# 9 Cushing's Syndrome in Children and Adolescents

*George Mastorakos, Christina Kanaka-Gantenbein*

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## 9.1 Definition and Etiology

*Cushing's syndrome* is a clinical syndrome caused by chronic glucocorticoid excess [3, 30, 31, 42, 44, 45]. The latter may be *exogenous,* as a result of chronic, long-standing exposure of the organism to the exogenous administration of glucocorticoids or ACTH [30, 31, 44, 45], or *endogenous,* due to the hypersecretion of cortisol, ACTH or CRH. The endogenous hypersecretion of ACTH of pituitary origin is called Cushing's disease.

The commonest cause of Cushing's syndrome in children and adolescents is by far the *exogenous administration* of glucocorticosteroids (iatrogenic Cushing's syndrome) as treatment of several chronic diseases, such as steroid-responsive, steroid-dependent nephrotic syndrome, juvenile chronic arthritis or severe asthma bronchiale [2, 31, 44]. Rarely, chronic local use of steroids in the form of inhaled steroids, dermatological creams or ointments, or even eye or nasal drops, has been reported to induce iatrogenic Cushing's syndrome [2, 10, 16, 17, 43].

*Endogenous Cushing's syndrome* is the result of excessive pituitary ACTH (Cushing's disease) or ectopic ACTH secretion (extremely rare in pediatric patients) [30, 31, 42, 44, 45, 48, 49]. These causes constitute *ACTH-dependent Cushing's syndrome,* accounting for about 75–85% of endogenous Cushing's syndrome cases in mostly peripubertal patients [4, 31, 48, 49]. A very small number of ACTH-dependent cases are due to ectopic CRH-secreting tumors, mainly reported in older (adult) patients. Furthermore, endogenous Cushing's syndrome can be the result of autonomous cortisol secretion by a cortisol-secreting adrenal tumor, bilateral micronodular or macronodular adrenal hyperplasia [5, 20, 30, 44, 45, 54] or other autonomous adrenal processes. These causes constitute *ACTH-independent Cushing's syndrome*. In children younger than 7 years ACTH-independent Cushing's syndrome, mainly due to adrenal carcinomas, is more frequently seen than ACTH-dependent Cushing's syndrome [20, 29, 30, 44, 45, 47] and is quite often accompanied by oversecretion of adrenal androgens. It is estimated that adrenocortical tumors account for about 70% of endogenous Cushing's syndrome in young children [20, 29, 44, 47]. Finally, rare cases of ACTH-independent Cushing's syndrome are due to activating mutations of the ACTH-receptor coupled Gs alpha subunit leading to cortisol hypersecretion in the broader spectrum of McCune-Albright syndrome [12, 23].

## 9.2 Incidence

Endogenous Cushing's syndrome is rare in childhood and adolescence. The incidence of endogenous Cushing's syndrome, in general, is two to five new cases per million of general population per year, with a 9:1

female to male ratio [30, 31, 42, 44]. About 10% of these new cases occur in childhood or adolescence. However, this female to male (F/M) preponderance observed in adulthood is not seen in pediatric patients [6, 31, 49]. In the long series of the National Institutes of Health (NIH) experience we found that in prepubertal children the F/M ratio was 1/5 whereas for adolescents this ratio was 3/1, indicating that there was a shift towards female preponderance after the onset of puberty and, therefore, the sexual dimorphism of the incidence of Cushing's syndrome in adulthood is clearly associated with puberty. Due to the rarity of endogenous Cushing's syndrome such young patients should optimally be managed by a multidisciplinary team consisting of a pediatric endocrinologist, an adult endocrinologist, a neuroradiologist, a neurosurgeon with special experience in transphenoidal surgery in young age as well as a specialized surgeon on adrenals and a radiotherapist [6, 26, 31, 48, 49].

## 9.3 Clinical Presentation

The main clinical features of pediatric patients with Cushing's syndrome differ somewhat from those observed in adult Cushing's patients (Fig. 1). The predominant features according to different series are reported in Table 1. They comprise weight gain usually with round moon facies, growth failure, fatigue, pubertal delay or arrest, hypertension, hirsutism, acne and striae [6, 26, 31, 34, 49, 50, 55]. It is noteworthy that striae are more frequent among older patients than among younger ones [55]. Further presenting symptoms are headache, emotional lability and features of pseudoprecocious puberty in young patients due to the adrenal androgen excess. Mental or behavioral problems are only rarely reported in children and adolescents with Cushing's disease, in contrast to the most frequent mental changes or job performance deterioration observed in adult patients with Cushing's disease [30, 31, 44, 49]. However, Devoe et al. reported as many as 44% of children and adolescents with Cushing's disease presenting with compulsive behavior and overachievement at school [6]. In cases of adrenocortical carcinoma various degrees of virilization due to the adrenal androgen excess may be the prevailing clinical finding [29, 31, 44, 47].

**Bone Age** ▸ Bone age of Cushing's patients may be retarded due to the long-standing hypercortisolism [31, 43, 48, 49]. However, if adrenal androgen excess is present, bone age may be even advanced [31, 44, 49]. Delayed bone age was found in 13% of the patients studied by Devoe et al. [6]. In the NIH series comprising predominantly adolescents, bone age was not found to be delayed [31] (Fig. 2). The combination of the retarding effect of hypercortisolism and the accelerating effect of androgens may in some cases lead to a bone age appropriate for the chronological age of the patient [31, 44, 49].

**Bone Mineral Density** ▸ The long-standing hypercortisolism may also have a negative effect on the bone mineral density of these patients, who may present with osteopenia or even osteoporosis [1, 6, 27].

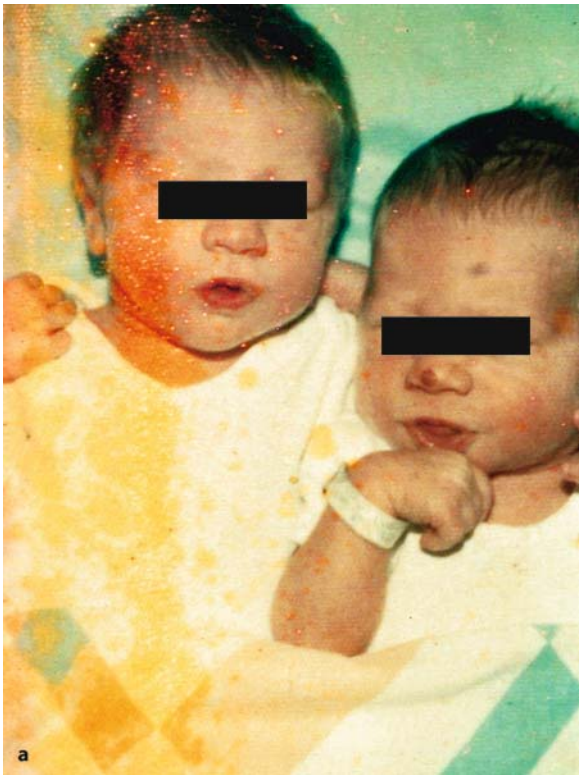
## 9.4 Diagnostic Assessment: Laboratory Investigation

### 9.4.1 Positive Diagnosis of Endogenous Hypercortisolism

The first step in the diagnosis of endogenous Cushing's syndrome is the biochemical confirmation of hypercortisolism. The most frequently used biochemical investigations are listed below.

**Table 1.** Clinical features at presentation

| Clinical manifestations | Savage et al. [49] | Devoe et al. [6] | Magiakou et al. [31] | Total |
|---|---|---|---|---|
| Weight gain | 100% | 92% | 90% | 90–100% |
| Growth failure | 71% | 84% | 83% | 71–84% |
| Hypertension | 75% | 63% | 47% | 47–75% |
| Pubertal delay/arrest | | 60% | 78% | 60–78% |
| Hirsutism | 53% | 46% | 78% | 46–78% |
| Striae | 53% | 36% | | 36–53% |
| Acne | | 46% | 47% | 46–47% |
| Emotional lability | | 44% | | 44% |
| Fatigue | | 67% | 44% | 44–67% |





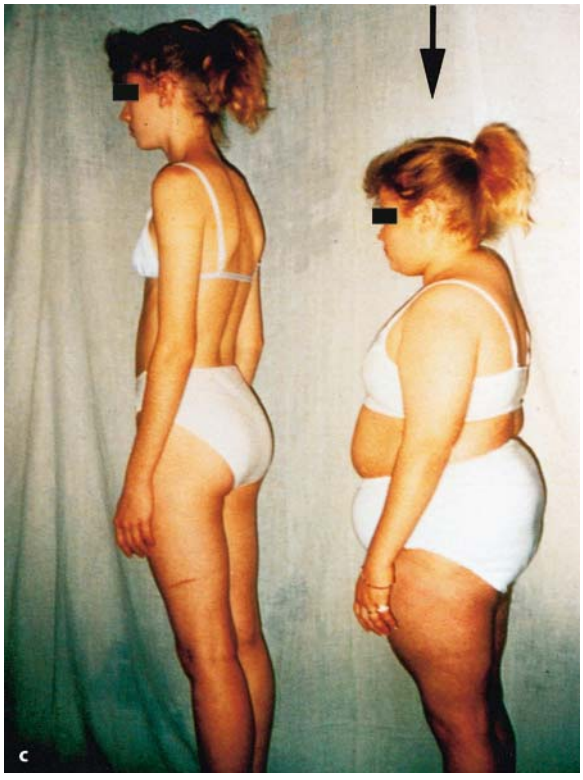



**Fig. 1a–c.** Chronological evolution of the clinical presentation of endogenous Cushing's syndrome in a young girl as compared to her healthy twin sister. (Courtesy of G.P. Chrousos)

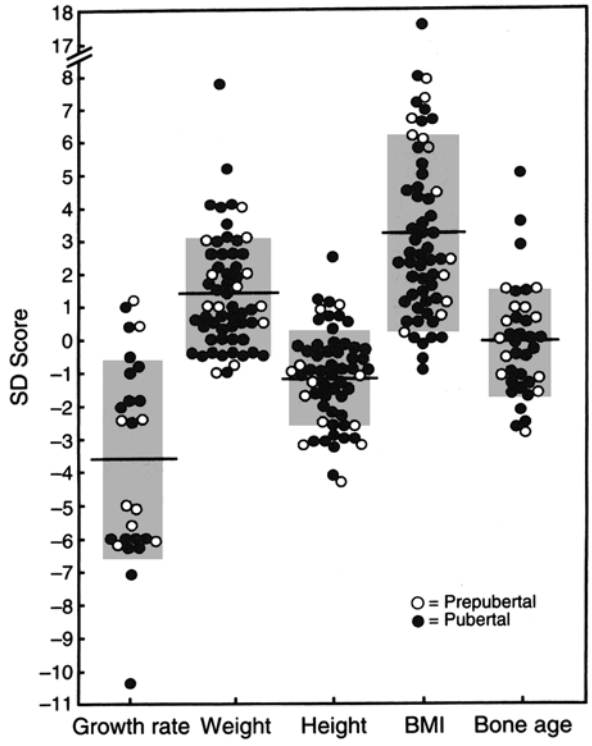



**Fig. 2.** Growth rate, weight, height, body mass index (*BMI*), and bone age of the NIH series as compared with expected values for age and sex [31]. The *horizontal lines* and the *shaded bars* indicate the means ± SD

#### *9.4.1.1 Baseline Biochemical Investigations*

*The 24-h mean urinary free cortisol (UFC) excretion* (corrected for body surface area) is an important first-line test. Values consistently in excess of 300 µg/day are virtually diagnostic for Cushing's syndrome [30]. Urinary free cortisol remains constant throughout life, when adjusted for square meter of body surface area, thus obviating establishing age-specific normal values in children or obese individuals. Normal values lie <70 µg/m$^2$/day [30] or <80 µg/m$^2$/day [6] according to different authors.

**The 24-h Mean Urinary Excretion of 17-OH-CS (17-OH-Corticosteroids)** ▶ High urinary 17-OH-CS excretion, i.e. more than 5 mg/m$^2$/day, also suggests Cushing's disease. In the series of Devoe et al. [6], the 24-h mean urinary 17-OH-CS excretion was a more sensitive marker than UFC, since 100% of Cushing's disease patients had high urinary 17-OH-CS excretion as compared to only 86% of patients demonstrating high UFC excretion (i.e. UFC>80 µg/m$^2$/day) [6].

**Serum Cortisol and ACTH Circadian Rhythm** ▶ In most cases of Cushing's disease the normal circadian rhythm of ACTH and cortisol secretion is abolished. It is therefore suggested that five consecutive morning and five consecutive evening plasma samples should be drawn for determination of diurnal variation of cortisol and ACTH secretion [30, 46, 49].

*Salivary cortisol concentrations* nowadays constitute an alternative to the multiple venepunctures needed for the determination of plasma cortisol variation. In a recent publication [13], measurement of salivary free cortisol by radioimmunoassay at 7.30 A.M., bedtime and midnight discriminated accurately children with Cushing's disease from healthy obese or non-obese children. Concretely, salivary cortisol was undetectable in 66% of healthy children at bedtime and in 90% of them at midnight. It has therefore been shown that, with cut-off points that excluded healthy children, a midnight salivary cortisol value of 0.27 µg/dl (7.5 nmol/l) identified 92.8% of Cushing's syndrome children, whereas a bedtime value of >1 µg/dl (≥27.6 nmol/l) detected 83.3% of Cushing's syndrome children, with the same diagnostic accuracy as the UFC per square meter body surface area [13]. Furthermore, in another study, it has been demonstrated that the combination of salivary cortisol determination at 2300 hours as well as after the dexamethasone suppression test is an easily performed and non-invasive method with high specificity and sensitivity for diagnosing Cushing's syndrome in children [35].

#### *9.4.1.2 Dynamic Tests*

**Low-dose Dexamethasone Suppression Test** ▶ In children 15 µg/kg body weight (maximal dose 1 mg) dexamethasone is given at midnight and blood for cortisol determination is withdrawn the next morning (8.00 A.M.). A morning plasma cortisol level of >5 mg/dl after midnight dexamethasone administration suggests hypercortisolism.

**Diagnostic Value** ▶ This is a screening test that is of use only when positive. The expected fall in cortisol levels may fail to occur in normal subjects because of stress, intercurrent psychiatric or other chronic or acute illnesses, states referred to as pseudocushing states [11, 30].

### 9.4.2 Positive Diagnosis of Endogenous Cushing's Syndrome; Diagnosis of Cushing's Disease

#### *9.4.2.1 Dynamic Tests*

**Standard Low- and High-dose Dexamethasone Suppression Tests** ▶ Samples of 24-h urine to determine concentrations of 17-OH-CS, free cortisol and creatinine are collected for at least 2 days before and during the entire period of dexamethasone administration, beginning at 8.00 A.M. Venous blood samples are also obtained daily at 8.00 A.M. to determine levels of cortisol. Dexamethasone is administered successively in a low dosage of 10 µg/kg body weight up to a maximum of 0.5 mg every 6 h on days 3 and 4 (standard low-dose dexamethasone suppression test), and a high dosage of 50 µg/kg body weight up to a maximum of 2 mg every 6 h on days 5 and 6 (high-dose dexamethasone suppression test). A weight-adjusted dosage of 20 µg dexamethasone/kg body weight has been recommended in pediatric patients for the standard low-dose test. Some protocols propose 3 days on low dosage and 3 days on high dosage [11, 34].

**Evaluation** ▶ The response to the standard low-dose dexamethasone suppression test is considered normal when serum cortisol concentrations on day 4 fall to <5 µg/dl (138 nmol/l) or to 50% of baseline levels, urinary 17-OH-CS levels decrease to <3 mg/24 h (8.3 µmol/day) or to values approaching zero and UFC levels fall to less than 50% of basal levels.

The normal response to the high-dose dexamethasone suppression test is observed when serum cortisol concentration falls to less than 1 µg/dl (27 nmol/l) and when levels of urinary 17-OH-CS or free cortisol decline to less than 90% of baseline concentration at the end of the test.

**Diagnostic Value** ▶ The standard low-dose test distinguishes normal subjects from patients with Cushing's syndrome in whom suppression is incomplete or never occurs. The high-dose test distinguishes patients with Cushing's disease (about 90% of these patients demonstrate suppression) from those with an adrenal adenoma, carcinoma or ectopic ACTH producing-tumors (who do not demonstrate any suppression) [11]. Suppression is incomplete in patients with adrenal incidentalomas [60].

**CRH Stimulation Test** ▶ During this test 1 µg CRH/kg body weight is injected i.v. Blood is withdrawn for determination of ACTH and cortisol 15 min before and 0, 15, 30, 60, 90, and 120 min after treatment [38, 40]. When baseline urinary steroid excretion is elevated, a CRH response is considered to be indicative of Cushing's disease if the plasma ACTH or cortisol values increase above the mean baseline value by at least 34% or 20% respectively [38, 40].

#### *9.4.2.2 Imaging Studies*

**Magnetic Resonance Imaging** ▶ Magnetic resonance imaging (MRI) scanning with gadolinium is the method of choice to visualize pituitary adenoma with a higher sensitivity than a computed tomography (CT) scan. However, since the majority of corticotroph microadenomas have a diameter of less than 5 mm, many are not visible even in the most advanced MRI scan [49].

**CT Scan** ▶ As already mentioned, CT scanning is not a method of choice to visualize pituitary microadenomas. In the case of ACTH-independent Cushing's syndrome, MRI or CT of the adrenals is performed to visualize the androgen secreting space-occupying lesion [29, 47].

#### *9.4.2.3 Invasive Diagnostic Methods*

**Bilateral Inferior Petrosal Sinus Sampling Before and After the Administration of CRH** ▶ The most direct way to demonstrate pituitary hypersecretion of ACTH is to document a central to peripheral vein ACTH gradient in blood draining the tumor [30, 41, 42, 49].

**Method** ▶ After a catheter is positioned in each inferior petrosal sinus, blood samples are withdrawn simultaneously from each sinus and from a peripheral vein: twice immediately before the peripheral venous injection of 1 µg of ovine CRH per kilogram of body weight and twice more, 2–3 min and 5–6 min after the injection [41]. If the sinus to peripheral vein plasma ACTH ratio for either sinus is ≥2.0 in either of the two basal sets of samples or ≥3.0 in either of the two sets of samples obtained after CRH injection, the diagnostic accuracy, sensitivity and specificity of the procedure are all 100%. The test is less reliable when the maximal ACTH concentration in the inferior petrosal sinus is less than 20 pg/ml (<4.4 pmol/l).

**Diagnostic Value** ▶ Central to peripheral ACTH ratios >2 indicate central ACTH secretion. The interpetrosal sinus ACTH gradient is able to indicate lateralization of

ACTH secretion that in most cases is confirmed at surgery [41,49]. The inferior petrosal sinus sampling gives an 82% prediction of correct tumor lateralization.

#### *9.4.2.4 Diagnostic Criteria*

The diagnosis of Cushing's disease is based on several of the above-mentioned parameters. A suggested algorithm of diagnostic assessment is presented in Fig. 3. Absent diurnal cortisol rhythm was found in 100% of Cushing's patients in several studies [6, 49]. As previously mentioned, according to Devoe et al., high 24-h urinary 17-OH-CS excretion (i.e. levels>5 mg/m$^2$/day) was found in 100% of their Cushing's patients, while high urinary free cortisol excretion (i.e. levels >80 μg/m$^2$/day) was found in 86% of their Cushing's patients [6]. Failure to suppress urinary UFC under

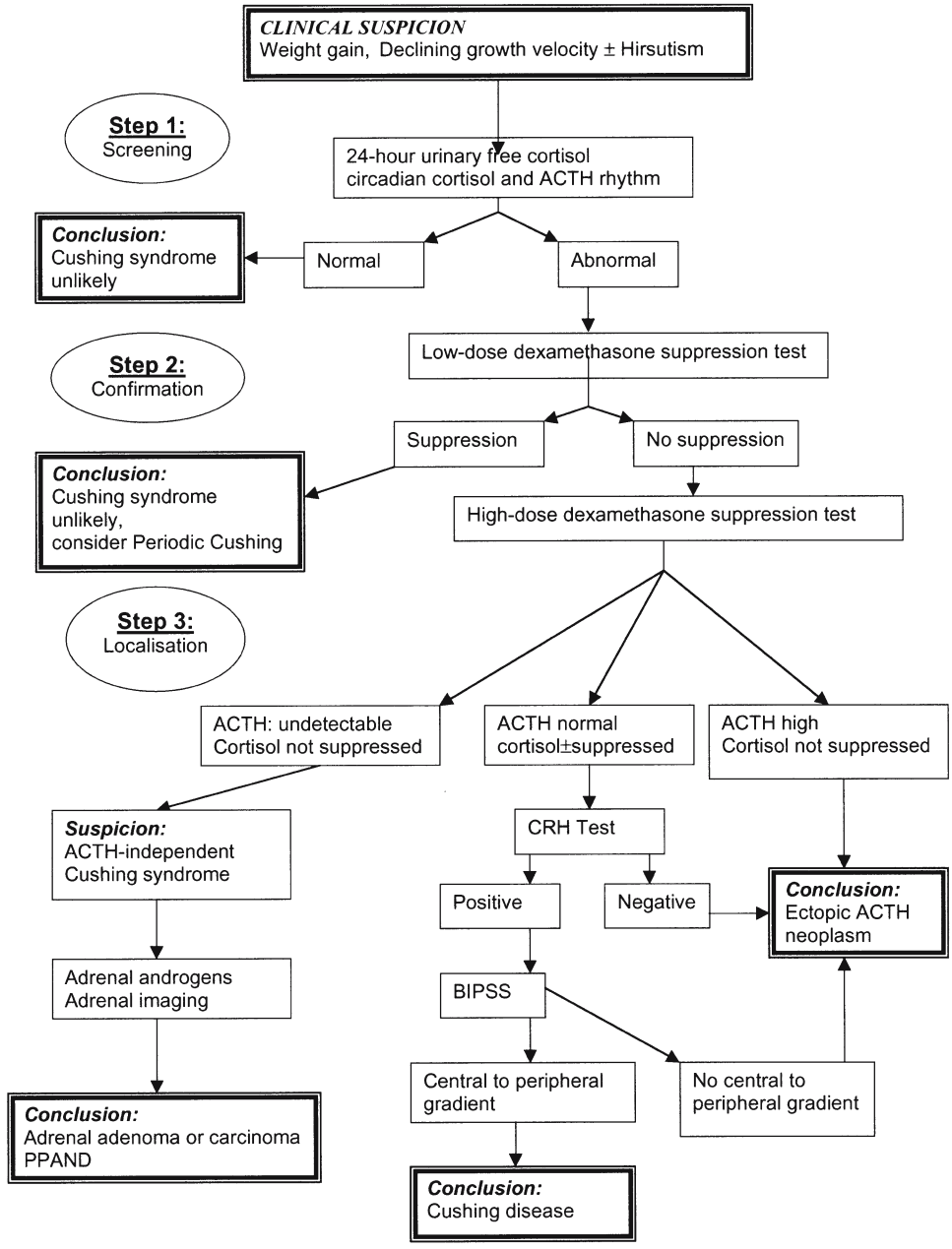



**Fig. 3.** Algorithm of diagnostic assessment in case of suspicion of Cushing's syndrome according to several authors [11, 34, 46]

25 μg/m²/day or urinary 17-OH-CS under 1.5 mg/m²/day after the standard low-dose dexamethasone suppression test was seen in 86% of their patients, while failure of suppression of UFC excretion or 17-OH-CS excretion by 50% or more was observed in 92% of their Cushing's patients [6].

Also in the study of Savage et al. [49] after the standard low-dose dexamethasone suppression test cortisol failed to suppress <50 nmol/l after 48 h in Cushing's patients. During the high-dose dexamethasone suppression test all patients with Cushing's disease showed suppression of cortisol to less than 50% of the basal pre-dexamethasone level, while no suppression was seen in one patient with an adrenal adenoma and in another with primary pigmented nodular adrenal hyperplasia (both cases of ACTH-independent Cushing's syndrome). The CRH test showed an increase of cortisol production in Cushing's disease patients, while patients with adrenal adenoma, primary pigmented nodular adrenal hyperplasia or ectopic ACTH production did not show a cortisol response to CRH [49].

## 9.5 Diagnosis

The diagnosis of endogenous Cushing's syndrome in children and adolescents is usually retarded. It is estimated that the elapse time between the onset of the clinical syndrome and the diagnosis is equal to or greater than 2 years [6, 26, 49], ranging from 0.5 to 10 years. A major effort must be therefore made to sensitize health care providers and specifically pediatricians to recognize Cushing's syndrome as early as possible. Thus, the deleterious and often non-reversible effects of hypercortisolism on growth and bone mineral density can be minimized, since the age of onset and duration of hypercortisolism before cure are features that contribute to the severity of growth failure and irreversible bone loss.

## 9.6 Treatment of Cushing's Syndrome

### 9.6.1 Cushing's Disease

#### *9.6.1.1 Transphenoidal Surgery*

Transphenoidal surgery with selective microadenomectomy is the worldwide accepted first-line treatment for Cushing's disease in both adults and children [6, 8, 9, 26, 31, 36, 41, 42, 49, 52]. In many centers transphenoidal surgery is accompanied by hemihypophysectomy [26, 31].

**Preoperative Treatment** ▶ In some centers [49] children and adolescents with Cushing's disease were preoperatively treated with either metyrapone or ketoconazole or a combination of both for a period of 4–8 weeks preoperatively, in order to normalize circulating cortisol levels. The dose of each drug was 0.75–2.25 g/day and 0.3–0.6 g/day for metyrapone and ketoconazole, respectively.

**Complications of Transphenoidal Surgery** ▶ In experienced hands, transphenoidal surgery seems to be a safe procedure with only minimal complications. About 10% of patients have postoperative complications, including cerebrospinal fluid rhinorrhea, usually transient diabetes insipidus or visual disturbances [41, 61]. In the NIH series panhypopituitarism has been reported in 19% of patients operated on [31]. Eight out of 42 operated patients (19%) presented transient diabetes insipidus that did not require medication at discharge in the series published by Devoe et al. [6], while in the series of Savage et al. [49] 1 patient out of 17 (5.9%) developed panhypopituitarism and two diabetes insipidus (11.8%). In the Mayo Clinic series, up to 6% of patients ended up with endocrine dysfunction, while 9/22 (40.9%) of patients presented transient diabetes insipidus [26].

**Definition of Cure After Transphenoidal Surgery** ▶ Postoperatively hydrocortisone is given for a minimum of 24 h. After transphenoidal surgery, serum cortisol levels are measured daily at 09.00 hours, at least 12 h after the last dose of hydrocortisone. Undetectable postoperative serum cortisol levels <50 nM define postoperative cure [49, 59]. However, residual pituitary function is among the criteria by which the surgical outcome is judged.

**Cure and Recurrence Rates** ▶ Rates of cure are reported to range from 70–95% in adult patients with Cushing's disease. In childhood cure rates are reported to reach 50–73% according to the experience of several centers [6, 8, 26, 36, 49]. It seems therefore that cure rates are much higher in adult patients when compared to childhood or adolescence Cushing's disease. This may be indicative of a more aggressive behavior of Cushing's disease at young ages or of a more conservative operative treatment at young ages [26]. However, since transphenoidal surgery, particularly in children, is a highly skilled procedure, the cure rates

may also be determined by the experience and skillfulness of the neurosurgeon [31, 41, 49]. For example, in the NIH experience cure rate after transphenoidal surgery for Cushing's disease in childhood is as high as 90% [31]. In this series 30% of the operated patients have been treated by hemihypophysectomy [26, 31]. In that cohort endocrine deficiency postoperatively was found in 19% of cases [31]. On the other hand, in the Mayo Clinic experience [26], cure rate after first transphenoidal surgery was lower, but also the percentage of endocrine deficiency was lower, namely only 6%. Thus, more aggressive surgery improves the efficacy of treatment but increases the incidence of postoperative hypopituitarism [26, 31, 33]. Furthermore, a significant number of the NIH patients have already been operated on in another center before being admitted to NIH. However, it should be emphasized that the duration of the long-term follow-up in the reported series can significantly influence the recurrence rates [6, 26, 31, 49] since many recurrences occur only about 4 years postoperatively [26]. Follow-up of patients in the NIH series extended up to 5 years with a mean of 22 months. Thus, the low recurrence rate in that cohort may be explained by the short follow-up period in that series [31]. In accordance with that, in the Mayo Clinic series, cure rate after long-term follow-up was only 50%, since after 5 years of follow-up 21% of patients presented with recurrence, and when follow-up was extended to 10 years, recurrence rate increased to 42.2% [26]. In the series of the University of San Francisco, follow-up was extended up to 13 years [6] and the overall remission rate after transphenoidal surgery was 73%, while the mean time to recurrence was 4.2 years (ranging from 0.75–6.2 years) [6]. Finally, in the London experience the median period of follow-up was 8 years (ranging from 0.5–24 years) and cure rate after transphenoidal surgery alone was 56%. Patients with persisting hypercortisolemia underwent pituitary irradiation. When both therapeutic strategies were considered together (transphenoidal surgery alone or surgery followed by pituitary irradiation) the overall cure rate for the median of 8 years of follow-up was 82% [49].

#### *9.6.1.2 Second-Line Treatment*

There is no clear agreement on the optimal therapy after unsuccessful transphenoidal surgery. The options are: repeat transphenoidal surgery, pituitary radiotherapy, adrenalectomy or drug therapy such as ketoconazole [42, 49, 52, 61]. The decision is primarily taken after consideration of the experience of the neurosurgeon, the general surgeon, the radiotherapist and of course in consideration of possible side-effects and residual sequelae of each therapeutic modality.

**Pituitary Radiotherapy** ▸ Pituitary radiotherapy is used in specialized centers with good experience of the treatment of pediatric Cushing's disease. There is evidence that Cushing's disease in children responds to pituitary radiation treatment more readily than does Cushing's disease in adults [9, 14, 26, 49, 51]. In cases where transphenoidal surgery fails to cure the patient, pituitary irradiation may lead to complete cure. The addition of pituitary radiotherapy as second-line treatment has brought the cure rate to over 80% in centers where transphenoidal surgery resulted in 50% cure rate [49, 52]. The dose currently used is 4,500–5,000 cGy [26, 49, 52] in 25 fractions over 35 days using a 6 MV linear accelerator. Until radiotherapy becomes effective, hypercortisolemia is controlled with ketoconazole at a dose of 200–600 mg/day and metyrapone at a dose of 750 $mg^{-3}$ g/day with or without aminoglutethimide (1 g/day) or o'p'DDD (3 mg/day) [49].

**Definition of Cure After Pituitary Radiotherapy** ▸ Cure of Cushing's disease after radiotherapy [52] is defined as mean serum cortisol on a 5-point day curve of less than 150 nM (5.4 μg/dl) after discontinuation of medical treatment in addition to midnight serum cortisol of less than 50 nM (1.8 μg/dl) and suppression of serum cortisol to less than 50 nM on the standard low-dose dexamethasone suppression test [52]. According to the London experience, based on young patients who underwent radiotherapy shortly after transphenoidal surgery because of persisting postoperative hypercortisolemia, indicating lack of cure, the mean interval from radiotherapy to cure (defined as mean serum cortisol on a 5-point day curve <150 nM) was 0.94 years, ranging from 0.25–2.86 years, while recovery of pituitary-adrenal function (defined as mean cortisol 150–300 nM) occurred at 1.16 years, ranging from 0.4–2.86 years postradiotherapy. Patients were followed up for a mean of 6.9 years (ranging from 1.4–12 years) [49, 52].

**Side Effects of Radiotherapy** ▸ After pituitary radiotherapy, *GH deficiency* occurred in 86% of patients. However, long-term follow-up to 9.5 years postradiotherapy indicated some recovery of GH secretion and preservation of other anterior pituitary function [49, 52]. The risk of precocious puberty after cranial irra-

diation is a well-known phenomenon and should also be taken into consideration in the decision of radiotherapeutic intervention, since the combination of GH deficiency with precocious puberty can significantly compromise final height [25, 39, 49, 52].

#### *9.6.1.3 Third-Line Treatment*

**Bilateral Adrenalectomy** ▶ This option has been most usually considered in older studies [18, 22, 37, 58]. However, the higher incidence of Nelson's syndrome after adrenalectomy in childhood renders this treatment modality not a preferred one [18, 26, 37, 58].

#### *9.6.1.4 Fourth-Line Treatment*

**Drug Therapy: Metyrapone or o,p DDD** ▶ These treatment modalities are rarely considered for Cushing's disease but may be helpful in cases of adrenocortical carcinoma [47].

### 9.6.2 Adrenocortical Adenoma or Carcinoma

The treatment of choice for an adrenocortical adenoma or carcinoma is the surgical resection of the adrenals by an experienced surgeon [29, 47]. In cases of adrenocortical carcinoma, surgical resection may be followed by chemotherapy such as mitotane treatment. Rarely, adrenocortical carcinoma may rupture and constitute a cause of pediatric acute abdomen [28]. The long-term prognosis of adrenocortical carcinoma is poor, when metastases are already present at diagnosis and when complete resection of the tumor is impossible. On the other hand, patients with completely resected tumor of small size or adrenocortical adenoma histology have a very good prognosis. In any case, however, precise and careful preoperative planning with special attention to electrolyte balance, hypertension and steroid replacement therapy because of suppression of the contralateral adrenal are required [29, 47].

## 9.7 Long-Term Consequences

### 9.7.1 Long-Term Consequences on Growth

#### *9.7.1.1 Growth During Cushing's Syndrome*

Growth retardation to complete growth arrest is one of the main clinical characteristics of children and adolescents with Cushing's syndrome [50] (Figs. 1, 2). Glucocorticoid excess is well known to induce growth impairment, exerting various effects at various levels of the GH-IGF-1-target organ axis [15]. First of all, at the level of arcuate nucleus glucocorticoid excess downregulates the Ghrelin receptors, while, at the hypothalamic level, it enhances somatostatin release. Patients with Cushing's disease have been shown to have both decreased spontaneous mean plasma 24-h GH concentration and subnormal GH levels after various provocative tests [15, 32]. Another possible mechanism of growth arrest in cases of glucocorticoid excess has been suggested to be mediated by a glucocorticoid-induced target tissue resistance to IGF-1 and other growth factors [15]. Finally, there is a lot of evidence that glucocorticoid excess has a direct deleterious effect on the growth plate cartilage and bone by downregulating GH receptor expression, by suppressing local IGF-1 generation, by accelerating hypertrophic cell apoptosis and inhibiting vascular invasion [15].

#### *9.7.1.2 Growth After Cure of Cushing's Disease*

Earlier studies on the natural course of the final height of such patients have reported a compromised final height of successfully treated young patients compared to their midparental or target height [33]. Growth velocity after cure of Cushing's disease has been reported to be abnormally low or to range from 1.8–7.6 cm/year [25, 32, 33, 49]. The abnormally low post-cure growth velocity with lack of catch-up growth has been considered to be responsible for the compromised final height. It has been shown that spontaneous as well as L-arginine or L-dopa stimulated growth hormone secretion is suppressed in Cushing's disease patients until 12 months after surgical treatment even in cases where a better post-cure growth rate has been documented and despite a normalization of body mass index after their surgical treatment [32]. It has specifically been suggested that early onset of Cushing's syndrome might be more critical for growth and that deficits occurring at that

critical time might not be self-corrected by an adequate post-cure catch-up growth [33]. However, earlier studies on stimulation of GH secretion by insulin-induced hypoglycemia 3–6 and 6–12 months after transphenoidal surgery in Cushing's patients have demonstrated normalization of GH secretory capacity [24, 56]. Of course, insulin-induced hyperglycemia is a stronger stimulus for GH secretion than L-arginine or L-dopa. Whether this fact could explain the different results in those studies remains just a plausible explanation. Moreover, recent studies from the London group have demonstrated that GH secretion after cure of Cushing's disease may be either deficient, or subnormal or even normal in several cases [25, 49]. As far as bone age is concerned, it is noteworthy that many children and adolescents with Cushing's disease have no bone age retardation as should have been expected from the glucocorticoid excess, but bone age appropriate for chronological age or even advanced, mainly due to the concurrent adrenal androgen excess. The lack of retarded bone age in such patients constitutes a further negative prognostic factor for their final height [33, 49]. A recent analysis of the GH status following treatment of Cushing's disease either by transphenoidal surgery alone or in combination with pituitary radiotherapy [19, 51], demonstrated that as many as 59% of surgically treated patients assessed within 2 years following remission had severe GH deficiency while this percentage dropped to 22% when assessed beyond 2 years following remission, suggesting that some patients demonstrated recovery of GH secretory status. Among the radiotherapy-treated patients 36% showed severe GH deficiency at a mean time of 99 months following remission. In conclusion, some surgically treated patients with Cushing's disease may have a recovery of their GH secretory capacity at a mean time of 19 months postoperatively and they may therefore be reassessed 2 years after surgery, while, on the contrary, radiotherapy treated patients may not demonstrate severe GH deficiency until many years (up to 8 years after radiotherapy) and should therefore be closely monitored for a long period of time [9, 19, 25].

#### *9.7.1.3 GH Treatment in Cushing's Disease*

Recent data on young patients with Cushing's syndrome, who have been successfully treated for their main disease and have been subsequently substituted with recombinant GH, with or without GnRH analogue to delay puberty, reported normal adult height of these patients, providing reassuring results [25, 49].

### 9.7.2 Impact on Other Hormonal Axes

#### *9.7.2.1 Thyroid Function*

It has been shown that endogenous or exogenous hypercortisolism can affect the hypothalamic-pituitary-thyroid axis at various levels [53]. Notably, TSH pulsatility and the nocturnal TSH surge are suppressed during Cushing's disease or after exogenous dexamethasone administration. Furthermore, glucocorticoids inhibit thyroid hormone 5′-deiodinase, resulting in decreased serum triiodothyronine ($T_3$) and increased serum reverse $T_3$. Furthermore, transphenoidal surgery can per se lead to disruption of the hypothalamic-pituitary function and can lead to transient or permanent complete or partial hypopituitarism. TSH deficiency after transphenoidal surgery is reported to range between 16% and 40% of cases [53]. Furthermore, resolution of hypercortisolism after treatment for adrenocortical adenoma has been reported to induce an exacerbation of autoimmune thyroid disease [57].

#### *9.7.2.2 Puberty*

Puberty is usually retarded or arrested during Cushing's syndrome and progresses normally after treatment of the underlying disease [27]. On the other hand, puberty may even be precocious after pituitary irradiation for Cushing's disease [9, 39, 49, 52].

#### *9.7.2.3 Diabetes Insipidus*

Diabetes insipidus is a possible, most usually transient, postoperative complication of transphenoidal surgery for Cushing's disease [6, 26, 49, 61].

### 9.7.3 Bone Mineral Density: Effect of Glucocorticoids on Bone

It is known that excess hypercortisolism negatively affects bone density, leading to osteopenia or even osteoporosis, depending on the duration of hypercortisolism until final cure. In the series of Devoe et al., there was a dramatic improvement in bone mineral density in the years following cure of hypercortisolism [6], while reports from the NIH experience pointed to a long-lasting deficit of bone mineral density despite cure of Cushing's disease [1, 27]. The underlying

mechanisms leading to bone loss are complex: Glucocorticoid excess hinders osteoblast function, decreasing bone formation, while the number of osteoclasts increases. It seems that the loss of bone mineral density is primarily the result of glucocorticoid suppression of osteoblast function [27]. Glucocorticoid excess further diminishes matrix collagen mineralization. Therefore, glucocorticoid excess leads to a relatively smaller trabecular bone volume and to a smaller bone mineral content. At the level of calcium metabolism, glucocorticoids diminish intestinal calcium absorption and reduced renal calcium reabsorption, leading to secondary hyperparathyroidism. Supplementation of vitamin D improves the intestinal calcium absorption [7, 15]. It is noteworthy that even after successful treatment of Cushing's disease patients may never recover normal bone density, since glucocorticoid excess during adolescence may induce a long-standing persistent deficit in bone mass [1, 7].

## 9.8 Conclusions

In conclusion, childhood obesity of recent origin or change in facial characteristics in comparison to older photos, especially when accompanied by growth deceleration, warrant special attention because of the possibility of Cushing's syndrome. When such a possibility is evoked it should be always ruled out. Screening tests should be initially performed, and, when suspicion becomes a real possibility, more laborious investigations should be promptly undertaken in order to make the diagnosis early enough to prevent the long-lasting deleterious effects of hypercortisolemia.

The overall diagnostic and therapeutic modalities, as well as the long-term follow-up of such patients, should be guided by a multidisciplinary experienced team in order to provide the best possible outcome devoid of further morbidity.

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