REVIEW ARTICLE

Cushing's syndrome in children and adolescents: Current diagnostic and therapeutic strategies

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INTRODUCTION

Endogenous Cushing syndrome (endogenous hypercortisolemia) is a rare condition in children and adolescents. Its general incidence is 2-5 new cases per million of population per yr with a female to male preponderance of 9 to 1, and approximately 10% of these cases occur during childhood and adolescence. The clinical manifestations of the syndrome are different from those in adults, with generalized obesity and growth retardation being the prevailing signs. It is important to suspect the diagnosis, since, in many cases, the signs and symptoms are subtle, and it may take several months or years for the full clinical picture to develop. The diagnostic evaluation of the syndrome is complicated and still challenges the skills of physicians. Correct differential diagnosis, which is achieved by biochemical, imaging and catheterization studies, usually leads to successful treatment and cure. Early diagnosis is significant for prevention of the chronic deleterious effects of hypercortisolism especially on growth.

ETIOLOGY

Harvey Cushing first described the homonymous syndrome in 1912 (1). Cushing syndrome results from prolonged exposure of the organism to high levels of glucocorticoids (cortisol). Its cause can be exogenous, resulting from the administration of cortisol or ACTH, or endogenous, secondary to increased secretion of cortisol, ACTH or CRH (2). Exogenous administration of glucocorticoids (iatrogenic) accounts for the majority of cases of Cushing syndrome, because supraphysiologic doses of glucocorticoids are frequently prescribed for a wide range of non-endocrine diseases (3).

The classification of endogenous Cushing syndrome and rate of occurrence for ages >7 yr are summarized in Table 1. Endogenous Cushing syndrome can result from ACTH excess (ACTH-dependent), which can arise from the pituitary gland or ectopic ACTH- or CRH-secreting tumors, or from autonomous secretion of cortisol (ACTH-independent) by primary adrenal disease (*i.e.* cortisol-secreting adrenal tumors, "micronodular" dysplastic adrenals in primary pigmented nodular adrenal disease or PPNAD, etc) (4-8). ACTH-dependent Cushing syndrome accounts for about 85% of endogenous cases, and is caused by pituitary ACTH secretion (micro- or macroadenomas) in 80% of cases and ectopic ACTH secretion in 20%. Pituitary ACTH secretion has been traditionally called "Cushing disease". A very small number of patients with ACTH-dependent Cushing syndrome might have tumors secreting CRH (9-10). Also, a very small number of patients with chronic Cushing disease develop adrenal macroadenomas autonomously secreting cortisol (11). This has been called a "transitional state".

In children younger than 7 yr ACTH-independent causes, primarily adrenal carcinoma, are more frequently seen than ACTH-dependent ones (2, 4).

The molecular pathophysiology of ACTH-secreting tumors, either in the pituitary or ectopically, remains elusive. Although abnormalities of the G proteins are not frequent, approximately 50% of these tumors aberrantly express the p53 tumor-suppressor gene (12). Adrenal adenomas or carcinomas are monoclonal in origin. Abnormalities of the p53 gene or of the inhibitory subunit of G proteins and over-expression of IGFs were identified in a subset of these

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Table 1 - *Classification of endogenous Cushing syndrome and rate of occurence*.*

Classification	Occurence %
ACTH-dependent	85
pituitary (disease)	80
ectopic ACTH	20
ectopic CRH	Rare
ACTH-independent	15
adrenal adenoma	30
adrenal carcinoma	70
micronodular adrenal disease	Rare
massive macronodular adrenal disease	Rare
Transitional states	Rare

*Ages over 7 yr. Modified from (2), with permission.

Table 2 - *Frequency of symptoms and signs in pediatric patients with Cushing syndrome (14).*

Symptom or sign	Frequency (%)
Weight gain	90
Growth retardation	83
Menstrual irregularities (primary/secondary amenorrhea)	78
Hirsutism	78
Obesity (BMI >85th percentile)	75
Violaceous skin striate	61
Acne	47
Hypertension	47
Fatigue or weakness	44
Early secondary sexual development	38
Bruising	25
Mental changes	19
Hyperpigmentation	14
Muscle weakness	12
Acanthosis nigricans	12
Bone age	
delayed	11
accelerated	8
Sleep disturbances	8
Hyperclacemia	7
Alkalosis	7
Delayed secondary sexual development	3
Hypokalemia	2
Slipped femoral capital epiphysis	2

neoplasms and might be implicated in their pathogenesis (13). PPNAD is a hereditary autosomal dominant disorder usually manifesting in childhood or young adulthood (5). It can be associated with cardiac myxomas and multiple spotty pigmentations of the skin and mucosae, a triad referred to as Carney's complex. Other endocrine and non-endocrine abnormalities may be present in this disorder.

CLINICAL PRESENTATION

Table 2 summarizes the clinical features of Cushing syndrome in children and adolescents. Weight gain and growth retardation are the prevailing signs, and pubertal disorders may be encountered (Fig. 1 and 2). Young children may have premature sexual development and accelerated epiphyseal maturation, as a result of increased adrenal androgen secretion, whereas older children and adolescents may develop delayed puberty, as a result of glucocorticoid-induced hypogonadism (14). Truncal obesity characterized by facial rounding (moon facies) and plethora, menstrual irregularities, hirsutism, purple skin striae, acne, hypertension are also some of the typical clinical features. Although all patients may exhibit some of these features at the time of diagnosis, few, if any, will have all of them. Pictures of a patient taken over a period of years are particularly helpful in the clinical evaluation (2, 4). Mental changes (including emotional lability, irritability or depression), muscle weakness, and sleep disturbances are rare in young childen and adolescents in comparison to adults with Cushing syndrome (14). Generally, rapidly progressing, very severe Cushing syndrome points toward the ectopic ACTH syndrome. Rapid and severe virilization is frequently due to adrenocortical carcinoma (15, 16).

Contrary to what was believed with respect to bone age in patients with hypercortisolism, the bone age of children and adolescents with Cushing syndrome was found consistent with the chronological age in 81%, accelerated in 8% and delayed in 11% of patients, with the latter findings being clinically correlated with early and delayed sexual development, respectively (14). Apparently, the bone age of the patient reflects the combined effects of cortisol, which should have an inhibitory effect, and adrenal androgens and gonadal steroids, which should have a stimulatory effect. Note the growth parameters of children and adolescents with Cushing syndrome in Figure 3.

DIAGNOSIS OF CUSHING SYNDROME

The diagnosis of Cushing syndrome is based on the history, the clinical evaluation and the biochemical documentation of hypercortisolism, which

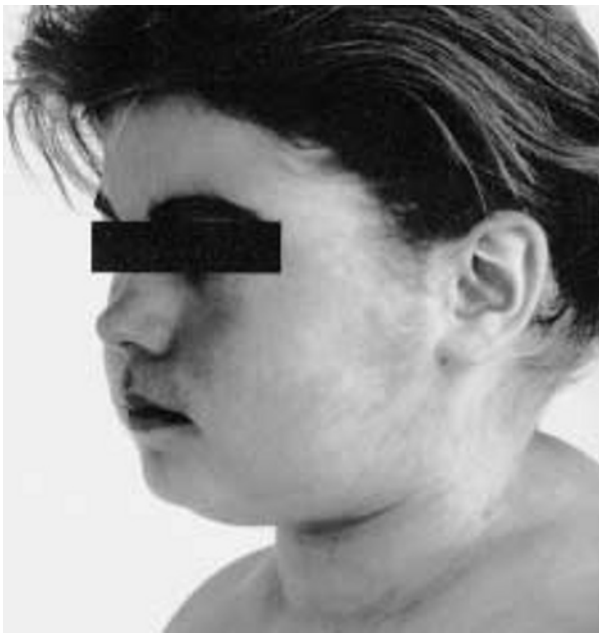

Fig. 1 - *Close-up of a 15-yr-old girl with Cushing disease. Note the facial rounding, the facial hirsutism, and the filling-in of the supraclavicular fossae.*

Fig. 2 - *Characteristic growth retardation and obesity in a 15-year-old patient with Cushing disease in comparison to her healthy identical twin sister.*

can usually be accomplished by outpatient tests. These include:

1) *Measurement of 24-h urinary free cortisol excretion (corrected for body surface area):* The determination of 24-h urinary free cortisol excretion is an excellent first-line test for documentation of endogenous Cushing syndrome (17). Normal values are <70 μg/m^2/day [37.5±15.1 μg/m^2/day (boys), 31.9±17.6 μg/m^2/day (girls)] (18). Assuming correct collection (it is recommended to collect 24-h urine for at least 3 consecutive days), there are very few false-negative results, whereas false-positive results may be obtained in several non-Cushing hypercortisolemic states (*i.e.* stress and depression).
2) *Measurement of 24-h urinary 17-hydroxysteroid excretion (corrected per g of excreted creatinine):* Urinary 24-h 17-hydroxysteroid excretion corrected for the urinary creatinine excretion gives an indirect measure of the rate of cortisol secretion and, thus, it also can be used for the establishment of hypercortisolism. Normal values are 2-7 mg/g creatinine/day.
   On rare occasions, there is discrepancy between the urinary free cortisol excretion value, which is normal or slightly elevated, and the value of 17-hydroxysteroid excretion, which is clearly elevated and more compatible with the Cushing manifestations of the patient. This is due to deviations in the activity of cortisol metabolizing enzymes, and in such instances the urinary 17-hydroxysteroids corrected per g creatinine should be employed as the index of hypercortisolism (19).
3) *Night-time salivary cortisol sampling* (at bedtime or midnight) has been recently proposed as a simple, accurate way to screen for hypercortisolisrn in children. Salivary cortisol values >1 μg/dl at bedtime and >0.27 μg/dl at midnight establish the diagnosis of Cushing syndrome in nearly all cases (20, 21).
4) *The overnight 1 mg (in children 15 μg/kg body weight) dexamethasone suppression test* is a useful screening procedure for hypercortisolism, but has a high incidence of false-positive results (15-20%). A plasma cortisol level >5 μg/dl suggests hypercortisolism (22, 23).

Cushing syndrome is generally excluded if the response to a single-dose dexamethasone suppression test and the 24-h urinary free cortisol or 17-

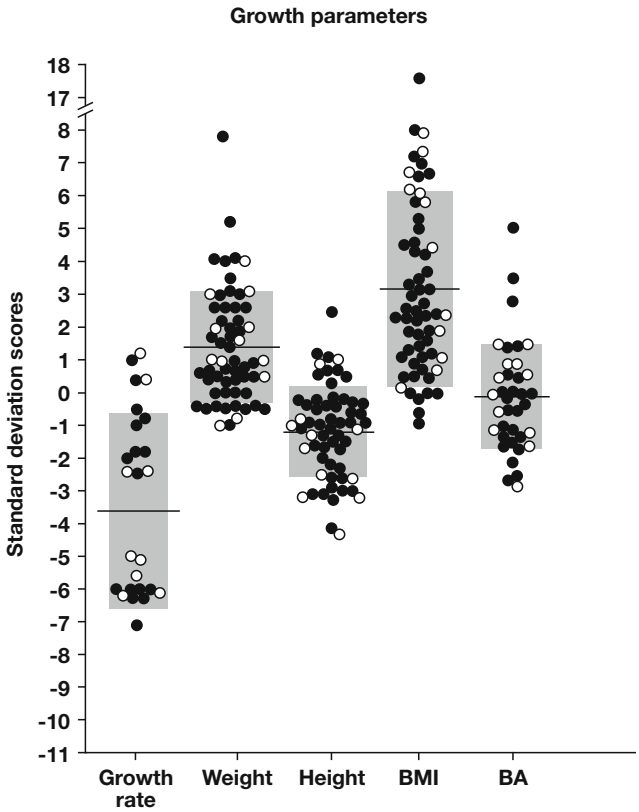

Fig. 3 - *Growth rate, weight, height, BMI, and bone age of 59 children and adolescents with Cushing syndrome, as compared with expected values for age and sex. The horizontal lines and the shaded bars indicate the means±SD. The SD score is defined as the number of standard deviations of the mean of the values in normal subjects of the same age and sex by which the values in the patients differed from normal (14).*

hydroxysteroid excretion tests are normal, although one should keep in mind that periodic and intermittent cortisol hypersecretion occurs in approximately 5-10% of patients with Cushing syndrome of any etiology, and may confuse the picture (24). In such patients, several weekly 24-h urinary free cortisol determinations for a period of 3 to 6 months may be necessary to establish the diagnosis.

Isolated plasma ACTH and cortisol determinations are of limited value since both hormones are secreted episodically and in a circadian fashion in normal subjects, and their secretion is influenced by physical or emotional stress. Five consecutive morning and 5 evening plasma samples should be drawn for determination of diurnal levels of cortisol, and the averages of the morning and evening values are used for the evaluation of the circadian rhythmicity of plasma cortisol values (14). Over 80% of patients with Cushing syndrome have equally elevated mean morning and evening values and, thus, no circadian rhythm. Also patients with Cushing syndrome frequently have single or several plasma ACTH and cortisol measurements in the normal range.

Hyperthyroidism, liver disease and renal failure may cause confusion in the interpretation of adrenal tests (2). Basal 17-hydroxysteroids and urinary free cortisol excretion after treatment with dexamethasone may be elevated in patients receiving drugs such as phenytoin, phenobarbital and primidone (25).

DIFFERENTIAL DIAGNOSIS

Once the diagnosis of endogenous Cushing syndrome has been established, testing should be undertaken to clarify the specific cause. The tests include: those that examine the biochemistry of the hypothalamus-pituitary-adrenal (HPA) axis (baseline hormone determinations and dynamic endocrine testing), several imaging techniques used mainly to examine the size and shape of the pituitary and adrenal glands or to detect and evaluate tumors, and catheterization studies to localize ACTH-secreting tumors in the pituitary *vs* a peripheral site (2, 4).

Baseline hormone determinations

Determination of plasma ACTH simultaneously with plasma cortisol provides useful information about the etiology of Cushing syndrome, as it would distinguish ACTH-dependent from ACTH-independent Cushing syndrome (26). Thus, adrenal cortisol-secreting tumors and micro- and macronodular adrenal disease are associated with suppressed levels of plasma ACTH, whereas Cushing disease and the ectopic ACTH syndrome are associated with normal or elevated plasma ACTH concentrations. The magnitude of elevation of plasma ACTH may have differential diagnostic value since patients with the ectopic ACTH syndrome often have greater plasma ACTH levels than those with Cushing disease (2, 4).

Endocrine dynamic testing of the HPA axis

It is essential that dynamic testing of the HPA axis is performed while the patient is hypercortisolemic. The major tests in the differential diagnosis of Cushing syndrome and results expected according to diagnosis are shown in Table 3.

Liddle dexamethasone suppression test

The standard high-dose dexamethasone test as described by Liddle is an established, reliable procedure for differentiating Cushing disease from the ectopic ACTH syndrome (27). In patients with Cushing disease

Table 3 - *Diagnostic testing in Cushing syndrome.*

Type	CRH	Liddle test (urinary 17-OHS)	Metyrapone test (urinary 17-OHS)	CT/MRI	BIPSS
ACTH-dependent					
pituitary	ACTH ↑ Cortisol ↑	Low dose - High dose ↓	↑	Pituitary± Adrenal ↑	Gradient Lateralization
ectopic ACTH	ACTH - Cortisol -	Low dose - High dose -	-	Pituitary - Adrenal ↑ (macronodules)	No gradient
ectopic CRH (rare)	High plasma CRH	Low dose - High dose	? ±	Pituitary - Adrenal ↑	(Gradient)
ACTH-independent					
adrenal adenoma	ACTH ↓ cortisol -	Low dose - High dose	-	+	ACTH ↓
adrenal carcinoma	ACTH ↓ Cortisol -	Low dose - High dose -	-	+	ACTH ↓
micronodular adrenal disease	ACTH ↓ Cortisol -	Low dose - High dose - (paradoxical ↑)	-	±	ACTH ↓

↑: elevation or enlargement; ↓: suppression; +: positive test; -: negative test or no change; ±: positive/negative; ?: theoretically expected; 17-OHS: 17-hydroxysteroid; BIPSS: bilateral inferior petrosal sinus sampling; CT: computed tomography; modified from ref. 2, with permission.

the abnormal corticotrophs are sensitive to glucocorticoid inhibition only at high doses of dexamethasone (120 µg/ kg/day divided in 4 doses every 6 h or maximum 2.0 mg every 6 h for 2 days). The mean values for urinary cortisol and 17-hydroxysteroid at baseline (two days) are compared with the values on the second day of high-dose dexamethasone administration (day 6 of the test). About 85% of patients with Cushing disease demonstrate a decrease in urinary 17-hydroxysteroid or urinary free cortisol excretion to values, respectively, less than 64 and 90% of the baseline values on day 6 of the test, whereas less than 10% of patients with the ectopic ACTH syndrome or ACTH-independent Cushing syndrome respond similarly (14, 28). Paradoxical responses to dexamethasone point towards either micronodular adrenal disease or ectopic ACTH-secreting tumors (14). A proposed modification of this test is administration of 8-mg dexamethasone orally at midnight as a single dose, and measurement of plasma cortisol concentrations in the following morning (29).

Metyrapone stimulation test

The standard metyrapone test is relatively simple but not as reliable as the dexamethasone suppression test. It is rapidly becoming obsolete but remains an option in cases in which all other tests mentioned here have failed to provide an unequivocal diagnosis. Eighty percent of patients with Cushing disease have normal or increased responses to metyrapone (>5% on day 2 or 3 of the test), whereas most patients with the ectopic ACTH syndrome fail to respond in this manner (30).

CRH test

The ovine (o)CRH test is of equal to or greater value than the standard dexamethasone suppression test in differentiating between Cushing disease and ectopic ACTH secretion (31-33). About 85% of patients with Cushing disease respond to oCRH with increases in plasma levels of ACTH and cortisol, whereas over 95% of patients with ectopic ACTH production do not. The (o)CRH test is rapidly superseding the classic tests of dexamethasone suppression and metyrapone stimulation because it is simple, brief, reliable, cost-effective and can be performed on an outpatient basis. However, the existing pitfalls concerning this test should be mentioned. About 5% of patients with ectopic ACTH tumors respond, whereas 15-20% of patients with Cushing disease do not respond to oCRH. Also, this test is useful only when the patient is hypercortisolemic.

The diagnostic power of the Liddle dexamethasone suppression test and the oCRH test is enhanced when both tests are employed. Negative results from both tests rule out the diagnosis of Cushing disease with a diagnostic accuracy of more than 98% (32).

Imaging evaluation

Imaging techniques can help clarify the etiology of hypercortisolism. These include CT scanning and MRI of the pituitary gland, and CT scan, MRI, and ultra-

sound imaging of the adrenal glands. CT and MRI scans of the chest and abdomen are also employed when tumors-secreting ectopic ACTH are suspected.

Pituitary

Over 95% of pituitary ACTH-secreting tumors are microadenomas with a diameter less than 7 mm. Plain *sella* radiographs and sella tomography are normal in the majority of patients, with less than 5% having a large enough tumor (macroadenoma) to cause changes in the *sella turcica*, including sellar enlargement or erosion of the floor. Less than 30% can be seen by CT of the sella (34).

The most appropriate initial procedure to detect pituitary ACTH-secreting tumors is an MRI scan of the pituitary. The availability of thin-section, high-resolution MRI scanners and the image enhancer gadolinium now permit recognition of approximately 50% of pituitary tumors secreting ACTH (14, 35, 36).

Adrenals

CT or MRI of the adrenal glands are useful in the distinction between Cushing disease and a cortisol-secreting adrenal adenoma or carcinoma. The adrenal CT or MRI scans of the adrenals in patients with Cushing disease demonstrate bilateral cortical hyperplasia, diffuse or nodular, including bilateral enlargement of the adrenal glands with thickening or nodularity and a relatively normal overall glandular configuration in about 60% of the patients (37, 38). On the other hand, most adrenocortical carcinomas, are quite large in patients with Cushing syndrome and, hence, are easily detectable by CT or MRI. Although adrenocortical adenomas are usually smaller (less than 5 cm in diameter) than carcinomas, most can also be demonstrated by CT or MRI. Generally, since most adrenal adenomas causing hypercortisolism are larger than 2 cm in diameter, they can be easily detected because of the excess retroperitoneal periadrenal fat present in Cushing syndrome. Although it may be functionally atrophic, the contralateral gland usually appears normal. Furthermore, adrenocortical adenomas show no enhancement at the T_2 relaxation time of the MRI, whereas adrenocortical carcinomas do (39). In patients with micronodular adrenal disease the adrenal CT shows bilateral or unilateral nodularity with normal size glands in about 60% of patients, and is grossly normal in the other 40% (5, 14).

The sensitivity and accuracy of ultrasonography are less than those of the CT or MRI scans. The iodocholesterol scan is nowadays rarely necessary in the evaluation of patients with Cushing syndrome, since this scanning procedure has been largely superceded by CT or MRI scans, which are simpler and faster and involve less radiation. It is now used primarily to localize ectopic adrenal tissue or an adrenal remnant that is causing recurrent hypercortisolism after bilateral adrenalectomy (40).

Ectopic tumors

A chest X-ray should be performed routinely and CT and/or MRI of the chest and/or abdomen should be obtained when ectopic ACTH- secreting tumors are suspected, since most of the tumors responsible for the ectopic ACTH syndrome are located in the thorax or in the abdomen. About 25-30% of ectopic ACTH-secreting tumors are occult at the time of the initial evaluation. Corticotropin-producing thymic carcinoids and pheochromocytomas are generally apparent on CT at initial presentation (41, 42).

Catheterization studies

The differential diagnosis of Cushing disease from the ectopic ACTH syndrome can be quite difficult, since both entities can have similar clinical and laboratory features. In addition, half of pituitary microadenomas and up to 30% of ectopic ACTH-secreting tumors may be radiologically occult. Simultaneous bilateral inferior petrosal venous sinus sampling (BIPSS) and peripheral vein catheterization for measurement of plasma ACTH concentrations before and after oCRH stimulation are two of the most specific tests available to localize the source of ACTH production (43-45).

Venous blood from the anterior pituitary drains into the cavernous sinus and subsequently into the inferior petrosal sinuses. Two separate catheters are led into each inferior petrosal sinus via the ipsilateral femoral vein. The location of the catheters is confirmed radiologically by injection of radiopaque solution. Samples for measurement of plasma ACTH are collected simultaneously from each inferior petrosal sinus and a peripheral vein both before and 3, 5, and 10 min after injection of 1 μg/kg of oCRH. Generally, patients with the ectopic ACTH syndrome have no ACTH concentration gradient between either inferior petrosal sinus and the peripheral sample before or after oCRH. On the other hand, an increased baseline or stimulated gradient (>2 and >3, respectively) of plasma ACTH between any or both of the inferior petrosal sinuses and the peripheral sample is highly suggestive of Cushing disease. Basal gradients distinguish 95% of patients with Cushing disease from those with ectopic. Stimulated gradients separate up to 98% (14) (Fig. 4).

In addition, to distinguishing between Cushing disease and ectopic ACTH secretion, BIPSS provides

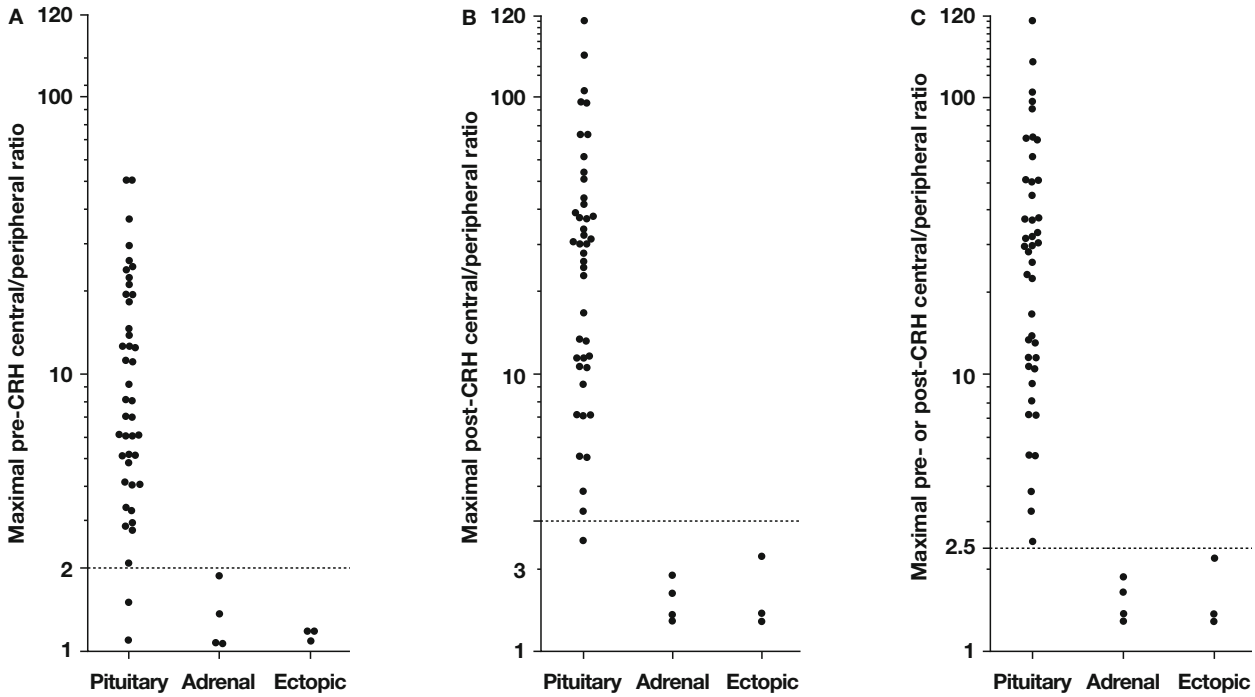

Fig. 4 - *Maximal ratio of corticotropin concentrations in the inferior petrosal sinuses to the concentrations in peripheral blood (central/peripheral ratio) before, after, and before or after administration of CRH in 50 children and adolescents with pituitary adenomas, primary adrenal disease, or ectopic corticotropin secretion. The broken line indicates the diagnostic threshold for each test (14).*

information about the side of the pituitary, in which the adenoma resides. The predictive value of lateralization in unoperated patients is approximately 75-80%. Thus, if a microadenoma cannot be identified at surgery, the only data on which the surgeon can base the decision to perform hemihypophysectomy are the results of BIPSS. The usefulness of BIPSS in distinguishing patients with previous transsphenoidal surgery from patients with ectopic ACTH secretion is as high as in unoperated patients. The value of this test in lateralizing an adenoma in patients with previous transsphenoidal surgery, however, is less than that in unoperated patients (43-45). The overall diagnostic value of the BIPSS depends upon its being performed while the patient is hypercortisolemic at the time of the study, and this should be always assured prior to performing the test.

BIPSS is technically difficult and, like all invasive procedures, can never be completely risk-free even in the most experienced hands (46, 47). It should be reserved only for patients with classic Cushing disease symptoms and negative or equivocal MRI findings of the pituitary, and patients with positive pituitary MRI findings but equivocal suppression and stimulation test results.

Proposed algorithm

We recommend the following diagnostic scheme in patients with Cushing syndrome. First, the presence of hypercortisolism should be established by demonstrating increased urinary cortisol or 17-hydroxysteroid excretion on several occasions. Second, plasma ACTH should be measured and a CRH test performed to distinguish between ACTH-dependent and ACTH-independent Cushing syndrome, and pituitary MRI scans should be obtained in all patients with the former type of disorder. In the case of a positive CRH test and an unequivocally positive pituitary MRI scan, the diagnosis of Cushing disease is made, and transsphenoidal surgery is indicated. If the pituitary MRI scan is negative or equivocal, BIPSS should be performed. Patients with CRH test results that suggest ectopic ACTH secretion and negative pituitary MRI scans should also undergo BIPSS and chest and abdominal CT or MRI scans. If an ectopic ACTH-secreting tumor is identified, it should be excised. If basal plasma ACTH values suggest ACTH-independent Cushing syndrome, CT or MR 1 scanning of the adrenal glands should be performed, to establish the diagnosis of primary adrenal disease (48) (Fig. 5).

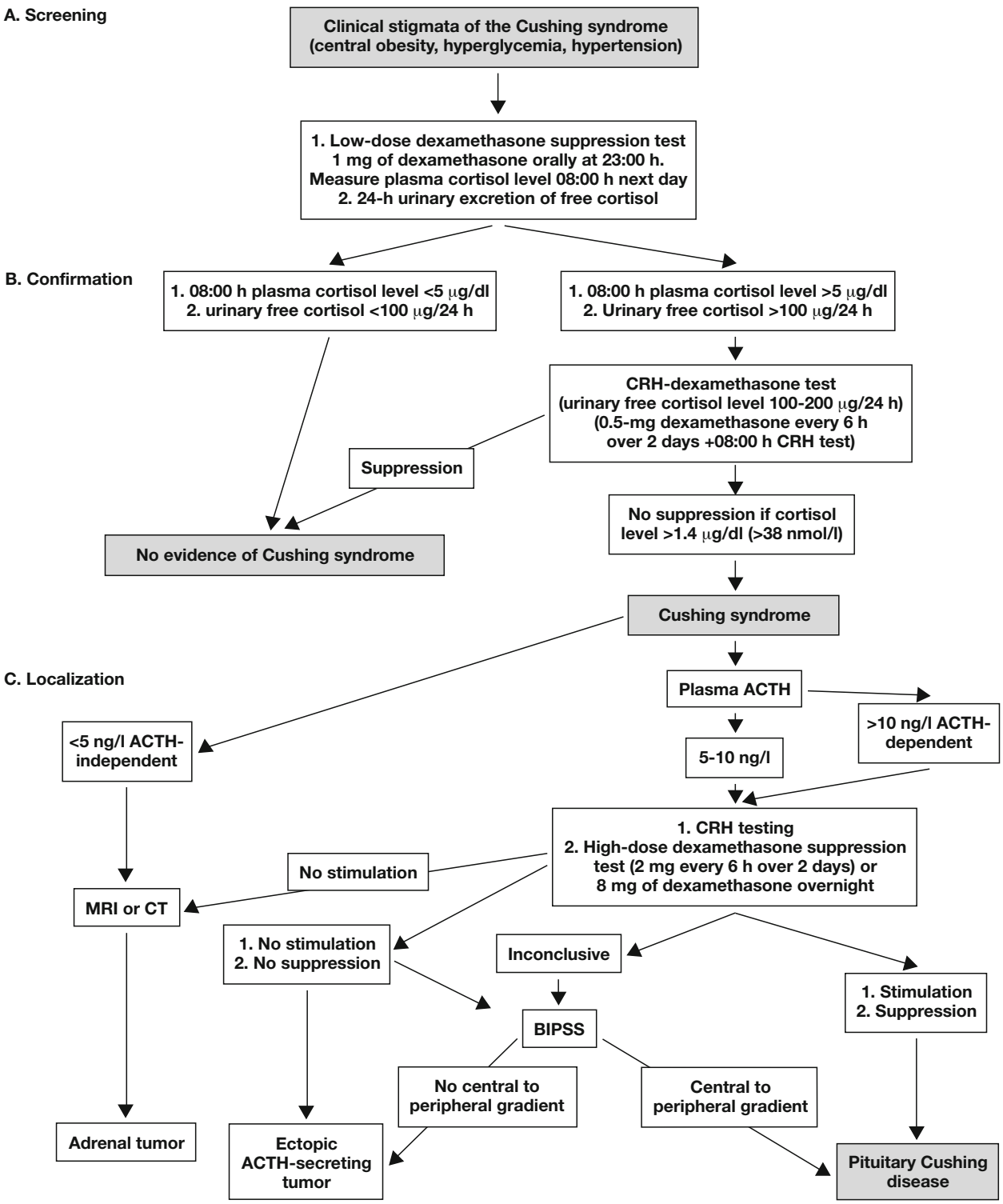

Fig. 5 - *Diagnostic algorithm for the Cushing syndrome. For the diagnosis of primary hypercortisolism, this algorithm suggests tests that are used for screening, confirmation, and localization of a cortisol-producing or corticotropin (ACTH)-producing tumor. If there is more than one item, follow the respective numbers throughout the algorithm. BIPSS: bilateral inferior petrosal sinus sampling. From (48), with permission.*

TREATMENT OF CUSHING SYNDROME

The treatment of choice depends upon the specific cause of the hypercortisolism, which must be established unequivocally. Optimal treatment is the correction of hypercortisolism without permanent dependence on hormone replacement.

Cushing disease

Currently, the following therapeutic modalities are available for the treatment of pituitary ACTH-secreting tumors: transsphenoidal removal of the adenoma, gamma knife and linear accelerator-mediated radiosurgery, pituitary irradiation with concomitant therapy with mitotane, combinations of other pharmacological agents, and bilateral adrenalectomy (2, 4, 49).

Transsphenoidal adenomectomy is the treatment of choice for most cases of Cushing syndrome caused by pituitary microadenomas (50-52). In most specialized centers the success rate of first transsphenoidal surgery exceeds 90%. If BIPSS has lateralized the microadenoma and the surgeon cannot identify it at surgery, 75-80% of patients can be cured by ipsilateral hemihypophysectomy. Successful surgery leads to cure of hypercortisolism with no need for permanent glucocorticoid replacement. A small percentage of patients (approximately 5%) suffer recurrences, however. The success rate of repeated transsphenoidal surgery is considerably lower in patients with recurrent Cushing disease after a previously successful operation, or in patients with a previously failed transsphenoidal operation, than in unoperated patients (53).

Transient diabetes insipidus and, less frequently, inappropriate antidiuretic hormone secretion may occur during the early weeks following surgery. Central and primary hypothyroidism (autoimmune), GH deficiency, hypogonadism and permanent hypocortisolism may occur. Permanent diabetes insipidus, hemorrage, cerebrospinal fluid rhinorrhea, injury of internal carotid, cranial nerve palsy and meningitis are uncommon complications but may occur more frequently in patients with repeated transsphenoidal surgery. The perioperative mortality rate of transsphenoidal surgery is probably less than 1%, but lower than that of bilateral adrenalectomy (approximately 3%). After a successful transsphenoidal operation in Cushing disease, a period of adrenal insufficiency ensues in most of patients cured, during which glucocorticoids must be replaced (see below).

Gamma knife and linear accelerator-mediated radiosurgery has been recently proposed as an alternative in treatment of functioning pituitary adenomas (54, 55). The success rate and the long-term effects are not yet known in children and adolescents. Combined pituitary X-irradiation and mitotane is a reasonable alternative treatment after failure of transsphenoidal surgery, presence of cavernous sinus wall invasion by the tumor, or as the first line of treatment in patients judged unsuitable for surgery. The recommended dosage of pituitary irradiation is 4500 to 5000 rad total. High-voltage, conventional X-radiation is given in 180- to 200-rad fractions over a period of 6 weeks. Biochemical and clinical amelioration occurs with preservation of pituitary and adrenal function, but is delayed by several months (6 to 18 months). Full effect can take years to occur. Heavy particle beam irradiation and Bragg peak proton irradiation therapy appear to be equally effective to conventional irradiation; however, the prevalence of post-radiation panhypopituitarism is higher with the former techniques. Progressive anterior hypopituitarism, including GH deficiency, hypothyroidism, and hypogonadism occurs in about 40% of patients receiving radiotherapy. These complications may occur several years after radiotherapy. Combined pituitary radiation and mitotane improves the success rate of either modality given alone curing approximately two- thirds of the patients (56, 57).

Drug therapy alone is rarely used to treat Cushing disease except temporarily, prior to definitive treatment. Mitotane is the only available pharmacologic agent that both inhibits biosynthesis of corticosteroids and destroys adrenocortical cells secreting cortisol, thus producing a long-lasting effect. Therapy with mitotane alone can be successful in 30-40% of patients with Cushing disease. Adrenal enzyme inhibitors (aminoglutethimide, metyrapone, trilostane, and ketoconazole) have been used alone or in combination with mitotane or each other to control some of the symptoms and metabolic abnormalities associated with the hypercortisolemia of Cushing disease (58, 59).

Bilateral adrenalectomy, the indications of which have been altered radically by the success and low morbidity of transsphenoidal surgery, could be considered for patients who have failed selective pituitary adenomectomy or hemihypophysectomy. When performed properly, it leads to cure of hypercortisolism. The major disadvantages of bilateral adrenalectomy are the following: the individual is committed to lifelong daily cortisol and fludrocortisone replacements; it fails to attack the cause underlying the hypersecretion of ACTH; relapses, although uncommon, can occur as a result of growth

of adrenal rest tissue or an adrenal remnant; the perioperative mortality is approximately three times higher than that of transsphenoidal surgery, although it can be minimized by careful perioperative management; and the risk of developing Nelson syndrome (large pituitary macroadenomas secreting great amounts of ACTH) in 10-15% of patients months or years after bilateral adrenalectomy (60).

Ectopic ACTH syndrome

The treatment of choice for ectopic ACTH secretion is surgical and directed toward complete excision of the tumor, if it is resectable and its location known. If there is evidence of invasion of adjacent lymph nodes, local radiation may be recommended after surgery. If surgical treatment is impossible, blockade of steroidogenesis is indicated, and combination chemotherapy or radiation therapy may be administered. With bronchial carcinoids, which are by far the most common tumors producing the ectopic ACTH syndrome, lung lobectomy may be sufficient for cure. Carcinoids, however, should not be considered benign. They may be extremely slow growing but have the potential for both local invasion and distant metastases.

In approximately 30% of all cases with ectopic ACTH secretion, tumors cannot be found despite severe hypercortisolism. These patients should be medically controlled as suggested above, in order to correct the symptoms and should have periodic imaging evaluations to localize the source of ACTH.

Medical control of hypercortisolism may allow eventual detection of an occult tumor and spare the patient from adrenalectomy. Repeat searches for the tumor should be undertaken every 6 to 12 months. If by 2 yr the tumor has escaped detection, or, if medical control is not possible, a bilateral adrenalectomy should be considered. This procedure may need to be done earlier in developing children in whom ketoconazole and other medications may interfere with growth and pubertal progression. Periodic evaluation must continue in the case of an occult tumor, until the tumor is found and removed (58).

Primary adrenal disease

The therapeutic approach to ACTH-independent Cushing syndrome is also surgical. Unilateral or bilateral adrenalectomy is the recommended therapy, depending on whether one or both adrenals are affected. The cure rate of benign adenomas and micronodular disease should be 100%.

Adrenocortical carcinomas are implicated in 0.2% of all cancer deaths. They usually require surgical excision followed by chemotherapy, and have a poor prognosis with practically a 100 percent rate of either local recurrence or distant metastases. Less than 30% of patients who undergo surgery survive for 5 years.

Medical control of hypercortisolism as suggested above with Cushing disease or ectopic ACTH secretion is indicated in cases in which surgical treatment is not an option at the time of the decision.

FOLLOW-UP AFTER TREATMENT

When to consider the patient cured

Success after surgery is defined as a drop in serum cortisol or urinary free cortisol to an undetectable level in the immediate postoperative period. Patients are considered cured if urinary cortisol values are <10 μg/24 h and morning plasma cortisol values are <1 μg/dl the 3rd day after surgery.

Post-operative glucocorticoid replacement

After a successful transsphenoidal operation in Cushing disease, a period of adrenal insufficiency ensues in most of patients cured, during which glucocorticoids must be replaced. This abnormality of the HPA axis can last as long as 1 year or longer, or, rarely, it can be permanent (61, 62). Intraoperatively, and during the first 2 post-operative days, 100 mg/m^2/day of hydrocortisone or its equivalent is given intravenously. Once the patient has recovered from the surgical procedure, oral replacement doses of hydrocortisone, 20 to 30 mg (12 to 15 mg/m^2) per day, are started. Patients often complain of weakness, lack of energy and irritability at these doses. This is a sign of successful surgery and the symptoms could be alleviated with pharmacological doses of glucocorticoids. The replacement dose of hydrocortisone is maintained for 3 months and adrenocortical function is evaluated at that time with a rapid Cortrosyn test (250 μg ACTH 1-24 iv bolus, with plasma cortisol measured at 0, 30, and 60 min). If the test is normal (cortisol >18 and >20 μg/dl at 30 and 60 min, respectively), glucocorticoid replacement is discontinued. If the response is subnormal, the patient is reevaluated at 3-month intervals. Seventy to 80% of the patients will have a normal test at 6 months postoperatively. Patients should be given extra glucocorticoids during stress (twice replacement for minor stress, such as febrile illness or dental surgery, and 8-10 times replacement for major stress, such as major trauma or surgery).

Post-operative evaluation for probable complications

Monitor:

1) the HPA axis for probable recurrence (repeated measurements of urinary free cortisol excretion every 3 months during the first post-operative year, and every 6 months during the second one). After the end of the second post-operative year the doctor should be alert for clinical signs and symptoms of recurrence;
2) the hypothalamic-pituitary-thyroid axis every 6 months;
3) the hypothalamic-pituitary-growth axis. Children and adolescents with Cushing syndrome should be monitored every six months in terms of linear growth.

Outcome after successful surgical treatment

1) *Growth.* It is known that growth retardation is one of the prevailing signs of Cushing syndrome. GH hyposecretion continues for at least a year after convalescence, in spite of significant increases in the growth rate of all growing patients. GH secretion recovers about 18 months after surgery (63, 64). Usually, catch-up growth is not achieved in children with Cushing syndrome even after successful surgical treatment, and their final height remains compromised (65). These findings underscore the significance of early diagnosis and treatment.
2) *BP.* Approximately half of children and adolescents with Cushing syndrome develop hypertension positively correlated to the duration of disease. BP is normalized within a year from the correction of hypercortisolism, suggesting that, as a rule, young patients with hypercortisolism do not develop essential hypertension (66).
3) *Thyroid function.* Children with Cushing disease demonstrate mild perturbations of the thyroid axis before and after surgery. The former are typical of the "low T_3" or "euthyroid-sick syndrome", while the latter are mostly transient (recover 6 months after surgery), usually of central origin, and apparently related to surgery. Clinically significant central hypothyroidism (transient or – rarely – permanent) is observed in about 17% of patients after surgery (67). Hashimoto's thyroiditis or Graves' disease may occur in the post-operative period.

CONCLUSIONS

The diagnosis of Cushing syndrome requires the demonstration of hypercortisolism, best achieved by 24-h urinary free cortisol excretion determinations. Distinction between ACTH-dependent and ACTH-independent Cushing syndrome is made on the basis of basal and oCRH-stimulated plasma ACTH determinations and adrenal CT. In the majority of cases of ACTH-dependent Cushing syndrome, differential diagnosis is achieved by the oCRH test and a pituitary MRI with gadolinium. If no discrete lesion is present or if the oCRH test is equivocal, BIPSS with oCRH administration is necessary to distinguish between a pituitary and an ectopic source. Once the source is identified, surgery is the treatment of choice for all forms of Cushing syndrome. In cases of Cushing disease, in which transsphenoidal surgery fails, or in which the disease recurs, repeat transsphenoidal surgery and radiation therapy in association with mitotane treatment are reasonable alternatives. Bilateral adrenalectomy effectively cures hypercortisolism if resection of the ACTH-secreting tumor is unsuccessful and radiation or medical therapy fails.

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