Pediatric Cushing's disease: Case reports and retrospective review

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Background. We report four pediatric subjects with Cushing's disease (CD) diagnosed in the Czech Republic. We focus on initial symptoms of Cushing's syndrome (CS) which can lead to early diagnosis, on typical symptoms of CS in children, their age and sex distribution, the mean length of symptoms prior to diagnosis, indication for examination, post-cure growth, sexual development and pituitary function in our four CD patients after transsphenoidal pituitary surgery (TSS). We describe the diagnostic process leading to confirmation of CD and we emphasize the biochemical and radiological diagnostic difficulties.

Conclusions. Pediatric CD has a number of features distinct from adult CD. Our retrospective analysis confirmed the presence of growth retardation and change in facial appearance with development of moon face as the first symptoms of CS. According to our observation, growth retardation is prior to development of moon face. The other typical symptoms frequently seen in pediatric patients are pseudo-precocious puberty in both sexes, hirsutism in pubertal girls due to excessive adrenal androgen secretion and pubertal delay. A corticotropin-releasing hormone (CRH) test and especially bilateral inferior petrosal sinus sampling for ACTH (BIPSS) contribute to confirming the diagnosis of CD and excluding ectopic ACTH syndrome in children with unvisible adenoma on pituitary magnetic resonance imaging (MRI).

Key words: Cushing's disease, transsphenoidal pituitary surgery, corticotropin-releasing hormone (CRH) test, bilateral inferior petrosal sinus sampling for ACTH (BIPSS), growth failure, pseudo-precocious puberty, hirsutism

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INTRODUCTION

Cushing's syndrome (CS) in childhood results mostly from the exogenous administration of glucocorticoids. Endogenous CS is a rare multisystem disorder that results from overproduction of the glucocorticoid hormone cortisol in adrenal glands[1-4]. The overall incidence of endogenous CS is 0.7–2.4 per million people per year; approximately only 10% of new cases occur in children every year[1,5]. CS is divided into two groups of adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent causes (Table 1). ACTH-dependent CS is caused by ACTH-secreting pituitary corticotroph adenoma (Cushing's disease), which is the most frequent form of CS in children and adults, and by overproduction of ACTH from a non-pituitary tumor (e.g. carcinoid tumors in the bronchus, pancreas, thymus, adrenal neuroblastoma or Wilms' tumour in children), called ectopic ACTH syndrome. Autonomous secretion of cortisol from the adrenal glands leads to ACTH-independent CS (Table 1) (ref.[1,2,4,6]). Approximately 75–80% of CS cases in children are due to Cushing's disease (CD). CD is the most frequent form of CS in children over 5 years of age. At all ages, corticotroph microadenoma are the commonest cause of CD. Macroadenomas occur in 10% of adult CD and are rarer in the paediatric age range[1,3,4,6,7]. Key presenting features in children include growth failure, weight gain and a change in facial appearance with development of moon face. Other common disorders reported in children include delayed sexual development, overproduction of adrenal androgens with pseudo-precocious puberty in girls and boys and hirsutism in pubertal girls[1,2,4,6]. The diagnosis of CS requires a series of standardised biochemical and radiological investigations (Table 2) (ref.[1,2,6,8]). Transsphenoidal pituitary surgery (TSS) consisting of selective removal of the adenoma is now considered first-line therapy for pediatric CD (ref.[7,9-11]).

The primary aim of CS treatment in children is rapid normalisation of serum cortisol due to the adverse affects of prolonged hypercortisolaemia on growth and development. Herein, we present four paediatric subjects with CD reported in the Czech Republic. We focus on initial symptoms of CS which can lead to early diagnosis and on typical symptoms of CS in children. We describe the diagnostic process leading to confirmation of CD and we emphasize the biochemical and radiological diagnostic difficulties.

PATIENTS AND METHODS

Description of subjects

Four pediatric patients (3 females and 1 male; mean age 13 years, range 11–14 years) with CD were investigated and treated in the pediatric endocrinology division of Faculty Hospital in Pilsen, Deparment of Paediatrics. Pediatric patients were diagnosed in our centre between 2005 and 2021. All patients fulfilled diagnostic criteria for CD.

METHODS

This retrospective study analysed initial and typical symptoms of CS in four CD subjects, their age and sex distribution, the mean length of symptoms prior to diagnosis, indication for examination by pediatric endocrinologist, biochemical and radiological diagnostic process leading to confirmation of CD, post-cure growth, sexual development and pituitary function after TSS. All patients had clinical features of hypercortisolaemia. The diagnosis of CD was biochemically based on confirmation of high urinary free cortisol excretion, loss of serum cortisol circadian rhythm, failure of serum cortisol to suppress during a low-dose dexamethasone suppression test (LDDST), a detectable 7.00 h plasma ACTH level (>10 pg/L), a corticotropin-releasing hormone stimulation test (CRH) and bilateral inferior petrosal sinus sampling for ACTH with CRH (BIPSS) performing for the differentiation of CD from ectopic ACTH secretion in patients with unvisible microadenoma on pituitary magnetic resonance imaging scan (MRI). Diagnostic tests were performed according to the published diagnostic endocrinology protocols (Table 2) (ref.[1,2,6,8]).

Table 1. ACTH-independent and ACTH-dependent causes of Cushing's syndrome.

ACTH-independent
1. Exogenous glucocorticoid administration
2. Adrenocortical tumor (adenoma or carcinoma)
3. Primary adrenocortical hyperplasia
a. Primary pigmented nodular adrenocortical disease (PPNAD)
b. Macronodular adrenal hyperplasia (AIMAH)
c. Mc-CuneAlbright syndrome
ACTH-dependent
1. Cushing's disease (ACTH-secreting pituitary adenoma)
2. Ectopic ACTH syndrome

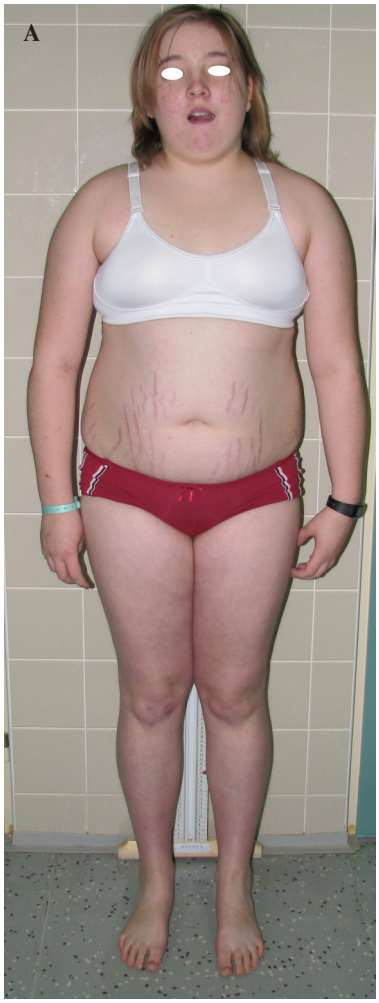
Table 2. Scheme of investigation for patients with suspected Cushing's syndrome.

Confirmation or exclusion of Cushing's syndrome
1. Urinary free cortisol excretion (24 h urine collection) daily for 3 days
2. Serum cortisol circadian rhythm study (09.00 h, 18.00 h, midnight (sleeping)
3. Low-dose dexamethasone suppresion test (LDDST)
• Dose: 0.5 mg 6 hourly (09.00 h, 15.00 h, 21.00 h, 03.00 h) for 48 h
• Dose for patients weighing <40 kg; 30 ug/kg/day
• Serum cortisol measured at 0 and 48 h
Definition of etiology of Cushing's syndrome
1. Plasma ACTH (09.00 h)
2. Corticotropin-releasing hormone stimulation test (CRH)
• Dose: 1.0 ug/kg i.v.
3. Adrenal or pituitary MRI scan
4. Bilateral inferior petrosal sinus sampling for ACTH with CRH (BIPSS)

RESULTS

Clinical symptoms of CS in CD patients at the time of diagnosis

Two of our four patients (50%, 2/4) had typical cushingoid appearance with obesity, moon face, striae at the time of diagnosis of CD (Table 3, Patients 1,2; Fig. 1,2). Two patients had subclinical presentation of



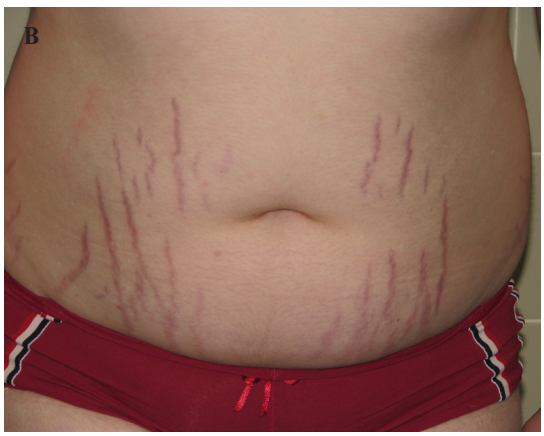


Fig. 1A. Patient 1. Typical cushingoid appearance with obesity, moon face, striae at the time of diagnosis of CD.
Fig. 1B. Patient 1. Purple striae in CS.

Table 3. Clinical features at diagnosis of Cushing's disease and indication for examination in our study group.

Patients (sex/age at diagnosis)	1 (♂/11 years)	2 (♀/14 years)	3 (♀/13 years)	4 (♀/14 years)
Indication for examination	progressive obesity	progressive obesity	fatigue muscle weakness sleep disorders	growth failure
Length of symptoms prior to diagnosis	2 years	2 years	2 month	1 year
Obesity	+	+	–	–
BMI kg/m² (body mass index) percentile	34.7 (>the 99th perc.)	29.4 (> the 99th perc.)	17.3 (the 25th perc.)	18.9 (the 25th–50th perc.)
Moon face	+	+	+	+
Striae	+	+	–	–
Growth failure	+	+	+	+
Overproduction of adrenal androgens/delayed puberty	pseudopubertas (pubic hair, penis stage III, testicular volume <4 mL)	hirsutism delayed puberty	hirsutism delayed puberty	hirsutism delayed puberty
Hypertension	+	+	+	–
Impaired glucose tolerance	+	+	diabetes mellitus	–
Emotional lability	–	–	depression insomnia	depression

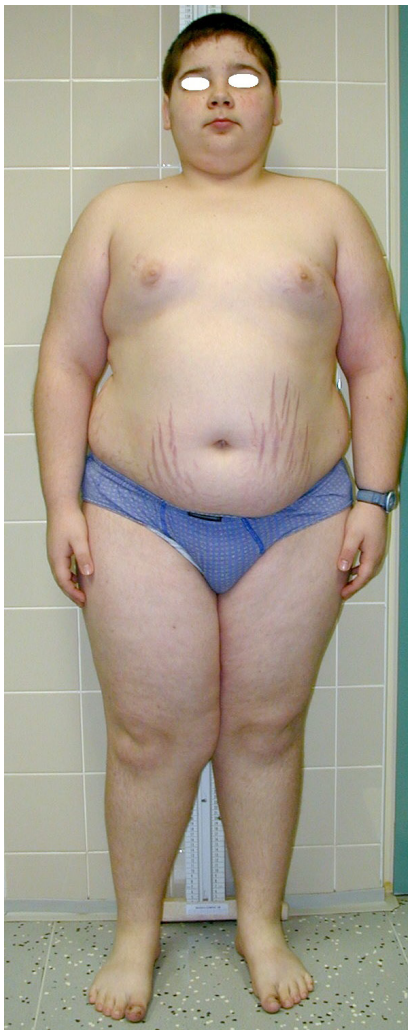
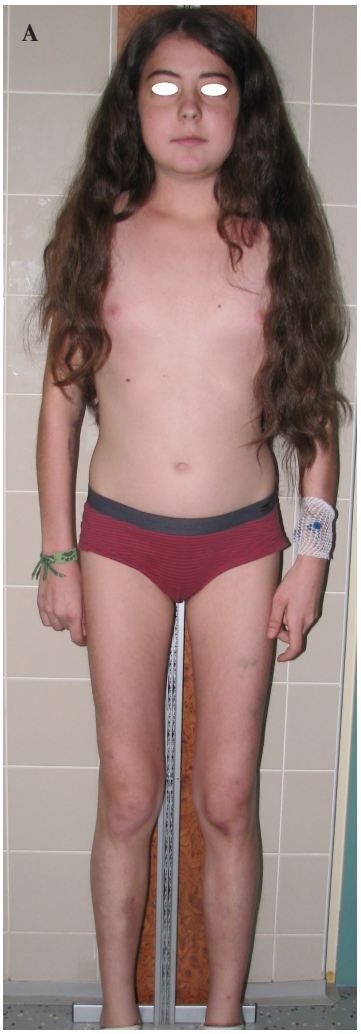
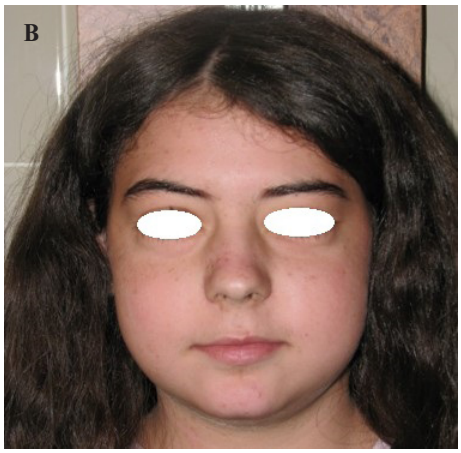


Fig. 2. Patient 2. Typical cushingoid appearance with obesity, moon face, striae at the time of diagnosis of CD.





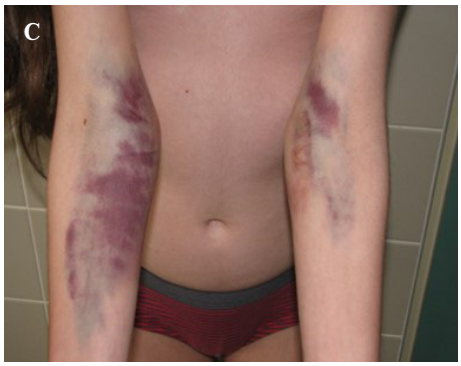


Fig. 3A. Patient 3. Subclinical presentation of CS only with moon face at diagnosis of CD.
Fig. 3B. Patient 3. Typical moon face in CS.
Fig. 3C. Patient 3. Fragile skin with bruising in CS.

CS only with moon face at the time of diagnosis (Table 3, Patients 3,4; Fig. 3,4). Indication for examination was progressive obesity in Patient 1 and 2 (Fig. 1,2), fatigue, muscle weakness and sleep disorders in Patient 3 and growth failure in Patient 4 (Fig. 3,4). The mean length of symptoms prior to diagnosis in four CD patients was 1.3 years (range 0.2–2.0) (Table 3,). Facial appearance with moon face was changed in all patients (100%). Striae were present in 2 patients (50%, 2/4) at the time of diagnosis of CD, in the other two patients (Table 3, Patients 3,4) striae gradually developed in the lower limbs; Patient 3 concurrently suffered from bruising and fungal infections. Patients 3 and 4 (50%) complained of fatigue, emotional lability (depression); Patient 3 suffered from insomnia. Hypertension (systolic or diastolic blood pressure >95th percentile for age and sex) was present in three patients (75%, Table 3, Patients 1,2,3). Patients 1 and 2 met criteria for impaired glucose tolerance; Patient 3 for diabetes mellitus. All patients (100%) had symptoms of overproduction of adrenal androgens with hirsutism in females (Table 3, Patients 2,3,4) and pseudopuberty in male at the age of 11 years (atypical advancement of pubic hair and penis Tanner stage III compared to prepubertal testicular volume <4 mL) (Table 3, Patient 1). All females had delayed sexual development. Growth failure with growth retardation was present in all of our subjects (100%) two years before CD diagnosis (Table 3, Fig. 5,6, pathological growth charts in Patients 3 and 4 with initial CS symptoms).

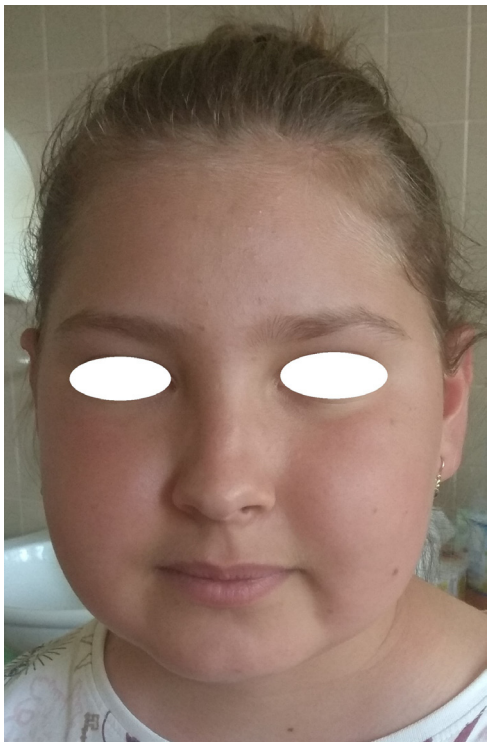


Fig. 4. Patient 4. Subclinical presentation of CS only with moon face at diagnosis of CD.

Table 4. Laboratory confirmation of Cushing's disease and pituitary imaging in our study group.

Patients (sex/age at diagnosis)	1 (♂/11 years)	2 (♀/14 years)	3 (♀/13 years)	4 (♀/14 years)
Serum cortisol circadian rhythm				
7.00 h (normal 250–600 nmol/L) 24.00 h (normal <50 nmol/L)	669 (7.00 h) 913 (24.00 h)	685 (7.00 h) 991(24.00 h)	1,903 (7.00 h) 1,267 (24.00 h)	729 (7.00 h) 665 (24.00 h)
Urinary free cortisol excretion (24 h urine collection) (normal <300 nmol)	1,600	1,219	11,404	1,304
Low-dose of dexamethasone supression test (LDDST; 0,5 mg, 6 hourly for 48 h) cortisol (normal <50 nmol/L, 6 h after the last dose)	288 → 57	668 → 287	1,520 → 510	729 → 342
ACTH (normal 10–60 pg/mL)	42 (N)	58 (N)	228 (↑)	45 (N)
Pituitary magnetic resonance imaging (MRI) scan → confirmation of microadenoma	–	+	+	–
Bilateral inferior petrosal sinus sampling (BIPSS) (CRH 100 ug i.v.)	ACTH ratio before >2 l.sin. (105/47 pg/mL)			ACTH ratio before >2 l.sin. (148/51 pg/mL)
confirmation of CD: central/peripheral ACTH ratio >2.0 before CRH i.v. central/peripheral ACTH ratio >3.0 after CRH i.v.	after >3 l.sin. (1,252/198) (problems with catheterisation l.dx.)			after >3 l.sin. (3,406/110) ACTH ratio before >3 l.dx. (298/51) after >1 l.dx. (158/110)

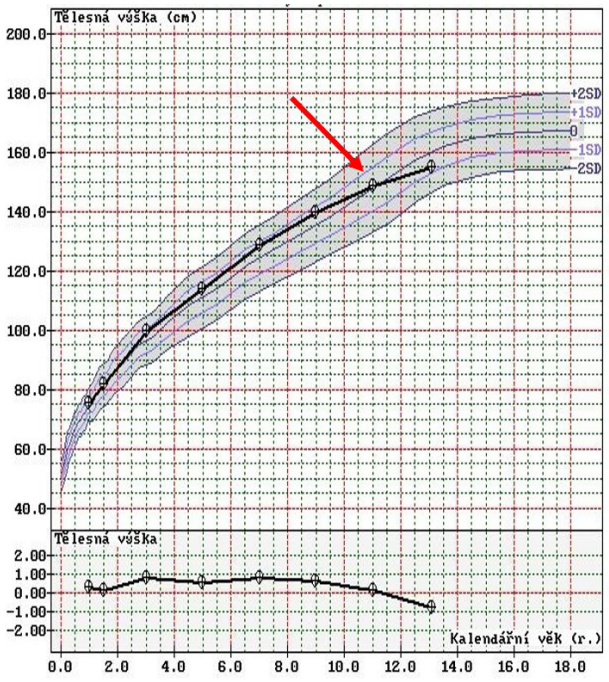


Fig. 5. Patient 3. Pathological growth chart with growth retardation two years before CD diagnosis in patient with initial CS symptoms.

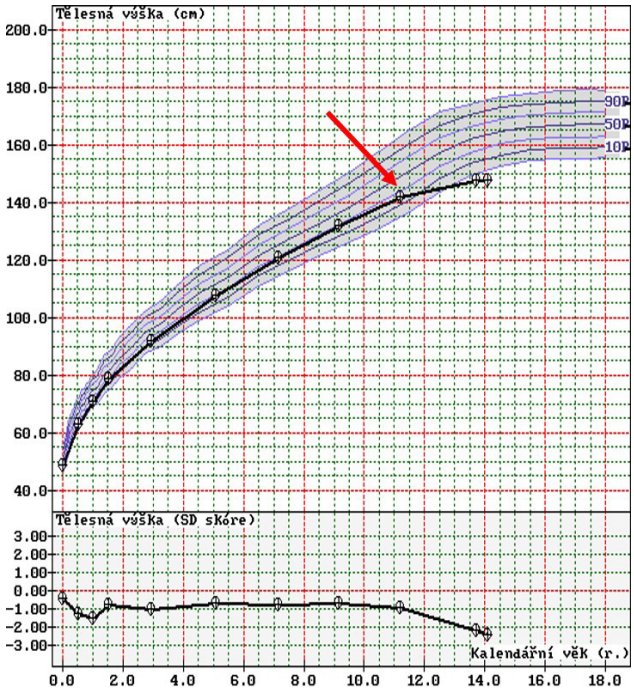


Fig. 6. Patient 4. Pathological growth chart with growth retardation two years before CD diagnosis in patient with initial CS symptoms.

Biochemical diagnosis of CD in analysed group

CS was biochemically diagnosed on the basis of high 24 h urinary free cortisol excretion, ranging from 1,219 to 11,404 nmol in all of our 4 subjects (normal urinary free cortisol <300 nmol/24 h); on loss of serum cortisol circadian rhythm, i.e. an elevated sleeping midnight cortisol level of >50 nmol/L, (ranging from 665 to 1,267 nmol/L in our group, normal midnight cortisol level <50 nmol/L) and on failure of serum cortisol to suppress to <50 nmol/L during a LDDST, ranging from 57 to 510 nmol/L in our group (the dexamethasone dose was 0.5 mg 6 hourly, 9.00, 15.00, 21.00, 3.00 h for 48 h; serum cortisol measured at 0 and 48 h) (Table 4). Diagnosis of ACTH-dependent CS (CD) was based on a detectable 7.00 h plasma ACTH level (>10 pg/L) in all of our patients, ranging from 42 to 228 pg/L (normal ACTH 10–60 pg/L) (Table 4). A CRH stimulation test (CRH 100 μg/kg i.v.) performing for the differentiation of CD from ectopic ACTH secretion in Patient 4 with unvisible microadenoma on pituitary MRI didn't confirm CD (serum cortisol did not increase by >20% and ACTH did not increase by >50%). BIPSS with CRH in Patients 1 and 4 with unvisible microadenoma on pituitary MRI confirmed central ACTH secretion (central to peripheral ACTH ratio >2.0 before and >3.0 after CRH 100 ug i.v. administration) (Table 4, Patients 1 and 4).

Radiological diagnosis of CD in analysed group

Preoperative MRI was performed in all of our subjects. Microadenomas with hypointense signal were visibile on pituitary MRI only in two patients, in Patient 2 on the right side of adenohypophysis (size 7 mm), and in Patient 3 on the left side (size 6 mm) (50%, 2/4, Table 4). Patient 1 and Patient 4 had invisible microadenoma on MRI. TSS confirmed, in accordance with BIPSS, macroadenoma in Patient 1 and microadenoma in Patient 4.

Transsphenoidal pituitary surgery, cure rate of TSS and outcome in analysed group

All four patients underwent TSS as the first-line therapy in Specialized Neurosurgery Center (The Military University Hospital Prague). Cure of CD by TSS was defined as an undetectable 9.00 h serum cortisol (<50 nmol/L).

In male Patient 1, the second TSS was successful, however, post-operative central diabetes insipidus (CDI) remained, as well as substituted panhypopituitarism including growth hormone, transient central hypocortisolismus (over three years) and spontaneous puberty. CD reccurence was 7 years later (age 18 years) with two unsuccessful TSSs and Leksell Gamma Knife stereotactic radiosurgery (GKSRS). This patient underwent bilateral adrenalectomy at the age of 20 years. Patient's 1 hight was 146 cm, BMI 34.7 (>99th percentile) at the time of CD diagnosis (age 11 years) and his final hight was 175 cm due to growth hormone therapy, his BMI 38.2 kg/m^2 (>99th percentile) in remission of CD at the age of 18 years (this patient was primarily obese).

Female Patient 2 has been in remission for 13 years after the first successful microadenoma surgical therapy with transient isolated substituted central hypocortisolism of over one year. Patient 2 had a height of 163 cm, BMI 29.4 (>99th percentile) at the time of CD diagnosis (age 14 years), and her final height was 168 cm outside the

genetically predicted range related to the parents' heights, BMI 24.8 kg/m² (the 90th percentile).

In female Patient 3 the first TSS was successful, and post-operative transient isolated substituted central hypocortisolism remained over one year. CD reccurence was 2 years later (age 15 years) with one unsuccessful TSS; then Gamma Knife stereotactic radiosurgery (GKSRS) was performed followed by poorly tolerated medical therapy (metyrapone and ketoconazole) aimed at lowering cortisol. She underwent bilateral adrenalectomy at the age of 18 years. Patient 3 had a height of 154 cm, BMI 17.3 kg/m² (the 25th percentile) at the time of CD diagnosis (age 13 years) and her final height was 161 cm in the genetically predicted range related to the parents' heights.

Female Patient 4 (age 14 years) has been in remission for 6 months after successful TSS confirming microadenoma, with transient post-operative central diabetes insipidus (CDI) and isolated substituted central hypocortisolism. Her height was 148 cm and BMI 18.9 kg/m² (the 25–50th percentile) at the time of diagnosis (age 14 years).

DISCUSSION

CD is a rare disorder in the pediatric age range, but may present a diagnostic and therapeutic challenge. If untreated, it results in significant morbidity, mortality and a reduction in quality of life. The recognition of CD features is crucial for early diagnosis and proper treatment leading to rapid normalisation of serum cortisol[1,3,6,12]. Here we report four paediatric subjects with CD from the Czech Republic.

Savage et al. analyzed gender distribution in 50 CD patients aged from 6 to 30 years and found a significant predominance of males in the pre-pubertal patients, similar incidence of males and females during puberty and an increasing predominance of females in the post-pubertal patients[2]. The peak incidence of pediatric CD is during adolescence with the median age of presentation of 14.1 years for 182 cases taken from the literature[2]. Our data are similar. The mean age in our study group of four CD patients was 13 years, range 11–14 years, with predominace of females.

Symptoms of CS in children are distinct from adults. The literature stresses supression of linear growth associated with weight gain and change in facial appearance with the development of a moon face as typical characteristics of hypercortisolaemia in childhood. Other typical symptoms frequently seen in pediatric patients are pseudo-precocious puberty in both sexes, hirsutism in pubertal girls due to excessive adrenal androgen secretion and pubertal delay or arrest caused by suppression of the hypothalamic-pituitary-gonadal axis by hypercortisolaemia[6]. Symptoms that are less seen in children compared to adults include sleep disruption, muscular weakness and problems with memory. Skin striae are also almost never present before the age of 5–7 years[1]. Savage et al investigated symptoms of CD in 37 patients aged from 5.8 to 17.8 years at the time of diagnosis. They emphasise that young children with CD often presented with only obesity and growth failure, without features of plethora, hirsutism, acne and striae[2]. Our observation is similar. In our group (Table 3), two of four patients (50%) had typical cushingoid appearance with obesity, moon face and striae at the time of CD diagnosis but two had subclinical presentation of CS only with development of moon face at the time of CD diagnosis. Striae were present only in two patients at the time of CD diagnosis. All patients had typical symptoms of overproduction of adrenal androgens with hirsutism in females and pseudopuberty in male. All females had delayed sexual development. Growth failure with growth retardation was present in all of our subjects two years before CD diagnosis. Two patients complained of symptoms less common in children such as fatigue, depression and insomnia.

Savage et al reported the mean length of symptoms prior to diagnosis in 37 CD patients 2.5 ± 1.7 years (range 0.5–6.6) (ref.[2]). The mean length of symptoms in our four CD patients was 1.3 years (range 0.2–2.0) (Table 3). Indication for examination in our group was progressive obesity, fatigue, muscle weakness, sleep disorders and growth failure (Table 3).

CS was biochemically confirmed in all of our four CD patients (Table 4). Storr et al published, in 2011, that majority of paediatric (8%) and adult CD patients (7%) failed to suppress serum cortisol levels during a LDDST (ref.[6]). We observed only one borderline result in our Patient 1 with supression of serum cortisol to 57 nmol/L during the LDDST (Table 4). Diagnosis of CD was based on detectable ACTH level above 10 pg/L in all of our patients. ACTH was in normal range in three CD patients and above normal range only in one patient (Table 4).

Savage et al. reported that most ACTH-secreting pituitary tumours in children are microadenomas with a diameter <5 mm and approximately 50% of them are unvisible on pituitary MRI. A CRH test and BIPSS contribute to confirming the diagnosis of CD and excluding ectopic ACTH syndrome. BIPSS also provide a method of identifying the lateral or the central sources of pituitary ACTH secretion[2]. Storr et al published CD confirmation by the CRH stimulation test for the differentiation from ectopic ACTH secretion in 92% pediatric patients (36/39) (ref.[6]). According to our data, the CRH test in our Patient 4 with unvisible microadenoma on pituitary MRI did not confirm CD but BIPSS in this Patient 4 and in Patient 1 with unvisible microadenoma on MRI confirmed CD (Table 4). In our opinion, BIPSS is crucial for CD diagnosis.

TSS resection of the ACTH secreting pituitary tumor remains the first-line therapeutic intervention in CD (ref.[2,7]). In specialized centers, the success rate of the first TSS is close to or even higher than 90% (ref.[13]). The succsess rate of repeated TSS is lower than the initial surgery, closer to 60% (ref.[1]). Biochemical cure of CD by TSS was defined as a persistently undetectable 9.00 h serum cortisol (<50 nmol/L) within a week of surgery[9]. After successful surgical therapy, there is a transitory hypocortisolism period due to supression of normal adrenal axis requiring glucocorticoid replacement therapy.

Post-operative complications include CDI, syndrome of inappropriate antidiuretic hormone secretion, hypopituitarism, infection and pituitary apoplexy. For patients not achieving an initial remission or developing recurrence after an initial remission, therapeutic options are limited. Pituitary radiotherapy is generally avoided in children due to complications of radiation (cerebral cortex toxicity, hypopituitarism). However, GKSRS is now available for CD treatment. Medical therapy for CD serves primarily in an adjunctive role after unsuccessful pituitary surgery. There are three mechanisms of action for drugs used in medical therapy: modulation of ACTH release, inhibition of adrenal steroidogenesis and glucocorticoid receptor blockade. Adrenalectomy is an option for refractory CD (ref.[1,14]).

All of our four patients underwent TSS as the first-line therapy in Specialized Neurosurgery Center. Summarilly, two patients are in remission of CD so far after first TSS, two patients with reccurent CD required repeated TSS, GKSRS followed by medical therapy and they underwent finally bilateral adrenalectomy. Three of our four patients had transient isolated central hypocortisolism lasting 1–3 year, only one patient with macroadenoma had permanent post-operative CDI and panhypopituitarism.

CONCLUSION

Cushing's disease is the commonest cause of CS in children over 5 years of age. The recognition of features which might alert a clinician toward the CD diagnosis is crucial for early diagnosis and proper treatment. Our retrospective analysis confirmed the presence of growth retardation and changes in facial appearance with the development of a moon face as the first symptoms of CS. From our observation, growth retardation occurs prior to the moon face. A CRH test and especially BIPSS contribute to confirming the diagnosis, thus excluding ectopic ACTH syndrome in children with invisible adenoma on pituitary MRI. TSS resection of the ACTH secreting pituitary tumor in specialized centers with experienced neurosurgeons is the first-line therapy in CD. Pediatric endocrinologists benefit from close consultation with colleagues in adult endocrinology.

ABBREVIATIONS

CD: Cushing's disease; CS: Cushing's syndrome; TSS: transsphenoidal pituitary surgery; CRH test: corticotropin-releasing hormone test; ACTH: adrenocorticotropic hormone; BIPSS: bilateral inferior petrosal sinus sampling for ACTH; MRI: magnetic resonance imaging; LDDST: low-dose dexamethasone suppression test; CDI: central diabetes insipidus; GKSRS: Gamma Knife stereotactic radiosurgery

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