
654 PN, Grossman AB & Savage MO. Final adult height and body mass index
655 after cure of paediatric Cushing's disease. *Clin Endocrinol (Oxf)* 2005 **62** 466-
656 472.
657 61. Boronat M, Marrero D, Lopez-Plasencia Y, Novoa Y, Garcia-Delgado Y &
658 Novoa FJ. Combined treatment with GH and anastrozole in a pubertal boy
659 with Cushing's disease and postsurgical GH deficiency. *European journal of*
660 *endocrinology / European Federation of Endocrine Societies* 2012 **166** 1101-
661 1105.
662 62. Leong GM, Abad V, Charmandari E, Reynolds JC, Hill S, Chrousos GP &
663 Nieman LK. Effects of child- and adolescent-onset endogenous Cushing
664 syndrome on bone mass, body composition, and growth: a 7-year prospective
665 study into young adulthood. *J Bone Miner Res* 2007 **22** 110-118.

63. Scommegna S, Greening JP, Storr HL, Davies KM, Shaw NJ, Monson JP, Grossman AB & Savage MO. Bone mineral density at diagnosis and following successful treatment of pediatric Cushing's disease. *J Endocrinol Invest* 2005 **28** 231-235.

64. Nicholl RM, Kirk JM, Grossman AB, Plowman PN, Besser GM & Savage MO. Acceleration of pubertal development following pituitary radiotherapy for Cushing's disease. *Clin Oncol (R Coll Radiol)* 1993 **5** 393-394.

65. Dorn LD, Burgess ES, Friedman TC, Dubbert B, Gold PW & Chrousos GP. The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. *J Clin Endocrinol Metab* 1997 **82** 912-919.

66. Merke DP, Giedd JN, Keil MF, Mehlinger SL, Wiggs EA, Holzer S, Rawson E, Vaituzis AC, Stratakis CA & Chrousos GP. Children experience cognitive decline despite reversal of brain atrophy one year after resolution of Cushing syndrome. *J Clin Endocrinol Metab* 2005 **90** 2531-2536.

67. McEwen BS. Cortisol, Cushing's Syndrome, and a shrinking brain-new evidence for reversibility. *J Clin Endocrinol Metab* 2002 **87** 1947-1948.

68. Keil MF, Merke DP, Gandhi R, Wiggs EA, Obunse K & Stratakis CA. Quality of life in children and adolescents 1-year after cure of Cushing syndrome: a prospective study. *Clin Endocrinol (Oxf)* 2009 **71** 326-333.

69. Shah NS & Lila A. Childhood Cushing disease: a challenge in diagnosis and management. *Hormone research in paediatrics* 2011 **76 Suppl 1** 65-70.

70. de Oliveira RS, de Castro M, Antonini SR, Martinelli CE, Jr., Moreira AC & Machado HR. Surgical management of pediatric Cushing's disease: an analysis of 15 consecutive cases at a specialized neurosurgical center. *Arquivos Brasileiros de Endocrinologica e Metabologia* 2010 **54** 17-23.

71. Leinung MC, Kane LA, Scheithhauer BW, Carpenter PC & Zimmerman D. Long term follow-up of transsphenoidal surgery for the treatment of Cushing's disease in childhood. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 2475-2479.

72. Dyer EH, Civit T, Visot A, Delalande O & Derome P. Transsphenoidal surgery for pituitary adenomas in children. *Neurosurgery* 1994 **34** 207-212; discussion 212.

Figure legends

Table 1. Clinical features and age at diagnosis in paediatric and adult-onset CD. Data from Storr *et al.* [8]

Table 2. Protocol for diagnosis of paediatric Cushing's disease (ACTH-secreting adenomas). Data from Guaraldi *et al.* [26]

Table 3. Reported cure rates and long term pituitary function following first-line transsphenoidal surgery (TSS) in childhood CD.

Table 1. Clinical features and age at diagnosis in paediatric and adult-onset CD. Data from Storr *et al.* [8]

Clinical feature	Adult CD subjects (n=183)	Paediatric CD subjects (n=41)		P- value
	No. with symptom or sign (%)	No. with symptom or sign (%)	Mean age ± SD (yr)	
Weight gain	119 (65)	40 (98)	12.3 ± 3.5	0.001
Weight loss	8 (4)	1 (2)	(age 13.2)	0.87
Facial changes	154 (81)	41 (100)	12.3 ± 3.5	0.01
Fatigue	48 (26)	25 (61)	11.6 ± 3.6	<0.0001
Virilisation	41 (22)	16/21 (76)	10.5 ± 2.8	<0.0001
Hirsutism	125 (68)	24 (59)	12.6 ± 3.3	0.37
Emotional lability/depression	75 (41)	24 (59)	11.8 ± 3.1	0.006
Headaches	57 (31)	21 (51)	12.7 ± 3.2	0.02
Striae	73 (40)	20 (49)	14.2 ± 2.6	0.38
Hypertension	140 (77)	20 (49)	11.8 ± 3.5	0.0009
Acne	49 (27)	18 (44)	13.9 ± 2.2	0.05

CD, Cushing's disease; No., number; SD, standard deviation.

Table 2. Protocol for diagnosis of paediatric Cushing's disease (ACTH-secreting adenomas). Data from Guaraldi *et al.* [26]

Type of test	Diagnostic cut-off	Sensitivity %[a]	Specificity %[a]
A. Confirmation of Cushing's syndrome 1. Urinary free cortisol excretion (24hr urine collection) for 3 days	>70 µg/m^2 (193 nmol/24hr)	88	90
2. Serum cortisol circadian rhythm study [09.00h, 18.00h, midnight (sleeping)]	≥1.8 µg/dl (50 nmol/l)[b]	100[b]	60[b]
3. 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 kg; 30 µg/kg/day c. Serum cortisol measured at 0, 24 and 48 hrs	≥1.8 µg/dl (50 nmol/l)	95	80
B. Confirmation of CD 1. Plasma ACTH (09.00hr)	>5 pg/ml (1.1 pmol/l)	68	100
2. CRH test (1.0 µg/kg IV)	Cortisol increase 14-22%	74-91	88-100
4. Pituitary MRI scan	Adenoma detection	63	92
5. Bilateral inferior petrosal sinus sampling for ACTH (with IV CRH)	Central:peripheral ACTH ratio ≥ 3 (after iv CRH)	100	

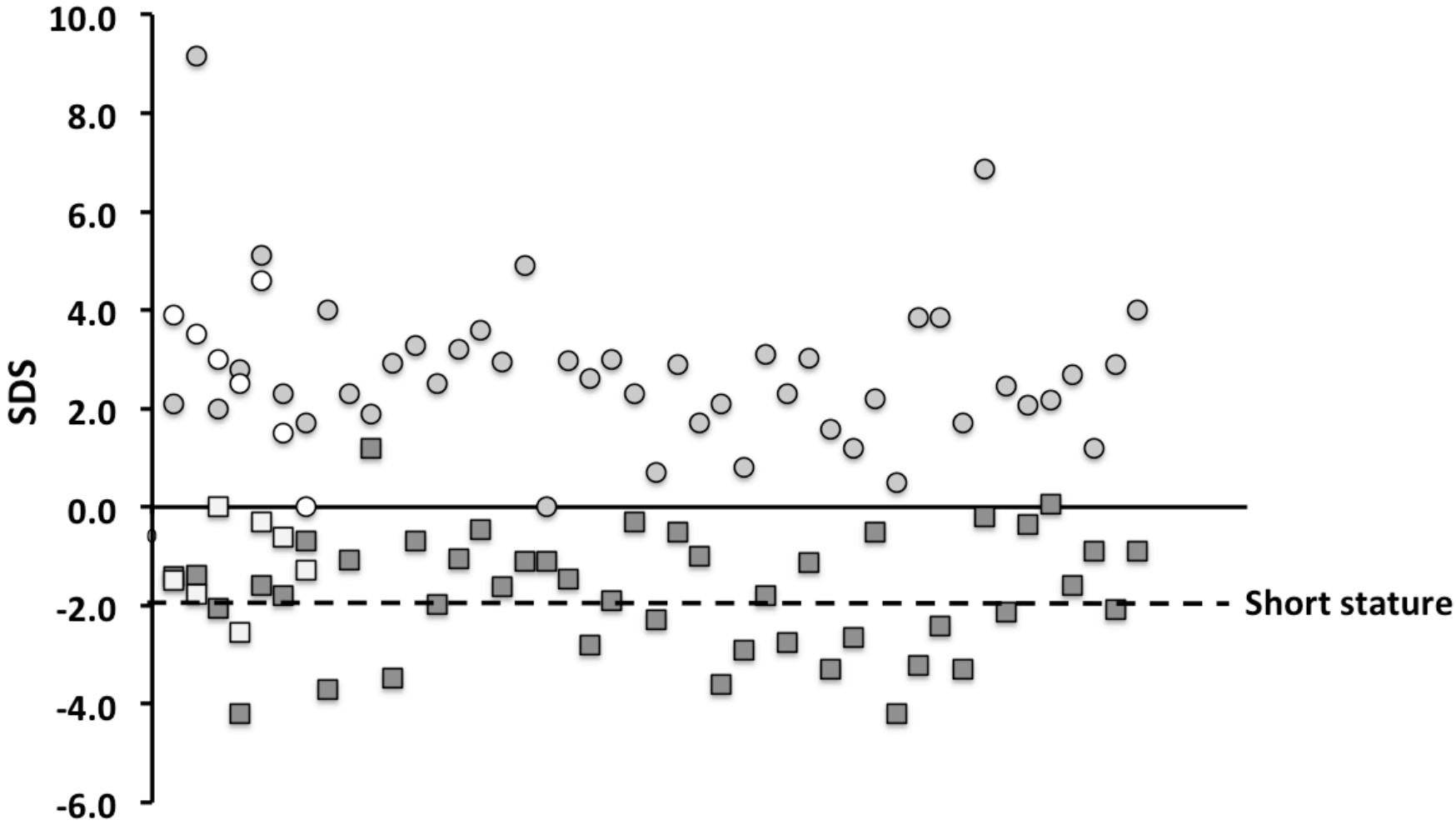
[a] Data from references [25, 27, 69], [b] Diagnostic cut-offs refer to midnight serum cortisol values

Table 3. Reported cure rates and long term pituitary function following first-line transsphenoidal surgery (TSS) in childhood CD.

Series	No. CD patients	Age (yrs)	No. of first-line TSS	Outcome	Long-term pituitary deficiencies
Lonser *et al*, (NIH, Bethesda, USA) [12]	200	4.0-19.0	173/200 (87%)	189/200 (95%) cured*	10/200 (5%) DI Incomplete data
Storr *et al*, 2011 (Barts Health, London) [8]	41 (1 macro-adenoma)	5.7-17.8	36/41 (88%)	24/35 (69%) cured* (macroadenoma not cured)	11/24 (46%) GH 2/24 (8%) DI 2/24 (8%) Hypopit
De Oliveira *et al*, 2010 (São Paulo, Brazil) [70]	15	6.0-18.0	15	9/15 (60%) cured*	1/9 (11%) Hypopit 1/9 (11%) GH 1/9 (11%) DI
Acharya *et al*, 2010 (Mumbai, India) [47]	48	9.0-19.0	48	27/48 (56%) cured*	Not published
Kanter et al, 2005 (Virginia, USA) [40]	33	5.0-19.0	33	76% cured*	1/33 (3%) ACTH 1/33 (3%) DI Incomplete data
Massoud *et al*, 1997 (Great Ormond Street Hospital, London) [38]	12	8.7-16.3	12	9/12 (75%) (clinical and biochemical remission)	7/9 (78%) GH 4/9 (44%) ACTH 4/9 (44%) GT 3/9 (33%) TSH 1/9 (11%) DI
Leinung *et al*, 1995 (Rochester, Minnesota, USA) [71]	22 (1 macro-adenoma)	10.1-18.9	22	10/22 (45%) cured* (macroadenoma not cured)	1/22 (5%) TSH Incomplete data
Magiakou *et al*, 1994c (NIH, Bethesda, USA) [3]	50	Mean 14.4±4	37/50 (74%)	35/37 (95%) cured*	6/37 (16%) TSH 3/37 (8%) DI 3/37 (8%) GH 1/37 (3%) GT
Dyer *et al*, 1994 (Suresnes, France) [72]	36	≤ 16.0	33/36 (92%) (23 selective, 8 subtotal)	23/33 (69%) (hypocortisolaemia or 'physiological' cure)	1/33 (3%) DI 1/33 (3%) Hypopit Incomplete data

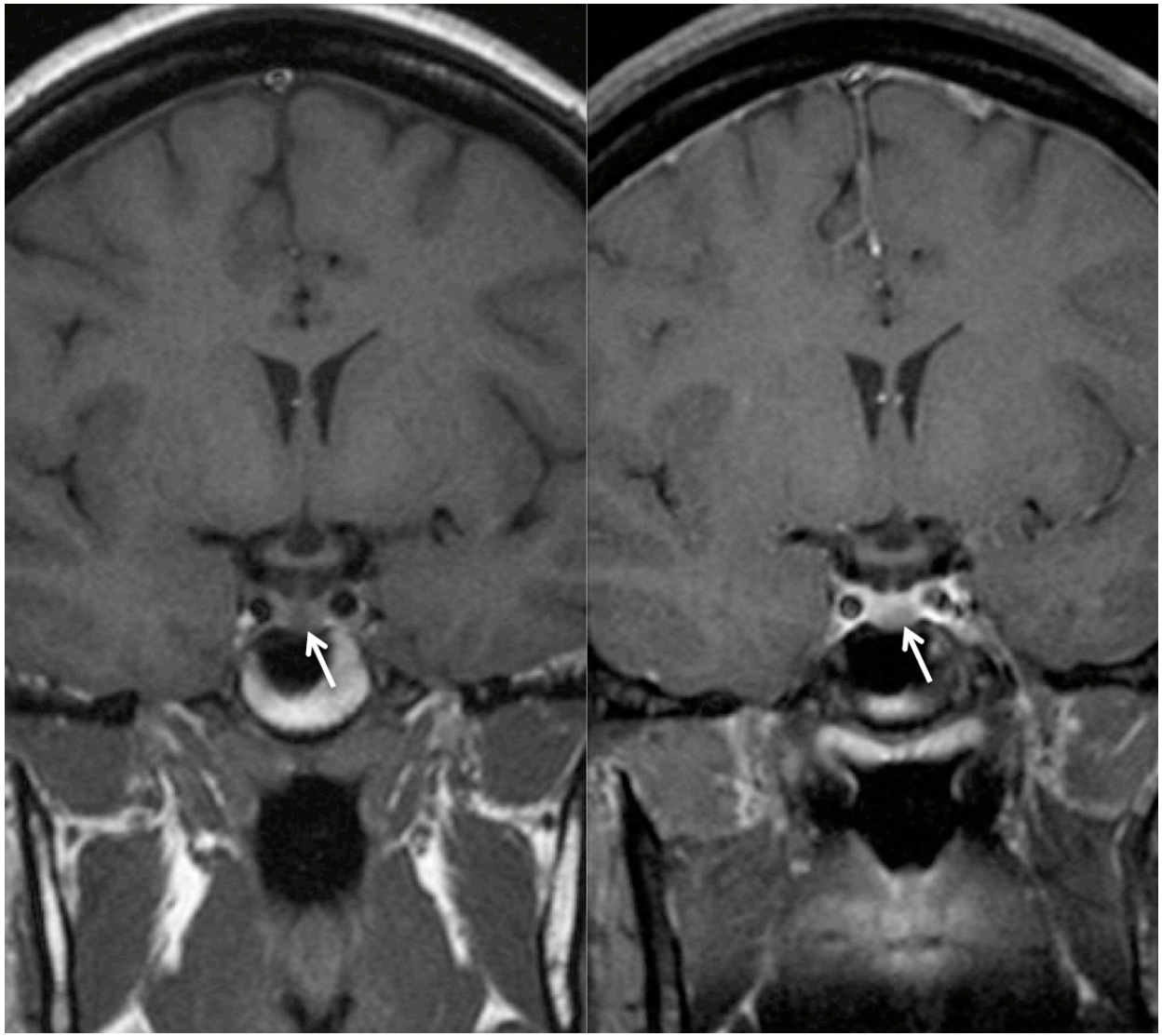
*'Cure' defined as undetectable serum cortisol in the immediate post-operative period (<50nmol/L). CD, Cushing's disease; No., number; yrs, years; GH, growth hormone; DI, cranial diabetes insipidus; hypopit, pan-hypopituitarism; ACTH, adrenocorticotropic hormone, GT gonadotropins, TSH, thyroid stimulating hormone.

Figure 1. Height and BMI SDS values at diagnosis in paediatric Cushing's syndrome (n=54)



Circles and squares represent BMI and height SDS, respectively: light and dark grey, paediatric patients with Cushing's disease (CD); white, CS of other etiologies.

Figure 2. A left-sided pituitary corticotroph adenoma in an 8.8 yr old boy with Cushing's disease



T1 weighted coronal MRI image before gadolinium (left) and after gadolinium (right). White arrows indicate corticotroph adenoma, which typically enhances less than the background pituitary gland after contrast administration.