Title: MANAGEMENT OF CUSHING SYNDROME IN CHILDREN AND ADOLESCENTS: EXPERIENCE OF A SINGLE TERTIARY CENTRE

Short title: Cushing syndrome in children and adolescents

Authors' names and departments in which the work was done: Maria Güemes[1,2], Philip G Murray[1], Caroline E Brain[1], Helen A Spoudeas[1], Catherine J Peters[1], Peter C Hindmarsh[1,2], Mehul T Dattani[1,2].

[1]London Centre for Paediatric Endocrinology and Diabetes, Great Ormond Street Hospital for Children, London, UK and University College London Hospital, London, UK

[2]Developmental Endocrinology Research Group, Section of Genetics and Epigenetics in Health and Disease, Genetics and Genomic Medicine Programme, UCL Institute of Child Health, London, UK

Author for Correspondence: Professor MT Dattani, Developmental Endocrinology Research Group, Section of Epigenetics and Genetics in Health and Disease, Genetics and Genomic Medicine Programme, UCL Institute of Child Health, 30 Guilford Street, University College London, London WC1N 1EH, UK. Tel: +44 0 20 7905 2657; Fax: 44 0 207 404 6191; E-mail: m.dattani@ucl.ac.uk

E-mail addresses of all authors:

Güemes Maria, maria.guemes@gosh.nhs.uk

Murray Philip G, philip.murray@manchester.ac.uk

Brain Caroline E, cbrain@nhs.net

Spoudeas Helen A, helen.spoudeas@gosh.nhs.uk

Peters Catherine J, catherine.peters@gosh.nhs.uk

Hindmarsh Peter C, peter.hindmarsh@gosh.nhs.uk

Dattani Mehul T, m.dattani@ucl.ac.uk

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Abbreviations

ACTH   Adrenocorticotropic Hormone

BMI   Body Mass Index

BP   Blood Pressure

CD   Cushing Disease

CRH   Corticotrophin-Releasing Hormone

CS   Cushing Syndrome

CT   Computed Tomography

DEXA   Dual-Energy X-ray Absorptiometry

HDDS   High Dose Dexamethasone Suppression

IPSS   Inferior Petrosal Sinus Sampling

LDDS   Low Dose Dexamethasone Suppression

MIBG   Metaiodobenzylguanidine

MRI   Magnetic Resonance Imaging

PET   Positron Emission Tomography

PPNAD   Primary Pigmented Nodular Adrenal Disease

SDS   Standard Deviation Scores

UFC   Urinary Free Cortisol

What is Known:

- Cushing syndrome is an extremely rare entity in the paediatric and adolescent age groups, so not many cohort studies have been published in this population.

-Several tests can be employed to firstly diagnose hypercortisolaemia and secondly, identify the source of origin of it. The efficacy and safety of these tests in children is still uncertain.

What is New:

-This study includes cases due to the different aetiologies of endogenous hypercortisolaemia (pituitary, adrenal and ectopic hypercortisolaemia) allowing us to compare the differences in presentation, diagnosis, management and long-term outcome between the groups.

-There is a difference in the prevalence of Cushing syndrome symptoms and in the performance of the tests in our cohort compared to previously published studies in the literature.

ABSTRACT:

The diagnosis and management of paediatric Cushing syndrome (CS) is highly challenging. This study aims to characterise its presentation, diagnosis, management and outcome by a retrospective case review of 30 patients (14 females) followed at a single tertiary paediatric endocrinology centre over a 30-year period.

At presentation, median age was 8.9 years (0.2-15.5) and the commonest manifestations were weight gain (23/30), hirsutism (17/30), acne (15/30) and hypertension (15/30). Growth retardation was present in 11/30. Median BMI was +2.1SDS (-6.5 - +4.6). Urinary Free Cortisol (UFC) was abnormal in 17/18 (94%), midnight cortisol in 27/27 (100%) and Low Dose Dexamethasone Suppression (LDDS) test in 20/20 (100%). High Dose Dexamethasone Suppression (HDDS) test was abnormal in: 6/6 (100%) of adrenal tumours, 1/10 (10%) of Cushing Disease (CD) and 1/2 (50%) of ectopic tumours. Bilateral Inferior Petrosal Sinus Sampling (IPSS) identified 5 CD cases and 1 ectopic tumour.

All patients underwent surgery and subsequently required cortisol replacement. Final diagnoses were 16 CD, 11 adrenal disease, 2 ectopic ACTH-secreting lesions and 1 case of unidentified aetiology. One year post-diagnosis, median BMI was 0.5SDS (-2.5 - +3.7), hypertension was present in 4/14 (28%) and 43% (12/30) of individuals were off hydrocortisone.

Conclusion: The prevalence of the clinical manifestations differs from that reported in other series. Screening tests were highly sensitive, with UFC, midnight cortisol and LDDS performing well. One year post-treatment, BMI and BP normalized in the majority of patients, and almost half of them were able to discontinue replacement hydrocortisone.

INTRODUCTION:

Pediatric Cushing syndrome (CS) is a rare disorder characterized by prolonged supraphysiological exposure to glucocorticoid concentrations [23]. In early childhood, there is a male predominance whereas later in childhood, there is a female predominance that decreases with age [35].

CS is most commonly caused by an exogenous iatrogenic exposure to glucocorticoids or ACTH (adrenocorticotropic hormone). Endogenous CS can be sub-classified into ACTH-dependent and ACTH-independent types. ACTH-independent CS (15% of cases in adults) is due to increased autonomous production of cortisol from an adrenal tumour (adenoma or carcinoma) or hyperplasia [22, 27]. In ACTH-dependent CS, the excess ACTH is produced either by the pituitary gland [Cushing's disease (CD), 75-80% in children] [31, 25] or by other tumours (ectopic CS, less common in the pediatric population than the 15% estimate in adults) [31] or rarely, due to tumour production of excess corticotrophin-releasing hormone (CRH). The biochemical confirmation of hypercortisolism requires a two-stage approach: initially the diagnosis needs to be confirmed, followed by further biochemical tests and imaging to localize the origin of this excessive secretion. In children, weight gain and growth retardation are considered the most common presenting features [24]. Additionally, most adrenocortical tumours in children present with virilisation or precocious puberty in addition to the features of CS [30].

Our aim was to describe the experience of a single UK tertiary center in the diagnosis and management of CS over a 30-year period. We also aimed to assess the efficacy of the tests used for establishing the etiology of CS.

PATIENTS AND METHODS:

We conducted a retrospective study of paediatric CS cases seen in the London Centre for Pediatric Endocrinology (a tertiary paediatric endocrinology center based at Great Ormond Street Hospital for Children and University College London Hospitals) over a 30-year period (1983-2013). The study group included 30 patients (14 females, 16 males). The source of hypercortisolaemia was found to be: ACTH-dependent CS due to a pituitary adenoma (16 patients), ACTH-independent CS (11 patients), ectopic ACTH (2) and unknown etiology (1).

Data relating to the *clinical presentation* of the patients were collected retrospectively, and included anthropometric characteristics, clinical features of CS and time frame between onset of symptoms and final diagnosis of CS. We also analyzed the *investigations* performed for the evaluation of CS and their test

performance; these included basal and stimulated hormonal values, imaging, bilateral inferior petrosal sinus sampling and genetics, if available. We collected information with respect to the *management* of the patients, including medical and surgical treatments. Post-surgical histology confirmation was procured. We also obtained information on both the immediate and longer-term post-operative clinical and biochemical outcomes (hydrocortisone replacement therapy, hormone deficiencies, complications, relapse, death, and auxology).

Clinical evaluation

The clinical characteristics were extracted through a review of the patients´ records. For blood pressure, standard deviation scores (SDS) were derived according to the British reference charts [14] and hypertension was defined as systolic (SBP) and/or diastolic blood pressure (DBP) >2 SDS for age and sex. In selected cases, medical therapy aimed to reduce cortisol concentrations and antihypertensives were used.

Biochemical and radiological investigations (Table 1)

Screening tests to confirm the diagnosis of CS were:

1. Urine Free Cortisol (UFC)

2. Midnight serum cortisol

3. Low dose dexamethasone suppression test (LDDS) [48-h of 20 µg/kg Dexamethasone (maximum 500 µg) orally 6-hourly]

Investigations to identify the etiology of cortisol excess included:

1. 8am plasma ACTH concentrations

2. High dose dexamethasone suppression test (HDDS) [80 µg/kg/dose Dexamethasone (maximum 2 mg) orally 6-hourly]

3. CRH test (100 µg CRH iv with subsequent measurement of ACTH increment)

4. Imaging: pituitary gland with magnetic resonance (MRI) and adrenal imaging with either ultrasound, computed tomography (CT) or MRI

5. Bilateral inferior petrosal sinus sampling (IPSS) (before and after iv injection of 100 µg of CRH) was performed in those patients in whom MRI was inconclusive.

When IPSS did not clearly identify the origin of the ACTH secreting lesion, CT of the thorax and somatostatin receptor (Ga-Octreotide) positron emission tomography (PET) scan were performed. Adrenal vein sampling was performed where MRI findings were inconclusive and an adrenal source was suspected.

Hormone analysis

Plasma cortisol was measured using DPC Coat-a-count RIA (1983-1992), Abbott TDX Fluorescent immunoassay (1992-1997), DPC Immulite 1000 (1997-2006), DPC Immulite 2000 (2006-2009), Siemens Immulite 2500 competitive immunoassay (2009–2012), and Siemens Immulite 2000XPi (2012-2013). ACTH was analyzed by Sequential immunometric assay (Immulite 2000XPi). UFC concentrations were determined using competitive chemiluminescent enzyme immunoassay (Immulite 2000XPi).

Diagnosis of CS was confirmed by the histological findings and/or evidence of clinical and biochemical remission after surgery. Postoperative remission was defined as undetectable serum cortisol (<28nmol/l) and in CD an ACTH <5ng/l on the first sample after surgery. If the postoperative morning plasma cortisol concentration was undetectable, hydrocortisone replacement was commenced immediately. Criteria for recurrence included: elevated plasma cortisol, elevated UFC and reappearance of clinical signs of hypercortisolism.

This study was conducted as part of a quality assessment audit and as such ethical approval was not required.

RESULTS:

Presenting signs and symptoms (See Table 2)

Median age at presentation differed depending on the etiology of hypercortisolaemia. The median delay between onset of symptoms and diagnosis was 1.0 year (range 0.04 to 6). The most frequent presenting manifestations in the whole cohort were weight gain (76.6%), hirsutism (56.6%) and acne (50%). For pituitary CD, growth retardation was the second commonest sign (62.5%). Alkalosis, hyperglycemia, hypercalciuria and menstrual irregularities were not reported in this cohort.

Median weight gain at presentation was 9.5kg (4 to 19). Median weight SDS at diagnosis was +1.7 (-2.8 to +4.0), with a median height SDS of -0.3 (-3.2 to +3.0) and a median BMI SDS of +2.1 (-6.5 to +4.6). Fourteen patients had a BMI SDS >2.0 while three patients presenting with hypertension had a BMI SDS <0 (one of these

patients was a case of congenital bilateral adrenal CS due to McCune Albright Syndrome presenting at 10 weeks of life with hypotonia, poor feeding, BMI -6.5SDS, hyperpigmented skin lesions and hypertension). At the time of diagnosis, 19 patients (63%) were prepubertal, 7 (23%) were in puberty and in 4 subjects (14%) Tanner staging was not available. Fifteen (50%) children were hypertensive. Median SBP and DBP SDS at diagnosis were +1.1 (-1.33 to +5.67) and +1.99 (-2 to +5.97) respectively. Neither SBP nor DBP correlated with the severity of hypercortisolaemia measured by UFC, 8.00 am or midnight cortisol. An uncommon paediatric presentation was that of a 16-year old with CD who manifested psychotic symptoms.

Investigations (See Table 1)

The median bone age delay at diagnosis (bone age – chronological age) in pituitary CD patients was -0.82 years (-1.77 to 1.8) whereas in adrenal CS it was +0.32 (-0.72 to 1.35). The urine steroid profile showed increased output of glucocorticoid metabolites in the 20/30 patients who had this test performed. Imaging showed abnormal findings in 17 patients on MRI brain/pituitary, including all 16 patients with pituitary-dependent CS. One patient with ectopic ACTH production also had a pituitary adenoma that, although initially was thought to be the cause of his CS, was ultimately proven to be a non-functioning adenoma after IPSS. All 11 patients with ACTH independent CS had an abnormality identified on imaging (either abdominal US/MRI/CT or adrenal vein sampling). In one patient with primary pigmented nodular adrenal disease (PPNAD) the CT adrenal only showed an unusually prominent left adrenal vein without evidence of a mass, and adrenal vein sampling showed left/right adrenal vein cortisol concentrations of 10015/530nmol/l. One child with an enlarged left thigh and left abdominal mass on MIBG (metaiodobenzylguanidine) scan was found to have a lesion in the left suprarenal area (adrenocortical tumour) and was subsequently confirmed on MRI to have a contralateral Wilm's tumour. The source of ectopic ACTH in one patient was identified as a potential bronchial carcinoid with a chest CT (negative Ga-Octreotide PET scan). In one patient no lesion was identified on imaging. In total, one lesion was identified in 26 cases and two lesions in 3 cases.

Genetic studies

TP53 was sequenced in 5 cases and one mutation identified (c.375+1 G>A donor splice site exon 4 in a patient with an adrenal carcinoma). Sequencing of *GNAS* in 1 patient with congenital CS in the context of

McCuneAlbright syndrome identified a heterozygous mutation in exon 8 (c.602G>A) in tissue. In the 2 cases of PPNAD, *PRKAR1A* sequencing was negative in one and in the other case the result is currently pending.

Management (See Table 2)

No patients had received previous treatment for CS prior to assessment in our center. After diagnosis, all of the patients underwent surgery (except for one lost to follow-up). Hypophyseal surgery for CD was transphenoidal in all cases. The lesion was positively identified during surgery in 22 cases but not identified in 7 cases. Eight patients (26.6%) received metyrapone but this was discontinued in 4 due to side effects (nausea and dizziness). Ketoconazole was subsequently used in 1 patient who also manifested unacceptable gastrointestinal side-effects. Radiotherapy was used as a second line treatment in CD if transphenoidal surgery was unsuccessful.

One 2.1-year-old female with tests initially suggestive of pituitary CS had a Cardiac Echo and CT chest for persistent tachycardia, which identified nodules under the diaphragm, and a further abdominal MRI showed a metastatic yolk sac tumor (malignant epithelial carcinoma) that had extensively spread through the peritoneal cavity. She received debulking and chemotherapy with autologous stem cell transplantation, but it recurred and dispersed into many intra-abdominal organs. She was subsequently enrolled in a phase I trial of HIPEC (hyperthermic intraperitoneal cisplatin administration) in a center in USA.

In 21 cases one surgical procedure was required, while in 4 patients (all CD) two surgical procedures were needed and for 4 patients (3 were CD), three surgical procedures were required.

Histological diagnoses showed that 16 patients had a pituitary ACTH-secreting adenoma (one with co-secretion of prolactin). Of the 11 patients with primary adrenal disease, 6 had an adrenocortical adenoma, 3 adrenocortical carcinoma, and 2 PPNAD. Of the two patients with ectopic ACTH secreting tumors, one was a bronchial carcinoid and the other a metastatic yolk sac tumor.

Outcome

Follow-up period in our hospital was a median of 2.76 years (0.1 to 10.11). Many of those patients who achieved a cure post-operatively (undetectable post-surgical cortisol) were transferred for follow-up to their local hospitals or to their countries of origin.

-Auxology and blood pressure (Height, weight, growth velocity, BMI and number of cases with obesity and hypertension during follow-up are collected in Table 3)

-Post treatment complications (See Table 4)

All patients required physiological glucocorticoid replacement post-cure in the form of hydrocortisone, but this was successfully discontinued in 12 patients (43%) after a median duration of 1.1 years (0.5 - 2.1). Fourteen patients (47%) remained on hydrocortisone at the time of this study.

One or more hormone abnormalities were present in 17 patients (56%). Eleven (36.6%) did not report other hormone disturbances (all adrenal or ectopic CS) and in 2 patients this information was unavailable. One patient with BMI of +3.77SDS had insulin insensitivity and was started on metformin but no patient had frank diabetes. Each hormone deficiency was treated with replacement therapy, although out of the 7 patients with GH deficiency, only 5 received GH treatment. Hormone unrelated complications were present in 51.7% of the patients.

At last follow-up, 20 patients remained in remission, 5 had relapsed and 5 were lost to follow-up. One patient with a pituitary adenoma required 2 surgical procedures and radiotherapy but experienced a further relapse so had a bilateral adrenalectomy subsequently resulting in Nelson syndrome 6 years later, for which he had further surgery and stereotaxic radiotherapy.

DISCUSSION:

This study presents clinical characteristics of a cohort of 30 children managed over the last 30 years in a tertiary pediatric endocrinology service. Overall, 53% had pituitary-dependent CS, 36% adrenal-dependent CS, 6.6% an ectopic source of CS, and in 1 case the aetiology remains unknown as the patient did not attend follow-up. Although this study confirms the predominance of CD in this age group, previous studies [31, 25] have reported higher prevalence rates of pituitary CS.

One of the novel findings of this study is the difference in prevalence of CS symptoms in our cohort compared to other studies; a decreased growth rate was less common in our cohort of patients [28]. Growth failure was common in pituitary CD patients but not in ACTH-independent CS. A referral bias leading to increased

prevalence of non-pituitary CS in our institution may explain this difference in clinical presentation. While pure cortisol-secreting pituitary CD would inhibit growth (cortisol suppresses GH production [37], combined with a possible pituitary mass effect leading to GH deficiency), adrenal CS tumors cosecreting androgens would promote growth and hence stature would be less affected. In a previous series of 72 children with CD, growth retardation was present in 82%, hypertension in 46% and striae in 40% [2]. In another cohort of 59 children with CS, growth retardation was found in 83%, hirsutism in 78%, striae in 61% and hypertension in 47% [24]. In the current study, within the whole group, growth retardation was present in 36%, hirsutism in 56% and hypertension in 50%. Weight gain was the most frequent presenting complaint, and changes in school performance and mood were commoner in our series (43%) compared to previous studies with a prevalence of 19% [24].

Interestingly, a small number of hypertensive patients in this study presented in an atypical fashion with a low BMI SDS, and clinicians should be aware of presentation in this manner to avoid delayed diagnosis. Up to 60% of children with CS can have hypertension at presentation [21]. Causative mechanisms hypothesized have included a state of functional mineralocorticoid excess, upregulation of the renin-angiotensin system and the effects of cortisol on the vasculature [32]. The degree of hypertension has been reported to correlate with the degree of hypercortisolaemia [16] although this was not the case in our study.

Onset of puberty can be affected in CS [10], either because of androgen secretion from the adrenal tumour or due to gonadotropin deficiency secondary to the effects of a pituitary adenoma or therapy provided [9]. This study included eight patients with early puberty and two with gonadotropin deficiency.

Both McCune Albright syndrome (1 case) and Carney complex (2 cases) are recognized causes of CS [5]. Carney complex and PPNAD is a rare cause of CS in children caused by autonomously functioning nodules in the adrenal cortex [13]. Published reports indicate that in 75% of cases the management has been bilateral adrenalectomy, although 20% undergo unilateral procedures and 5% subtotal procedures [16]. One of our patients with PPNAD was treated with bilateral adrenalectomy, whilst another had unilateral excision and remains free of recurrence to date.

The time frame between the appearance of first symptoms of hypercortisolism and the recognition of CS was

shorter than in other series [33]. Delay in diagnosis may have been due to difficulties in recognition of CS in childhood by general practitioners and pediatricians. Improving the time to diagnosis will require increased awareness of the disorder, and may prevent the complications that are frequently seen in this condition.

Here, as in other studies, bone age was within the normal range in 83% of cases [24]; although androgens accelerate bone maturation, hypercortisolaemia delays it [38, 11]. Another difference is that pituitary MRI identified a lesion in all our 16 CD patients, in contrast with other studies where up to 30–50% of children with CD have normal pituitary imaging [24, 3, 1, 18]. This increase in identification may be due to improvements in MRI technology over time. The identification of incidental lesions in the pituitary is a significant risk (up to 35% of adults) [19]. In this study, one patient with ACTH-dependent CD was almost incorrectly identified with an ACTH secreting adenoma because of an incidental pituitary lesion. The ectopic ACTH source (a bronchial carcinoid) was identified due to the lack of a central-peripheral gradient on IPSS. A French study identified 10 cases of ectopic CS in children and adolescents during a 23-yr period; 8 were well-differentiated endocrine lung tumors, with one Ewing's sarcoma and one nested stromal epithelial liver tumour [28]. Because ectopic ACTH-secreting tumors can be extremely small, cross-sectional 5-mm–thick slices CT [20] or MRI of the neck-thorax-abdomen is considered the first-line investigation for these lesions in adults [26]. Unlike our case, other reports [28, 3] found Octreotide scintigraphy/18 F-DOPA PET scans useful to identify bronchial carcinoids.

The biochemical diagnosis of CS can be challenging. In keeping with previous literature, both midnight cortisol and LDDST performed well, and identified all patients with CS [8]. The next best test was UFC, which was abnormal in 94% of patients.

HDDST accurately identified 90% of patients with CD, higher than other series where the test was positive in 68% of CD patients [24]. The accuracy of HDDST has been questioned in several studies in adults [31, 32, 3, 19, 29] and in children it has been found to lack specificity, in that patients with ectopic CS may also show a degree of cortisol suppression on HDDST [28]. One of our patients with ectopic ACTH demonstrated a 75% reduction in serum cortisol, illustrating the fallibility of the HDDST. CRH test identified 89% (8 out of 9 patients) of CD, similar to other reports [24]. This test also does not reliably differentiate CD from an ectopic ACTH source [28]. In our hands, HDDST and CRH test reliably distinguished between pituitary and adrenal disease but performed less well in cases of ectopic ACTH secretion. IPSS is considered to be the gold standard

to distinguish CD from ectopic and is a safe procedure in children under expert hands [25, 18]. As in other studies, IPSS had a diagnostic accuracy of 100% [24].

Surgical removal of the source of hypercortisolaemia is the gold standard treatment [33]. In the case of CD, trans-sphenoidal resection is the optimal approach, with pediatric cure rates of 45% to 97% [24, 32, 34]. For those who relapse with pituitary CD, this mostly occurs within the first 2 years post surgery [21, 34]. Where relapse occurs, options include repeat trans-sphenoidal surgery, radiotherapy and mitotane, and if these fail, bilateral adrenalectomy will guarantee cure from CS but with the subsequent risk of Nelson syndrome [24], as observed in one of our subjects.

Medical agents such as antihypertensives, inhibitors of steroidogenesis (metyrapone, ketoconazole and mitotane), anti-glucocorticoid agents (mifepristone), and ACTH release modulators (dopamine and somatostatin agonists) [36] can be used as adjunctive treatment prior to surgery - potentially reducing the surgical risk [4] - or when surgery is contraindicated or the patient has not been fully cured [21, 4]. Metyrapone and ketoconazole were the only two medical agents used during this study. Their use was restricted to reducing cortisol concentrations while awaiting surgery and in one case (metastatic yolk sac tumor) where surgical therapy was not possible. They both have a rapid onset of action, although metyrapone may exacerbate hypertension by increasing mineralocorticoid production [32] and cause virilization since precursors are shunted into androgens [36]. Common side effects of ketoconazole are gastrointestinal discomfort and skin rash; serious hepatic injury is exceptional [38]. In our patients ketoconazole was poorly tolerated due to gastrointestinal side effects and deranged transaminases.

Hypertension in the majority of children and adolescents, unlike in adulthood, was previously thought to regress completely within one year post-surgical cure, possibly due to vascular protective mechanisms in the young and shorter-lasting hypercortisolaemia compared to adults [25]. Other studies have shown that 1-year after surgical treatment of CS, the prevalence of systolic and diastolic hypertension was 16% and 4% respectively [3], which is similar to our results except for the diastolic hypertension, which in our study was up to 14% at this point. This can be a contributing factor to the known prothrombotic tendency in these individuals, as occurred in one of our patients who developed a deep vein thrombosis post-operatively. Another side effect of hypercortisolaemia is the decrease in bone mineral mass and therefore fracture risk, but in our cohort, DEXA (dual-energy x-ray absorptiometry) scan was only available in one patient at the time of diagnosis, showing a Z

score of -1.7.

As in other reports [10, 36], postoperative hydrocortisone was required in all of our patients. Almost half of them were able to discontinue hydrocortisone by 1-year post-definitive treatment; in others this recovery may take up to 2 years.

Other pediatric reports have suggested that, despite effective therapy, CS results in a reduction in final height [7, 17], increased prevalence of hypertension [21], increased visceral fat mass [7, 17] and reduced quality of life [15]. Growth effects may be due to the adenoma itself, surgery, radiotherapy or glucocorticoid exposure [12]. Several studies have reported a high BMI SDS and visceral fat mass after several years of follow-up post-cure [7, 17]. In our patients, end of growth stature was available for four individuals, two of whom proved to be GH deficient, albeit only one of them received GH therapy. In this small sample the median final height SDS was not significantly impaired. This could be in keeping with the lower prevalence of growth impairment at presentation and the short delay in diagnosis among our patients (median of 1 year). BMI SDS, however, remained elevated, even several years after treatment. Long-term pituitary hormone deficiencies were common in our patients with CD, GH being the commonest permanent pituitary hormone deficiency, followed by ACTH deficiency. Post-operative diabetes insipidus was common but persistent diabetes insipidus was rare (2 patients). Another long-term study of patients with CD who had received radiotherapy showed that GH deficiency was frequent but could recover, gonadotropin secretion was usually preserved with early or normal puberty and TSH and ACTH deficiencies were rare [6].

To conclude, this single center study illustrates the challenges in the management of CS in the pediatric population, the broad spectrum of manifestations, the often equivocal test results, and the considerable morbidity on follow-up.

Authors'contributions: M. Güemes, P. Murray and M. Dattani designed the study, collected the patients´data and wrote the manuscript. The rest of the authors have significantly contributed to this study with patient´s data and writing up of the manuscript.

Compliance with ethical standards

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REFERENCES:

1. Batista D, Courkoutsakis NA, Oldfield EH, Griffin KJ, Keil M, Patronas NJ, Stratakis CA (2005) Detection of adrenocorticotropinsecreting pituitary adenomas by magnetic resonance imaging in children and adolescents with Cushing disease. J Clin Endocrinol Metab 90:5134–5140

2. Batista DL, Oldfield EH, Keil MF, Stratakis CA (2009) Postoperative Testing to Predict Recurrent Cushing Disease in Children J Clin Endocrinol Metab 94:2757–2765

3. Bhansali A, Walia R, Rana SS, Dutta P, Radotra BD, Khandelwal N, Bhadada SK (2009) Ectopic Cushing's syndrome: experience from a tertiary care centre. Indian J Med Res 129:33–41

4. Biller BMK, 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 JA, Boscaro M (2008) Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 93:2454–2462

5. Brown RJ, Kelly MH, Collins MT (2010) Cushing Syndrome in the McCune-Albright Syndrome. J Clin Endocrinol Metab 95:1508–1515

6. Chan L, Storr HL, Plowman PL, Perry LA, Besser GM, Grossman AB, Savage MO (2007) Long-term pituitary function inpatients with paediatric Cushing´s disease treated with pituitary radiotherapy. Eur J Endocrinol 156:477-482

7. Davies JH, Storr HL, Davies K, Monson JP, Besser GM, Afshar F, Plowman PN, Grossman AB, Savage MO (2005) Final adult height and body mass index after cure of paediatric Cushing's disease. Clin Endocrinol (Oxf) 62:466–472

8. Dias R, Storr HL, Perry LA, Isidori AM, Grossman AB, Savage MO (2006) The discriminatory value of the low-dose dexamethasone suppression test in the investigation of paediatric Cushing's syndrome. Horm Res 65:159–162

9. Dupuis CC, Storr HL, Perry LA, Ho JT, Ahmed L, Ong KK, Dunger DB, Monson JP, Grossman AB, Besser GM, Savage MO (2007) Abnormal puberty in paediatric Cushing's disease; relationships with adrenal androgens, sex hormone binding globulin and gonadotrophin concentrations. Clin Endocrinol (Oxf) 66(6):838-43

10. Dutta D, Jain R, Maisnam I, Mishra PK, Ghosh S, Mukhopadhyay S, Chowdhury S (2012) Isolated Cushing's Syndrome in Early Infancy Due to Left Adrenal Adenoma: An Unusual Aetiology J Clin Res Pediatr Endocrinol 4(3):164-168

11. Garge S, Bawa M, Kanojia RP, Gupta K, Rao KLN (2013) A rare case of isolated Cushing syndrome in a 3-month-old boy. J Pediatr Endocr Met 26(5-6):599–603

12. Greening JE, Storr HL, McKenzie SA, Davies KM, Martin L, Grossman AB, Savage MO (2006) Linear growth and body mass index in paediatric patients with Cushing's disease or simple obesity. J Endocrinol Invest 29:885–887

13. Gunther DF, Bourdeau I, Matyakhina L, Cassarino D, Kleiner DE, Griffin K, Courkoutsakis N, Abu-Asab M, Tsokos M, Keil M, Carney JA, Stratakis CA (2004) Cyclical cushing syndrome presenting in infancy: An early form of primary pigmented nodular adrenocortical disease, or a new entity? J Clin Endocrinol Metab 89:3173-3182

14. Jackson LV, Thalange NKS, Cole TJ (2007) Blood pressure centiles for Great Britain. Arch Dis Child 92:298–303

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

16. Kumorowicz-Czoch M, Dolezal-Oltarzewska K, Roztoczynska D, Chrupek M, Prokurat AI, Drabik G, Starzyk J (2011) Causes and consequences of abandoning one-stage bilateral adrenalectomy recommended in primary pigmented nodular adrenocortical disease – case presentation. J Pediatr Endocr Met 24(7-8):565–567

17. Leong GM, Abad V, Charmandari E, Reynolds JC, Hill S, Chrousos GP, Nieman LK (2007) Effects of child- and adolescent-onset endogenous Cushing syndrome on bone mass, body composition, and growth: a 7-year prospective study into young adulthood. J Bone Miner Res 22:110–118

18. Lienhardt A, Grossman AB, Dacie JE, Evanson J, Huebner A, Afshar F, Plowman PN, Besser GM, Savage MO (2001) Relative contributions of inferior petrosal sinus sampling and pituitary imaging in the investigation of children and adolescents with ACTH-dependent Cushing's syndrome. J Clin Endocrinol Metab 86:5711–5714

19. Lindsay JR, Nieman LK (2005) Differential diagnosis and imaging in Cushing's syndrome. Endocrinol Metab Clin North Am 34:403–421

20. Liou LS, Kay R (2000) Adrenocortical carcinoma in children. Urol Clin North Am 27:403–21

21. Lodish MB, Sinaii N, Patronas N, Batista DL, Keil M, Samuel J, Moran J, Verma S, Popovic J, Stratakis CA (2009) Blood pressure in pediatric patients with Cushing syndrome. J Clin Endocrinol Metab 94:2002–2008

22. Loridan L, Senior B (1969) Cushing's syndrome in infancy. J Pediatr 75:349-359

23. Magiakou MA, Chrousos GP (2002) Cushing's syndrome in children and adolescents: Current diagnostic and therapeutic strategies. J Endocrinol Invest 25:181–194

24. Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler GB Jr, Nieman LK, Chrousos GP (1994) Cushing's syndrome in children and adolescents: Presentation, diagnosis, and therapy. N Eng J Med 331:629–36

25. Magiakou MA, Mastorakos G, Zachman K, Chrousos GP (1997) Blood pressure in children and adolescents with Cushing's syndrome before and after surgical cure. J Clin Endocrinol Metab 82:1734–38

26. McEvoy MP, Rich BS, New M, Tang LH, La Quaglia MP (2011) Thymic Carcinoid Presenting With Cushing's Syndrome in a 17-Year-Old Boy: A Case Report and Review of the Literature. Journal of Clinical Oncology 29;(25):716-718

27. Miller WL, Townsend JJ, Grumbach MM, Kaplan SL (1979) An infant with Cushing's disease due to an adrenocorticotropin-producing pituitary adenoma. J Clin Endocrinol Metab

48:1017-1025

28. More J, Young J, Reznik Y, Raverot G, Borson-Chazot F, Rohmer V, Baudin E, Coutant R, Tabarin A (2011) Ectopic ACTH Syndrome in Children and Adolescents. J Clin Endocrinol Metab 96:1213–1222

29. Newell-Price J, Trainer P, Besser M, Grossman A (1998) The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev 19:647–672

30. Rescorla FJ (2006) Malignant adrenal tumors. Semin Pediatr Surg 15:48–56

31. Savage MO, Chan LF, Grossman AB, Storr HL (2008) Work-up and management of Paediatric Cushing´s syndrome. Curr Opin Endocrinol Diabetes Obes 15:346-351

32. Sharma ST, Nieman LK (2011) Cushing's Syndrome: All variants, detection, and treatment. Endocrinol Metab Clin North Am 40(2):379–391

33. Storr, H.L. Afshar F, Matson M, Sabin I, Davies KM, Evanson J, Plowman PN, Besser GM, Monson JP, Grossman AB, Savage MO (2005) Factors influencing cure by transsphenoidal selective adenomectomy in paediatric Cushing's disease. Eur J Endocrinol 152:825–833

34. Storr HL, Chan LF, Grossman AB, Savage MO (2007) Paediatric Cushing's syndrome: epidemiology, investigation and therapeutic advances. Trends Endocrinol Metab 18:167–174

35. Storr HL, Isidori AM, Monson JP, Besser GM, Grossman AB, Savage MO (2004) Pre-pubertal Cushing's is more common in males, but there is no increase in severity at diagnosis. J Clin Endocrinol Metab 89:3818–3820

36. Valassi E, Crespo I, Gich I, Rodríguez J, Webb SM (2012) A reappraisal of the medical therapy with steroidogenesis inhibitors in Cushing's syndrome. Clin Endocrinol (Oxf) 77:735–742

37. van Aken MO, Pereira AM, Frölich M, Romijn JA, Pijl H, Veldhuis JD, Roelfsema F (2005) Growth hormone secretion in primary adrenal Cushing's syndrome is disorderly and inversely correlated with body mass index. Am J Physiol Endocrinol Metab 288(1):63-70

38. White PC (2007) Adrenal tumors. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF eds. Nelson Textbook of Pediatrics. Saunders Elsevier. Edn 18, ch. 580, p. 2372.