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Advances in the Management of Paediatric Cushing's Disease

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Abstract
Cushing's disease (CD) is rare in the paediatric age range, but may present a difficult therapeutic challenge. Most paediatric endocrinologists have limited experience managing children or adolescents with CD and thus benefit from close consultation with adult colleagues. Prior to definitive treatment, a diagnostic protocol for investigation is required which broadly follows the model for adult patients. Treatment strategies for CD are described and critically appraised. The management of paediatric CD patients after cure also presents challenges for optimizing growth, bone health, reproduction and body composition from childhood into and during adult life.

Introduction

Cushing's disease (CD) in childhood and adolescence is very rare, compared to the more common endocrine pathologies such as disorders of growth, puberty and thyroid which make up the major part of paediatric endocrine practice. CD is caused by an ACTH-secreting pituitary adenoma and is the commonest cause of Cushing's syndrome (CS) in children over 5 years of age [1–3].

Some aspects of paediatric CD differ from those present in adults. Examples are the increased frequency in prepubertal males compared to females, the frequent absence of radiological evidence of a corticotroph adenoma on pituitary scanning, the higher incidence of lateralisation of ACTH secretion demonstrated by inferior petrosal sinus sampling (IPSS) and the more rapid response to external beam pituitary radiotherapy. These, together with other aspects of therapy for paediatric CD, will be discussed.

A further theme of the article will be to emphasise that very few, if any, paediatric endocrinology units have sufficient experience to manage CD in isolation and that consultation and joint decision-making with more experienced adult endocrinology units will be beneficial to the care of the patient.

Diagnostic Aspects of Paediatric Cushing's Disease

Epidemiology

The peak incidence of paediatric CD occurs during the adolescent or preadolescent years with median age of presentation in 182 cases taken from the literature being 14.1 years (fig. 1). The youngest child in our own series of 32 cases was aged 6.2 years at diagnosis. Whereas in adults, CD comprises 49–71% of CS cases, in paediatrics it accounts for 75–80% of cases [1, 4]. Paediatric CD is almost always caused by a pituitary microadenoma [5]. We have seen only one macroadenoma out of 32 paediat-

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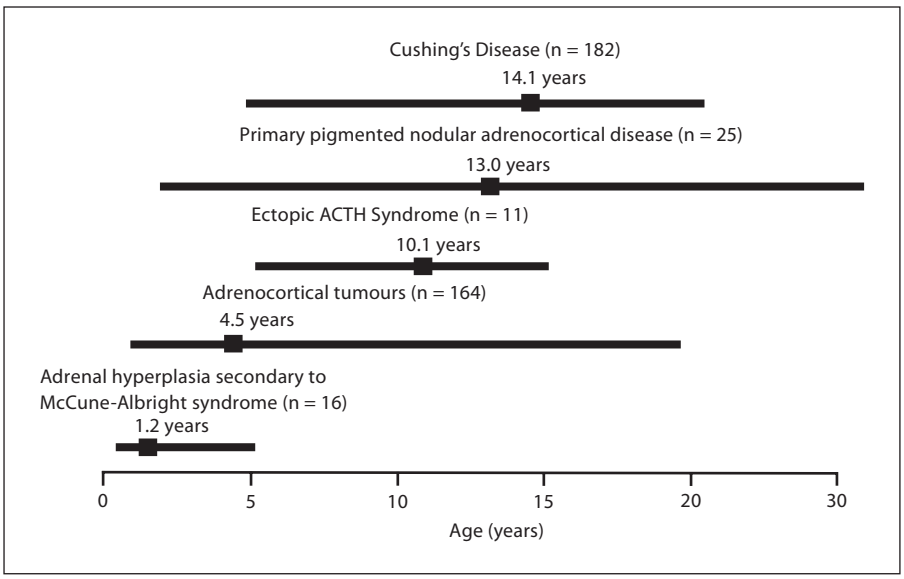

Fig. 1. Differing aetiologies of paediatric Cushing's syndrome from the literature (n = 398 cases) shown at ages of peak incidence.

ric cases [6]. However, very rarely this has been reported [7] and may even invade the cavernous sinus [8]. Pituitary macroadenoma has also been described as an early manifestation of MEN1 [9].

In adults, CD has a female preponderance [10]. Until recently, no comment had been made about sex distribution in children [12, 13]. We analysed sex at diagnosis in 50 CD patients aged from 6 to 30 years and found a significant predominance of males in the prepubertal patients [14]. There were similar incidences of males and females during puberty and an increasing predominance of females in the post-pubertal patients. Our report was the first to describe this male predominance in young patients; however, examination of cases in the large series from the NIH [3] reveals the same phenomenon. No clear explanation for this exists, although it is tempting to suggest that the oestrogenic milieu during female puberty may be related to the relative increase in females with CD during and following adolescence.

Key Clinical Diagnostic Features

The recognition of features which can alert the clinician to the diagnosis of CD is of crucial importance in early diagnosis and treatment. Most children and adolescents have a typical cushingoid appearance. A subtle or subclinical presentation or even cyclical features are uncommon. However, parents and general practitioners frequently fail to recognise the pathological nature of the change in the child's appearance. In 32 CD patients who we have managed, the mean length of symptoms prior to diagnosis was 2.5 years (range 0.5–6.6). Facial appearance was always changed and 100% of our patients complained of weight gain. Striae were present in 53% of our patients, being more frequent in the older patients. It was not unusual for a young child with CD to present with obesity and poor growth, but without the classical features of plethora, hirsutism, acne and striae. Additional features were hypertension (47%), emotional lability (53%) and fatigue (59%). Muscle weakness and easy bruising were rare.

Growth and Puberty

Short stature (height <–2.0 SD) was present in 40% of our patients and growth velocity when available was subnormal. One of the most striking features was the contrast between height SDS, being almost always below the mean, and BMI SDS being consistently above it (fig. 2), as has been previously reported [1]. We compared height and BMI SDS values in 29 patients with CD and 44 age-matched patients with simple obesity and showed a significant difference in the ratio of these two variables between the two groups [15], height being increased in simple obesity and decreased in CD. Bone age (BA) at diagnosis in 17 of our CD patients was delayed in 15 (mean delay 2.0 years; range –0.5 to 4.1) and correlated negatively with height SDS ($r = -0.70$; $p < 0.01$), duration of symptoms ($r = -0.48$; $p = 0.05$) and age at diagnosis ($r = -0.48$; $p = 0.05$) [16].

There are few reports of pubertal development in CD, although it is recognised that virilisation with pseudo-

Table 1. Scheme of investigation for patients with suspected Cushing's syndrome

Confirmation or exclusion of Cushing's syndrome
1 Urinary-free cortisol excretion (24-hour urine collection) daily × 3
2 Serum cortisol circadian rhythm study (09:00, 18:00 h, midnight [sleeping])
3 Low-dose dexamethasone suppression test (LDDST)
– Dose: 0.5 mg 6-hourly [09:00, 15:00, 21:00, 03:00 h] × 48 h
– Dose for patients weighing <40 kg: 30 μg/kg/day
– Serum cortisol measured at 0 and 48 h
Definition of aetiology of Cushing's syndrome
1 Plasma ACTH (09:00 h)
2 CRH test (1.0 μg/kg i.v.)
3 Analysis of change in serum cortisol during LDDST
4 Adrenal or pituitary MRI scan
5 Bilateral inferior petrosal sinus sampling for ACTH (with CRH)

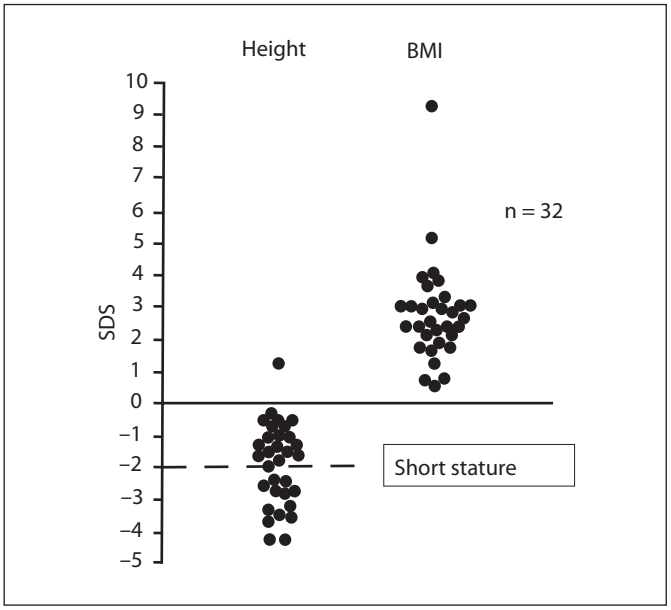

Fig. 2. Height and body mass index (BMI) SDS values in 32 paediatric patients with Cushing's disease.

precocious puberty frequently occurs [1, 3]. We analysed pubertal development in 27 patients and identified abnormal virilisation, defined as unusual advance of Tanner pubic hair stage compared to testicular volume or breast development in 12 [17]. Values of serum androstenedione, DHEAS, as previously reported [18], and testosterone SDS were higher (p = 0.03, 0.008, 0.03, respectively) than in subjects without abnormal virilisation and SHBG SDS values were lower (p = 0.006). Gonadotrophin levels were subnormal in the patients who had commenced true puberty suggesting a suppressive effect of chronic hypercortisolaemia.

Investigations Leading to Definitive Treatment

Biochemical Confirmation of Cushing's Disease

In patients suspected of having CD, we routinely perform measurement of basal plasma ACTH. In all of our patients with CD (n = 32), ACTH was detectable, ranging from 12 to 128 ng/l (NR 10–50 ng/l). We also perform a CRH test (1 μg/kg i.v.) and in 27 CD patients serum cortisol increased by >20% (range 106–554%) [21]. Although it is arguable that ectopic ACTH syndrome is so rare in children that the CRH test is not justified, we find an increased cortisol response contributes to the diagnosis of CD. We no longer perform a routine high-dose dexamethasone suppression test (HDDST). This recent decision follows an analysis of serum cortisol suppression during low-dose dexamethasone suppression test (LDDST) and HDDST. In adult patients with ACTH-dependent CS, the change in cortisol during LDDST has been shown to distinguish between pituitary and ectopic ACTH secretion, questioning the value of the HDDST [22].

We have now reported similar findings in children [23]. In 24 patients with CD, mean baseline serum cortisol values of 590.7 ± 168.8 nmol/l decreased to 337.4 ± 104.0 nmol/l at 48 h during LDDST ($p < 0.05$; mean decrease, 45.1%) with 66% decreasing by >30%. Cortisol suppression during LDDST correlated with that during HDDST ($r = +0.45$, $p < 0.05$). Consequently, decrease of cortisol during the LDDST strongly supports the diagnosis of CD (table 1).

Radiological Investigations

Pituitary imaging using MRI is an important step towards the successful treatment of CD by transsphenoidal surgery (TSS). As previously mentioned, most paediatric ACTH-secreting pituitary tumours are microadenomas with a diameter <5 mm [5]. The majority of these have a hypointense signal on MRI, which fails to enhance with gadolinium [19]. In the large NIH series, approximately

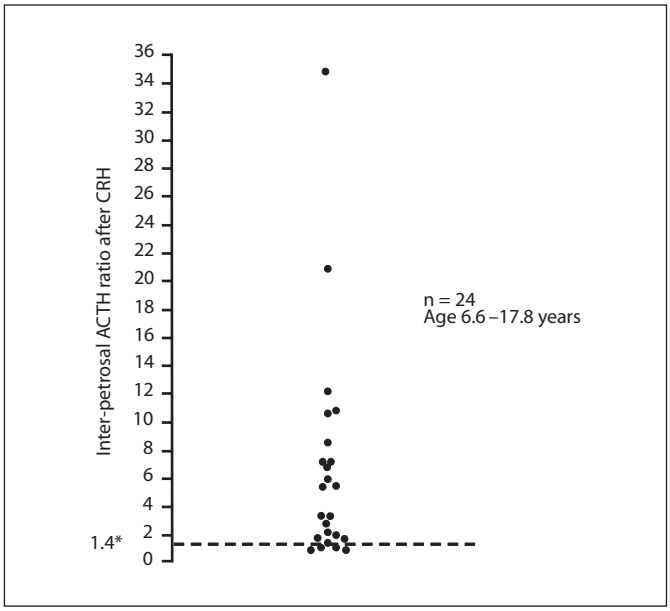

Fig. 3. Inter-petrosal ACTH ratio during bilateral inferior petrosal sinus sampling in paediatric patients with Cushing's disease. * Ratio of ≥1.4 indicates lateralisation of ACTH secretion, 19/23 (83%) showed lateralisation of ACTH secretion.

50% of microadenomas were visible on pituitary MRI [3]. 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 (table 2) [6].

Table 2. Pituitary imaging, surgical identification of adenoma and cure by TSS

Total patients n	Adenoma CT/ MRI image, n	Concordance of image with surgery, n	Cure by TSS, n
31	17 (55%)	9 (52%)	20 (64%)

n = Number of patients; MRI = magnetic resonance imaging; CT = computed tomography imaging; TSS = transsphenoidal selective adenomectomy.

Bilateral Inferior Petrosal Sinus Sampling for ACTH (BIPSS)

The technique of BIPSS was developed mainly at the NIH during the 1980s [24] and has become routine in adult practice. It was hoped that BIPSS would distinguish CD from ectopic ACTH syndrome and also provide a method of identifying a lateral or central source of pituitary ACTH secretion [19]. In children, because of the extreme rarity of ectopic ACTH syndrome, the aim of BIPSS is primarily to demonstrate possible lateralisation of ACTH secretion. The first paediatric data were reported in the large NIH series [3] where a predictive value of lateralisation was 75–80% [1]. We have been performing BIPSS in paediatric patients since 1987 and previously reported our experience, suggesting that ACTH sampling gave a better prediction of the site of the microadenoma than pituitary imaging [25].

BIPSS is a highly specialised technique and in our unit is performed by the same radiologist who regularly 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 24 paediatric CD patients, without complications, and have shown lateralisation (inter-petrosal sinus ACTH ratio of >1.4 after CRH) [6] in 79% of patients (fig. 3). A more recent study from the NIH described 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 [26]. The percentage of lateralisation however increased to 70% (51/73) after exclusion of 18 centrally located and 4 bilateral lesions.

Treatment of Cushing's Disease

Historical Aspects

CD in childhood causes considerable morbidity and 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 while effective in lowering hypercortisolaemia, the pituitary adenoma remained in situ, and there was an appreciable risk of post-adrenalectomy Nelson's syndrome [27, 28]. In the management of 33 cases of CD, we have only performed adrenalectomy twice, when the patients were extremely unwell and not fit to undergo pituitary surgery. In 1 of these patients, the hypercortisolaemia was uncontrollable by oral metyrapone and treatment was given with intravenous etomidate which successfully controlled the cortisol levels prior to adrenalectomy [29]. Medical therapy to lower cortisol using

Table 3. BIPSS results, surgical identification of adenoma and cure by TSS

Total patients n	BIPSS results			
	lateralisation, n	non-lateralisation, n	concordance of BIPSS result with surgery, n	cure by TSS, n
24	19 (79%)	5 (21%)	20 (83%)	18 (75%)

n = Number of patients; BIPSS = bilateral simultaneous inferior petrosal sinus sampling; TSS = transsphenoidal selective adenomectomy.

metyrapone or ketoconazole is a short-term option but cannot be recommended as a long-term definitive therapy for CD.

Transsphenoidal Surgery

Transsphenoidal surgery (TSS) consisting of selective removal of the adenoma is now considered first-line therapy for paediatric CD. TSS is regarded as a safe and effective procedure in children [30–33]. Adult CD studies show variable surgical success rates depending on which definition of cure is adopted. Our adult endocrine unit has traditionally used the definition of undetectable postoperative serum cortisol (<50 nmol/l) for successful treatment, i.e. cure [34]. We use the same definition. In adult practice, recurrence of CD following TSS, using this definition of cure, is extremely uncommon [34].

Selective microadenomectomy can be technically very difficult in children. As discussed above, the microadenomas may be very small and an appreciable rate of failure, in terms of definite cure, exists even in the hands of the most experienced neurosurgeons. We have recently analysed our experience over the past 25 years and considered the factors which contributed to successful surgical therapy [6]. The overall cure rate from TSS in 31 paediatric patients treated from 1982 to 2007 was 64% and in 25 of these patients, treated since routine IPSS was introduced as pre-operative preparation, the cure rate was 75% (table 3). We therefore feel that the ability of IPSS to correctly identify the lateral or central position of the adenoma has contributed to an increased rate of surgical success [44]. Other paediatric series report cure rates varying from 45 to 78% [12, 13, 35, 36], but very few report rates of >90% [3, 5].

Successful selective adenomectomy consists of retaining normal pituitary tissue, which is key to the child's development and quality of life. Following complete surgical removal of the microadenoma, the patient has adrenal insufficiency because of lack of function of normal corticotrophs. In all of our cured patients, repeated undetectable values of cortisol were recorded during the 1-month period following TSS. Hydrocortisone replacement is therefore required, which should be given in physiological doses. Recovery of the pituitary adrenal axis may take many months and is detected by careful withdrawal of hydrocortisone followed by demonstration of endogenous cortisol secretion in a day curve reaching a mean value of ~150 nmol/l. Post-operative hypopituitarism is therefore a potential complication of TSS; however, low rates have been reported in several large series [31, 35]. An important potential hormone deficiency for future growth is that of growth hormone (GH) which will be discussed below.

Pituitary Radiotherapy

Pituitary radiotherapy (RT) has been considered a therapeutic option for paediatric CD for many years. Children with CD have been shown to respond more rapidly than adults [37, 38]. In our centre, external beam RT is used as second-line therapy, following unsuccessful TSS. Our practice is to make a decision to proceed to RT, usually within 2–4 weeks of TSS, when it is clear from circulating cortisol levels that complete removal of the adenoma has not been achieved [39]. The RT protocol we follow consists of delivering 45 Gy in 25 fractions over 35 days [40]. We have treated 12 patients during the past 25 years with a successful cure rate of 92%, which occurred at a mean interval of 0.83 years (range 0.13–2.86) following completion of therapy. We have recently analysed long-term pituitary function in 6 of these patients and have shown that although GH deficiency was frequent initially, some recovery may occur [41]. Gonadotrophin secretion was generally preserved with normal, or early [42] puberty, and TSH and ACTH deficiency was minimal. We have not studied cognitive function following pituitary RT. However, we know of no data demonstrating a decrease in IQ related to targeted pituitary RT, as opposed to therapy using a broader field as for paediatric brain tumours.

Post-Cure Growth and Development

Most patients with paediatric CD have subnormal growth rates and short stature at diagnosis [1, 43]. The challenge is to reverse these problems so as to achieve acceptable adult height and body composition. A key article from the NIH described the abnormalities of height and GH secretion [44] together with a rather pessimistic view

of post-treatment catch-up growth and adult height [45]. We have also documented disappointing post-cure catch-up, which we attribute to continuing GH deficiency, occurring either from TSS, pituitary RT or the long-standing effects of chronic hypercortisolaemia on pituitary and growth plate physiology [43].

Our approach now is to test for GH deficiency 3 months after TSS or completion of RT. If GH therapy is demonstrated, we start therapy in a standard GH dose of 0.025 mg/kg/day. GnRH analogue therapy may be added to delay puberty and epiphyseal closure. Results demonstrate that catch-up growth usually occurs and adult height within range of target height is achieved for the majority of patients [46]. GH deficiency may persist for many years [47] but in the adult follow-up patients was usually not severe enough to indicate GH replacement as recommended for the adult GH deficiency syndrome.

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 [46]. A long-term follow-up study of childhood and adolescent CD showed that total body fat and the ratio of visceral to subcutaneous fat was abnormally high in the majority of patients studied 7 years after cure [48]. The implications of chronic excess visceral fat in terms of risk for adult metabolic syndrome deserve future study. Bone mineral density was closer to normal, a finding which we also reported, together with some patients having normal bone mineral density at diagnosis [49].

Conclusion

Paediatric CD contains a number of features which characterise this age range. Delay in diagnosis is frequent because of the lack of appreciation of the nature of the pathology by parents and general practitioners. Once suspected, CD should be diagnosed using a formal investigation protocol. The choice and interpretation of tests is most productively discussed with an adult specialist with experience of CD. Effective and curative therapy requires a multidisciplinary approach and referral should be considered to a centre combining paediatric and adult endocrinology, TSS and pituitary RT. The choice of neurosurgeon experienced in TSS in children is likely to significantly improve the chance of cure. Whereas the prognosis for cure is good in the majority of children and adolescents, post-treatment management presents challenges for optimization of growth, puberty and body composition.

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