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Diagnosis and Complications of Cushing's Syndrome: A Consensus Statement

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In October 2002, a workshop was held in Ancona, Italy, to reach a Consensus on the management of Cushing's syndrome. The workshop was organized by the University of Ancona and sponsored by the Pituitary Society, the European Neuroendocrine Association, and the Italian Society of Endocrinology. Invited international participants included almost 50 leading endocrinologists with specific expertise in the management of Cushing's syndrome. The consensus statement on diagnostic criteria and the diagnosis and treatment of complications of this syndrome reached at the workshop is hereby summarized. (*J Clin Endocrinol Metab* 88: 5593–5602, 2003)

Part I: Criteria for Diagnosis and Cure of Cushing's Syndrome (CS)

Endogenous CS results from chronic exposure to excess glucocorticoids produced by the adrenal cortex. It may be caused by excess ACTH production (80–85%), usually by a pituitary corticotroph adenoma [Cushing's disease (CD)], less frequently by an extrapituitary tumor (ectopic ACTH syndrome), or very rarely by a tumor secreting CRH (ectopic CRH syndrome). CS can also be ACTH-independent (15–20%) when it results from excess secretion of cortisol by unilateral adrenocortical tumors, either benign or malignant, or by bilateral adrenal hyperplasia or dysplasia (1–4).

Regardless of the etiology, some of the tumors responsible for CS can show variable secretory activity over time. In addition, tumoral cells may have maintained or lost their physiological regulation by hormones or growth factors or may even have acquired new regulatory mechanisms (5). The spectrum of cortisol overproduction may thus vary from barely detectable to marked oversecretion, especially in cyclical CS (2).

The suspicion of CS in a patient clearly arises in the presence of central obesity with supraclavicular fat accumulation, a cervical fat pad, thinned skin, purple striae, proximal muscle weakness, fatigue, high blood pressure, glucose intolerance, acne, hirsutism, and menstrual irregularity. Neuropsychological disturbances including depression, emotional irritability, sleep disturbances, and cognitive deficits are also frequently observed. Muscular atrophy and purple striae are particularly helpful stigmata in adults, whereas in children growth retardation is frequently present. The clinical phenotype is not always florid, and suspicion should also arise with a less complete picture, particularly if concomitant recent weight gain, impaired glucose tolerance, and high blood pressure are present (1–3). Thus, some of the patients with metabolic syndrome might require screening for CS, especially if young and resistant to conventional treatment.

Due to the variable pattern of the biochemical parameters and the nonspecificity of clinical manifestations, the diagnosis of CS is often a challenge for clinicians. This is particularly true

Abbreviations: BIPSS, Bilateral IPS sampling; BMD, bone mineral density; CBG, corticosteroid-binding globulin; CD, Cushing's disease; CS, Cushing's syndrome; CT, computed tomography; DEXA, dual energy x-ray absorptiometry; DST, dexamethasone suppression test(s); IPS, inferior petrosal sinus; MRI, magnetic resonance imaging; UFC, urinary free cortisol.

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in states of mild hypercortisolism and in some patients with adrenal incidentalomas (2). Primary care physicians may suspect CS and proceed to the initial biochemical screening tests. However, due to the potential complexity of investigation, further evaluation and treatment of this syndrome should be conducted in specialized endocrinology referral centers.

The diagnosis of endogenous CS should begin with a careful case history and a thorough physical examination, looking for the characteristic features while excluding exogenous intake of oral, parenteral, inhaled, or topical corticosteroids. The extent of laboratory investigations will depend on the clinical index of suspicion. In addition, biochemical screening must take into consideration the fact that some patients have episodic or periodic increases in cortisol secretion (6, 7). More specific tests relating to the differential diagnosis should be performed only after hypercortisolism has been confirmed, because they only differentiate one cause of CS from another. In cases where the diagnosis of CS is suspected clinically but initial screening tests are normal, the patient should be reevaluated at a later date, and invasive procedures should be postponed.

Diagnosis of CS

Several tests have been used extensively as first line screening tests, but none has proven fully capable of distinguishing all cases of CS from normal and/or obese individuals. More recently introduced tests have attempted to improve the efficiency of the initial screening and will also be considered here.

First-line screening tests

Twenty-four-hour urinary free cortisol (UFC). The 24-h urinary cortisol gives an integrated index of the free (unbound) cortisol that circulated in the blood during this period of time. In contrast to plasma cortisol levels, which measure total cortisol, unbound and bound, it is not affected by factors that influence corticosteroid-binding globulin (CBG) levels (7, 8). Due to the possibility of intermittent hypercortisolism, if the index of suspicion is high and the first result is normal, up to three 24-h urine collections should be performed. If cortisol excretion results are normal in three collections, then CS is highly unlikely, providing that renal function is normal. Mild CS is also unlikely although the alteration of the other tests can define a mild CS. Urinary creatinine may also be measured to verify the adequacy of the urine collection. If glomerular filtration rate is less than 30 ml/min, the urinary cortisol excretion is decreased and may thus be normal despite the presence of excessive cortisol production. In children, the urinary cortisol excretion should be corrected for body surface area/1.72 m^2. Measurement of urinary cortisol by immunoassays (RIA, immunometric assays) is influenced by various metabolites of cortisol and some synthetic glucocorticoids, whereas measurements using HPLC allow the separation of various urinary glucocorticoids and metabolites. HPLC has a high sensitivity and specificity, but occasionally interfering substances, such as carbamazepin and digoxin, can also coelute with cortisol and produce false elevations of the UFC (9, 10). The recent introduction of mass spectrometry combined with gas chromatography or HPLC may overcome these problems; however, these techniques are more expensive, are not widely available, and have not yet been validated extensively. UFC values can be extremely variable in CS. UFC values 4-fold greater than the upper limit of normal are very rare, except in CS, and therefore can be considered diagnostic for this condition. Milder elevations of urinary cortisol can be found in conditions such as chronic anxiety, depression, and alcoholism, all of which are also known as pseudo-Cushing states (4, 7), and in normal pregnant women. Urinary cortisol may not identify subclinical or preclinical CS in which hypercortisolism is still mild, and for this reason and the others cited above, it cannot be considered as a universal single screening test for the detection of CS.

Low-dose dexamethasone suppression tests (DST). The low-dose DST are used to differentiate CS patients from those who do not have CS (4, 8). The overnight low-dose (1 mg) DST consists of the oral intake of 1 mg dexamethasone between 2300 and 2400 h, followed by measurement of fasting plasma cortisol between 0800 and 0900 h the following morning. The original criterion for normal level of suppression was a plasma cortisol level below 5 μg/dl (138 nmol/liter). More recently, this cut-off level has been reduced to less than 1.8 μg/dl (50 nmol/liter) (10–11), greatly enhancing the sensitivity of the overnight DST, especially in patients with mild hypercortisolism. A serum cortisol level below 1.8 μg/dl (50 nmol/liter) excludes active CS at that time. The specificity of the test is, however, limited, due to potential misclassification of patients with increased CBG, acute and chronic illness, or pseudo-CS. Occasionally, otherwise healthy individuals fail to suppress cortisol to this level also. For outpatient screening, the advantages of the 1 mg overnight DST are its ease of execution and low cost. The classical 2-d 2 mg DST is another way to conduct the test and is used as a first line screening test in some centers (4) (see below). For any DST, interfering conditions causing an apparent lack of suppression include: decreased dexamethasone absorption, drugs enhancing hepatic dexamethasone metabolism (barbiturates, phenytoin, carbamazepine, rifampicin, meprobamate, aminoglutethimide, methaqualone), increased concentration of CBG (estrogen treatment, pregnancy) and pseudo-Cushing states. Moreover, the cortisol assay must have a sensitivity of 1 μg/dl (27.6 nmol/liter) or less (4–8).

Late-night salivary cortisol. This is a recently introduced test that appears to be promising for the screening of CS. Cortisol concentration in saliva is highly correlated with free plasma cortisol, independent of salivary flow rates, and stable at room temperature for 1 wk. The normal reference ranges are assay-dependent and should be validated for each laboratory. Late night (2300 h) salivary cortisol is a simple way to screen for CS and could become increasingly used because it has been found to have high diagnostic sensitivity and specificity (12, 13). It could be particularly useful in investigating patients with cyclical CS with repeated evening measurements over time. Wider availability of validated commercial assays and larger studies will be necessary before late-night salivary cortisol could be considered to substitute for UFC or low-dose DST as a first-line screening test.

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Second-line screening tests

Plasma cortisol circadian rhythm—midnight plasma cortisol. Patients with CS often have early morning serum cortisol concentrations within or slightly above the normal range, but lack a normal circadian rhythm. Plasma cortisol levels are above a cut-off value of 1.8 μg/dl (50 nmol/liter) when measured at midnight in hospitalized, sleeping CS patients (14). This cut-off value has a very high degree of sensitivity, but its specificity was not tested. Others have adopted a higher cut-off value (7.5 μg/dl, 207 nmol/liter) to achieve 100% specificity for normal individuals and those with pseudo-Cushing (15). The test requires inpatient admission for a period of at least 48 h. Measurement of cortisol at other time points appears to be relatively unhelpful (15).

Low-dose DST and combined DST-CRH test. In the classical 2-d low-dose DST, the patient takes 0.5 mg dexamethasone orally every 6 h. Urine is collected for UFC on 2 baseline days and on the second day of dexamethasone administration, or alternatively serum cortisol is measured at 0900 h and 48 h after the first dose. A normal response consists of a decrease of UFC to less than 10 μg (27 nmol) per 24 h on the second day of dexamethasone administration or of plasma cortisol to less than 1.8 μg/dl (50 nmol/liter) on the morning after the last dose of dexamethasone (11). Use of the plasma cortisol end point results in a sensitivity and specificity of more than 95% (4). Adequate urine collections and normal bioavailability and metabolism of dexamethasone are required for the procedure to be valid. As noted above, some centers use the classical 2-d low-dose DST as a first-line screening test (4).

The combined DST-CRH test was shown by one center to be highly accurate in distinguishing CS from pseudo-CS; it is postulated that patients with pseudo-CS are thought to be under chronic CRH stimulation due to their stressful situation and show a blunted response to exogenous CRH after dexamethasone administration. The test is performed by giving dexamethasone orally 0.5 mg every 6 h for 48 h, starting at 1200 h, and then administering ovine-sequence CRH (1 μg/kg) iv at 0800 h (2 h after the last dose of dexamethasone). The plasma cortisol value 15 min after CRH is greater than 1.4 μg/dl (38 nmol/liter) in patients with CS, but remains suppressed in normal individuals and in patients with pseudo-CS (16). This test would be useful when pseudo-CS is suspected. Its advantages over the classical 2-d low-dose DST remain to be validated by additional studies from different centers. Its use with human-sequence CRH also requires validation. Importantly, the precision of the majority of cortisol assays in routine use at the quoted cut-off level is poor, and caution is needed in interpretation. Therefore, the use of highly sensitive cortisol assays is strongly suggested for all dexamethasone suppression tests.

Differential Diagnosis of CS

If CS is confirmed, its cause will be categorized initially by determination of plasma ACTH values. If ACTH is not suppressed, ACTH-dependent causes will be investigated. An occult ectopic source of ACTH may mimic pituitary-dependent disease because such tumors may express glucocorticoid and/or CRH and/or vasopressin receptors, and thus behave as a misplaced pituitary in the course of all standard dynamic tests. If ACTH is suppressed, adrenal computed tomography (CT)/magnetic resonance imaging (MRI) scanning will identify the type of adrenal lesion(s) responsible for CS.

ACTH measurement. ACTH is rapidly degraded by plasma proteases. To prevent this, the assays for the determination of plasma ACTH levels require collection of blood into a prechilled EDTA tube, placement in an ice water bath, and rapid delivery to the laboratory for refrigerated centrifugation. Only assays such as the two-site immunoradiometric assays, which can reliably detect values less than 10 pg/ml (2 pmol/liter), should be used. ACTH concentrations below the level of detection or below 10 pg/ml (2 pmol/liter) at 0900 h with concomitant increased production of cortisol suggest an ACTH-independent cause of CS. However, ACTH levels may not be fully suppressed in some patients with adrenal CS and intermittent or concomitantly relatively low secretion of cortisol. Plasma ACTH values greater than 20 pg/ml (4 pmol/liter) suggest an ACTH-dependent cause. For values between 10 and 20 pg/ml (2–4 pmol/liter), a CRH stimulation test is indicated, with measurement of plasma ACTH. ACTH levels tend to be higher in ectopic ACTH-secreting CS than in CD; however, the overlap in ACTH values is such that ACTH values alone rarely distinguish between the two conditions (1, 4).

High-dose DST. High doses of glucocorticoids partially suppress ACTH secretion from most corticotroph adenomas (80–90%), whereas ectopic tumors are resistant to feedback inhibition. However, some benign differentiated neuroendocrine tumors (usually the carcinoid tumors of bronchus, thymus, and pancreas) may be sensitive to feedback inhibition of ACTH like pituitary tumors. In adrenal CS, there is a lack of cortisol suppression after high-dose DST because cortisol secretion is autonomous and the ACTH secretion is already very low and cannot be further reduced.

There are several versions of the high-dose DST, including the standard 2-d oral high dose (2 mg every 6 h for eight doses), the 8-mg overnight oral, and the iv 4–7 mg tests (4).

Plasma and/or urinary cortisol levels are evaluated before, during, and/or after dexamethasone administration. These tests distinguish pituitary from ectopic sources of ACTH with a sensitivity varying from 60 to 80% and with high specificity when a cut-off of plasma cortisol suppression above 50% is used (17). The specificity can be improved using a cut-off of cortisol suppression greater than 80%, although a specificity of 100% can never be attained. However, no variation in protocol or criteria allows for complete discrimination between CD and an ectopic source of ACTH.

CRH stimulation test. Most pituitary tumors, and also a few ectopic ACTH-secreting tumors, respond to CRH administration with an increase in plasma ACTH and cortisol levels. In adrenal CS, there is usually little or no cortisol or ACTH response to CRH. The test is performed by injecting iv 1 μg/kg or 100 μg synthetic ovine or human CRH. There is not yet consensus on the criteria for interpreting the response to CRH test. Variability in the interpretation depends on the type of CRH used (human *vs.* ovine), biochemical parameters considered (increase above baseline in ACTH, 35–50%; *vs.*

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cortisol, 14–20%) and evaluated time points (ACTH, 15–30 min; cortisol, 15–45 min) (18–20). However, because ectopic ACTH-producing tumors can also respond to CRH, increasing the cut-off level of the response will not produce 100% specificity, thus preventing complete reliance on this test alone.

Desmopressin and other tests under investigation. Intravenous administration of desmopressin (a preferential V2 and V3-vasopressin receptor agonist) 10 μg increases ACTH secretion in 80–90% of patients with CD and only rarely in normal individuals or patients with pseudo-CS. Desmopressin is easily available and inexpensive, and it does not cause significant adverse effects. However, 20–50% of ectopic ACTH-secreting tumors respond to desmopressin, thus limiting its usefulness in distinguishing the source of excess ACTH (21). The combination of CRH and desmopressin appeared to increase the discriminatory value above either test alone, but more recent data cast doubt on the clinical value of the combined test (21). Desmopressin might be useful in the differential diagnosis between CD and pseudo-CS (22) and in the postoperative assessment of CD (see below) (23).

In CD, GH secretagogues are more potent than CRH and vasopressin in stimulating ACTH release, particularly in pituitary microadenomas and, to a lesser extent, in macroadenomas (24). However, GH secretagogues can also stimulate ACTH secretion from ectopic ACTH-secreting tumors. For these reasons, these substances cannot be recommended for standard clinical practice.

Opiate agonists, such as loperamide, have been shown to inhibit ACTH in most normal individuals but not in patients with CS; opiate antagonists, such as naloxone, can stimulate ACTH in patients with CS to a lesser extent than in normal individuals. However, there appears to be overlap between patients with CS and healthy individuals, and it will be necessary to investigate a larger number of patients, including some with ectopic ACTH secretion, to better evaluate the utility of these substances (4). Additional studies using other regulators of ACTH, such as IL-6, or the CRH receptor antagonists, such as antalarmin, will be of interest.

Caution should be exercised when interpreting tests used for differential diagnosis if the history is short, if the clinical signs are modest, if there has been recent use of drugs such as ketoconazole or metyrapone, or if UFC levels are only modestly raised because in these situations, normal corticotroph cells may not be suppressed and may respond to the stimulation tests.

Pituitary MRI. A pituitary MRI with gadolinium enhancement should be performed in all patients with ACTH-dependent CS. This procedure will reveal a discrete pituitary adenoma in up to 60% of patients (2, 20). In the patient with a classic clinical presentation and dynamic biochemical studies compatible with pituitary CS, the presence of a focal lesion (>6 mm) on pituitary MRI may provide a definitive diagnosis, and no further evaluation may be required. However, it is important to realize that 10% of the general population harbor incidental pituitary tumors disclosed on MRI, although the majority of these lesions are less than 5 mm in diameter.

Bilateral inferior petrosal sinus sampling (BIPSS). BIPSS for ACTH determination should be recommended in patients with ACTH-dependent CS whose clinical, biochemical, or radiological studies are discordant or equivocal. BIPSS has rarely been associated with significant complications including deep vein thrombosis, pulmonary emboli, and brain stem vascular damage. The procedure should be performed when cortisol levels are elevated, indicating currently active secretion of ACTH by the tumor, and avoiding testing during an inactive cycled-out phase of CS. Because the results of BIPSS as well as the incidence of these adverse events are related to the experience of the radiology team, this procedure should be performed only in specialized centers.

After the radiologist catheterizes both inferior petrosal sinuses (IPSs), blood samples for ACTH are obtained in the basal state and at 3 and 5 min (and at 10 min in some centers) after iv ovine or human CRH (1 μg/kg or 100 μg iv) simultaneously from both IPSs and a peripheral vein. Subtraction digital angiography should be used to verify appropriate catheter placement and normal petrosal sinus anatomy.

An IPS to peripheral ACTH ratio (IPS/P) greater than 2.0 in the basal state and/or greater than 3.0 after CRH is consistent with CD. BIPSS in experienced centers has a very high sensitivity (95–99%) for CD (25). However, technical factors as well as anomalous venous drainage may result in false-negative results in patients with a pituitary source of ACTH. Lower IPS/P ratios suggest an ectopic ACTH-secreting tumor with a specificity of 95–99% although patients with CD (which is ~10 times more common) may very rarely show similar low ratios.

The use of IPSS for the localization of pituitary microadenoma to the right or left side of the pituitary gland is controversial, and its diagnostic accuracy in identifying the site of a pituitary microadenoma is disputed (4, 25). However, in a recent study in a small series of children, BIPSS appeared to be more accurate than other imaging studies (26).

In recent years, different sites of venous sampling (cavernous and jugular veins) have been used, but BIPPS remains the best test for the identification of CD.

Search for occult ectopic ACTH-secreting tumors. The majority of nonpituitary ACTH-secreting tumors are neuroendocrine neoplasms such as bronchial/thymic/pancreatic carcinoids, islet cell pancreatic tumors, medullary thyroid cancer, and pheochromocytomas. If BIPSS confirms the lack of a pituitary ACTH gradient, CT and/or MRI of the neck, thorax, and abdomen should be performed. MRI of the chest may uncover bronchial carcinoid tumors overlooked on CT imaging. Somatostatin analog scintigraphy with ^{111}In-pentetreotide may identify a few occult ACTH-secreting tumors with somatostatin receptors that were not clearly identified by CT or MRI imaging (27). The utility of positron emission tomography scanning in the search for occult ACTH-secreting tumors is not yet established.

Criteria for Biochemical Assessment of Remission or "Cure" of CD

It is important to treat CD as rapidly as possible to limit its long-term morbidity. Transsphenoidal surgery, the first-line treatment, offers both a possibility of prompt remission of the condition and a return to normal. The goal of the

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treatment is the complete resection of the pituitary adenoma with correction of hypercortisolism without inducing permanent pituitary deficiencies. There is still no widespread agreement regarding the definition of apparent cure, and the remission rates after such surgery vary according to the criterion used and the time of assessment. Indeed, the definition of cure and the prognostic effect of subtle or unrecognized residual hypercortisolism have a major clinical impact on the follow-up and therapeutic decisions in patients with CD. Most series from major centers quote remission rates of 70–80%, defining remission as a series of normal postoperative cortisol levels, either as a mean of serial serum cortisol measurements, obtained throughout the day, of 5.4–10.8 μg/dl (150–300 nmol/liter), or as a UFC in the normal range, associated with resolution of clinical stigmata. However, the long-term follow-up of such patients shows a significant incidence of recurrence (~25% at 10 yr) (20, 28, 29).

Very low serum cortisol below 1.8 μg/dl (50 nmol/liter at 0900 h) within 2 wk after surgery is probably the best index of remission, but even when this is the case very occasional late relapses have occurred (30–32). Cortisol is usually measured 5–14 d after surgery and at least 24 h after the last dose of hydrocortisone (33). With this criterion 1.8 μg/dl (<50 nmol/liter), the surgical remission rate is only 40–65% even in the most experienced hands. It should also be borne in mind that the 0900 h serum cortisol may fall with time after the operation, occasionally over several weeks, and that mild or cyclical hypercortisolism may complicate the interpretation of test results (34).

Dynamic tests such as CRH or desmopressin stimulation, DST, and loperamide inhibition can be used to predict recurrence. Recent studies have confirmed the usefulness of an early CRH test (20, 35), the rationale being that early responsiveness may indicate the presence of residual tumor. The use of the desmopressin test is also promising (20). Nevertheless, it should be kept in mind that although each test can differentiate patients who recur from those who do not as a group, none has sufficiently high diagnostic predictive value for an individual patient.

It is becoming apparent that long-term results of transsphenoidal surgery may not be as favorable as previously thought and that success rates drop during long-term follow-up. Indeed, the risk of relapse persists for at least 10 yr after surgery, if not longer. This fact, and possible ongoing subtle abnormalities in patients in apparent remission and with the risks of surgically induced hypopituitarism, warrant serious discussion regarding the results of surgery, and also emphasize the need for stringent and indefinite follow-up of these patients.

Part I conclusions

The evaluation of patients with suspected CS is complex and expensive, and the diagnosis is often a challenge for clinicians. Most patients initially suspected of having CS will not have this condition, and therefore efficient screening procedures are needed to identify the few patients who will need additional investigation in specialized centers.

Atypical clinical presentations (mild hypercortisolism, cyclical CS, subclinical CS) or forms of pseudo-CS (depression, alcoholism) further complicate the assessment.

The laboratory investigations of CS are based on the demonstration of inappropriate cortisol secretion with loss of its physiological negative feedback. Several tests have been used extensively, but none has proven fully capable of distinguishing all cases of CS, and an appropriate ordered cascade of tests is necessary (Fig. 1). Measurement of cortisol in more than one 24-h urinary collection and/or the low-dose DST are recommended as first line screening test, with the recognition that false-positive tests are common, depending on the criterion for interpretation that is used. Late-night salivary cortisol also is

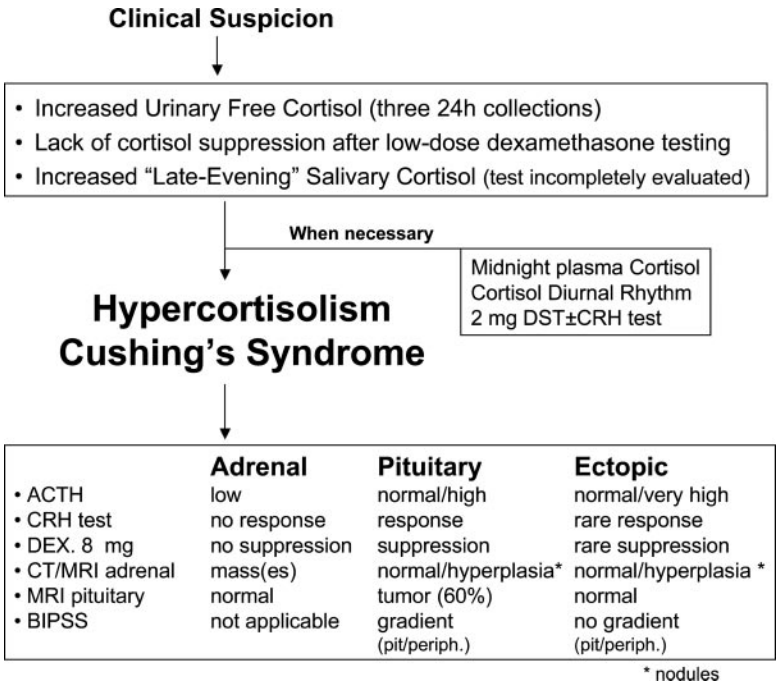

FIG. 1. Pathways to the diagnosis of CS.

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proposed as a useful screening test, although published data are still preliminary. The diagnostic evaluation should not proceed to attempt to establish the precise etiology of hypercortisolism unless the diagnosis of CS is unequivocal. ACTH levels, the CRH stimulation test, the high-dose DST, and appropriate imaging are the most useful noninvasive investigations for the differential diagnosis of CS. BIPSS for ACTH measurement is recommended in patients with ACTH-dependent CS whose clinical, biochemical, or radiological studies are discordant or equivocal.

There is still no widespread agreement regarding the definition of cure after surgery. A very low serum cortisol early after surgery seems to be the best index of remission. Dynamic tests cannot predict recurrence in a given individual, although they may suggest increased or decreased risk.

Part II: Diagnosis and Treatment of Complications of CS

Patients with CS have a mortality rate four times higher than age- and gender-matched subjects; this is due to the complications of the syndrome (36). The majority of the complications are correlated with direct and/or indirect effects of glucocorticoid excess, and therefore, the primary goal in the prevention and treatment of complications is the correction of hypercortisolism.

Cardiovascular risk factors and complications

The higher mortality rate observed in CS seems to be mainly caused by cardiovascular complications. Chronic hypercortisolism is associated with an increased incidence of cardiovascular risk factors such as systemic arterial hypertension, impaired glucose tolerance or diabetes, central obesity, hyperlipidemia, and hypercoagulability. In the following section, the cardiovascular effects of hypercortisolism will be reviewed.

Hypertension. Arterial hypertension is a common feature in CS (70–80% of the patients) and may be the first sign of CS. There is no apparent difference in the prevalence in hypertension among patients with adrenal or pituitary CS. Patients with severe hypercortisolism may present with hypokalemia as well, due to the mineralcorticoid effect of cortisol. The prevalence of hypertension increases with age (37) and, whereas it is less frequent than in adults (up to 50%), it is a common hallmark in children and adolescents with CS (38).

Although hypertension in CS is usually mild to moderate, it may be severe, and the physiological nocturnal decline in blood pressure may be absent. Hypertension-induced organ damage, particularly cardiac hypertrophy, is frequent. Long-lasting exposure to excess circulating cortisol also may contribute directly to left ventricular concentric remodeling in patients with CS (39). Although not routine, some use echocardiography in the initial evaluation and the follow-up of selected patients with CS and hypertension. Similarly, ultrasound scanning of the carotid arteries may be useful for the determination of the global cardiovascular risk in CS patients.

Conventional antihypertensive therapy (thiazides, angiotensin-converting enzyme inhibitors, and calcium antagonists are generally considered as first choice) may be only partially effective, whereas the additional successful use of cortisol-lowering agents may improve blood pressure control (40). Hypertension remits in most patients after successful treatment but may persist, presumably because of microvessel remodeling and/or concomitant underlying essential hypertension (41).

Vascular damage is one of the multiple mechanisms involved in the pathogenesis of glucocorticoid-induced hypertension. Other possible mechanisms include: activation of the renin-angiotensin system; enhancement of cardiovascular inotropic and pressor reactivity to vasoactive substances (including catecholamines, vasopressin, angiotensin II, and erythropoietin) and suppression of vasodilatory mechanisms, including nitric oxide synthase, prostacyclin, and kinin-kallikrein. In addition, cortisol has intrinsic mineralocorticoid activity, and in the presence of very high cortisol levels, the regulatory renal enzyme 11β-hydroxysteroid-dehydrogenase type 2 may not be able to inactivate the hormone, leading to hypertension and hypokalemia particularly in the ectopic ACTH syndrome (42). Some adrenal tumors may secrete other mineralcorticoids such as deoxycorticosterone.

In conclusion, hypertension is common in adults with CS and should be treated by both correcting the hypercortisolism and using standard practice for essential hypertension, before and after remission of the syndrome.

Impaired glucose tolerance and diabetes. Hypercortisolism promotes the development of hyperglycemia and decreased carbohydrate tolerance by increasing hepatic glycogen and glucose production and decreasing glucose uptake and utilization by peripheral tissues.

Epidemiological studies have shown a variable prevalence of abnormalities of glucose metabolism: 20–50% of the patients suffer from overt diabetes mellitus whereas impaired glucose tolerance is present in 30–60% of patients. The prevalence of glucose metabolism abnormalities is probably underestimated, because an oral glucose tolerance test is not always performed in patients with active CS. Thus, an oral glucose tolerance test may be useful for the assessment of global cardiovascular risk in these patients (43).

Obesity. Increased body weight is one of the earliest signs of CS, with a characteristic redistribution of fat from peripheral to central parts of the body, mainly in the abdominal region. Glucocorticoids play a central role in the abdominal accumulation of body fat. An increased local generation of cortisol may take place in visceral adipose tissue because of high activity of 11β-hydroxysteroid dehydrogenase type I, resulting in high local concentrations of cortisol, by converting inactive cortisone into active cortisol. Visceral obesity is an independent risk factor for reduced life expectancy and also correlates with increased risk for disorders such as insulin resistance and diabetes, hyperlipidemia, hypertension, and atherosclerosis of coronary, cerebral, and peripheral vessels (44).

Hyperlipidemia. In hypercortisolism, there is an increase in circulating very low-density lipoprotein and low-density lipoprotein, but not high-density lipoprotein, with consequent elevation of total triglycerides and cholesterol levels. The mechanisms for these changes are probably multifactorial,

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including direct cortisol influences on very low-density lipoprotein synthesis, free fatty acid production, and hepatic endothelial lipase activity (44–46). The insulin resistance state induced by glucocorticoid excess is likely to play a key role in the determination of lipid abnormalities.

Coagulopathy. A complex derangement of the hemostatic system, characterized by both hypercoagulability and impaired fibrinolysis, is responsible for the thrombophilic state observed in patients with CS. Increased cortisol levels stimulate the synthesis of several clotting factors, such as fibrinogen by the liver, and von Willebrand factor by endothelial cells. Glucocorticoids also up-regulate the synthesis of plasminogen activator inhibitor type 1, the main inhibitor of the fibrinolytic system (47, 48).

This hypercoagulability state is a crucial factor predisposing CS patients to thromboembolic events, mostly after surgery and during IPS sampling. Therefore, patients with active CS should be treated as having a prothrombotic disorder, and antithrombotic prophylaxis should be considered. In the absence of prospective randomized trials, there is general agreement that patients with CS should be given heparin during IPS sampling, and low-dose heparin treatment should be considered in the immediate perioperative period.

Metabolic syndrome. In summary, patients with CS develop the manifestations of the metabolic syndrome or syndrome X, including insulin resistance, visceral adiposity, dyslipidemia, carbohydrate intolerance, and/or diabetes mellitus type 2, coagulopathy, and hypertension as a direct or indirect consequence of concurrent and chronic cortisol excess. The abnormalities enhance the global cardiovascular risk that is responsible for the increased mortality of these patients. Therefore, quantification of cardiovascular risk is important, especially if therapy does not normalize cortisol levels or the patients relapse. Additionally, increased cardiovascular risk may persist after the cure of CS (49).

Patients with the metabolic syndrome require treatment of hypercortisolism as well as treatment of cardiovascular risk factors, according to standard practice.

Osteoporosis

Pathological fractures can be the presenting manifestation of CS (50, 51). Limited data from cross-sectional studies show that 30–50% of patients experience fractures, particularly at the vertebral level. These are serious complications not only because they can cause back pain, kyphosis, and height loss, but also because they can anticipate subsequent, nonvertebral fractures independent of bone mineral density (BMD) (51). Using dual energy x-ray absorptiometry (DEXA), the prevalence of osteoporosis in adult patients with CS was approximately 50% (51).

Bone alterations cause greater morbidity in children because of the severe growth failure and pubertal arrest leading to reduced final adult height. Hypercortisolism in children may also lead to a reduction in peak bone mass, presumably increasing the long-term risk of osteoporosis (52). Glucocorticoids influence bone and calcium metabolism at many levels, although the exact mechanisms are not fully understood (53). It is thought that glucocorticoids cause loss of cortical osteocytes and thus prevent bone repair. Inhibition of GH secretion, hypogonadism, and target tissue effects of growth factors, as well as direct effects of glucocorticoids on osteoblasts, also may decrease BMD (52, 54). Glucocorticoids decrease bone collagenous matrix synthesis and increase its degradation. The decrease in osteoblast number and function is reflected by decreased serum levels of osteocalcin and alkaline phosphatase, both markers of osteoblastic function (55). Glucocorticoids inhibit calcium absorption from the gut through a mechanism independent of vitamin D, and also inhibit calcium reabsorption by the renal tubule. PTH does not seem to play a major role in glucocorticoid-induced osteoporosis (56).

There is some evidence to suggest that deficits in bone mass may be partially reversed after remission of hypercortisolism. Osteoblastic activity increases, as judged by increased osteocalcin levels, within months after normalization of glucocorticoid excess (51). Long-term studies have demonstrated an overall improvement of BMD in patients successfully treated for CS, and even normalization of BMD after a mean period of 9 yr (57). The recovery of BMD may be explained by the preservation of trabecular architecture despite trabecular thinning in glucocorticoid-induced osteoporosis. This contrasts with the loss of trabecular bone that occurs in other forms of osteoporosis. It is reasonable to measure BMD, with DEXA, at the level of lumbar spine in all patients with CS and to consider antiresorptive therapy in those with osteoporosis. Quantitative ultrasound has been proposed as a useful tool for assessing bone microarchitectural involvement in CS, but its relevance cannot be ascertained in the absence of the availability of longitudinal data (51). Vertebral CT scan also can be used to assess osteoporosis in patients with CS (51). Patients with severe osteopenia have a high risk of fracture. Therefore, in these patients, the use of antiresorptive medication could be useful. Data suggest that alendronate may induce a more rapid improvement in BMD than cortisol normalization alone, probably by restoring the balance between bone formation and bone resorption (58). Although there are no large prospective studies in patients with CS, additional therapeutic strategies, such as provision of adequate calcium and vitamin D and sex hormone replacement in men or women with hypogonadism, are likely to have benefit.

New data on the use of PTH in glucocorticoid-induced osteoporosis are encouraging (59) and suggest a potential role for this anabolic therapy.

The risk of fractures persists some time after cure of hypercortisolism, and the decision to discontinue antiresorptive therapy should be based on clinical monitoring and DEXA measurements.

Psychological and cognitive alterations

Glucocorticoids affect behavior, mood, neural activity, and a number of specific biochemical processes in the central nervous system. A number of psychiatric and psychological disturbances may be associated with CS, regardless of its etiology. Depending on the series, 50–80% of patients with CS meet Diagnostic and Statistical Manual of Mental Disorders IV criteria for major depression (60, 61). A minority of patients have other psychopathological manifestations including mania, anxiety, and cognitive dysfunction. If psychotic symptoms occur, they are likely to be a complication

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of mania or severe depression. Suicidal tendency also has been reported in patients with CS (61). The presence of depressive symptoms can be an early manifestation of CS and correlates with the severity of the clinical presentation (60).

In contrast to adults, hypercortisolemic children have been reported to exhibit obsessive-compulsive behavior (62). Physicians should address psychiatric, cognitive, and quality of life issues in CS patients; this includes questioning all patients about anxiety, depression, and suicidal ideation with consideration of referral to a psychiatrist, if appropriate.

Normalization of cortisol, ideally with surgery, is the mainstay of treatment of depression. Successful medical inhibition of steroid production generally improves depressive as well as other disabling psychological symptoms (60, 63, 64). Although antidepressants are less effective, they may be the only treatment option while patients are undergoing evaluation that requires persistent hypercortisolism.

Despite cure of hypercortisolism, many patients exhibit residual symptoms in the first postoperative year or even longer, including problems with social and interpersonal relationships, anxiety, irritability, and demoralization, while children may show a deterioration in school performance (60, 64). The long-term reversibility of psychiatric symptoms has not been well-studied. After normalization of cortisol levels, treatment may incorporate both psychotherapeutic strategies and utilization of psychotropic drugs treatment (antidepressant agents such as tricyclics or selective serotonin reuptake inhibitors). In cases of severe anxiety, benzodiazepines (*e.g.* clonazepam at small doses) may also be helpful (60).

Adults with hypercortisolism have also impaired cognitive function associated with reversible apparent loss of brain volume. Cognitive deficits are often specific to the medial temporal lobe declarative memory system. Adult patients studied 1 yr after surgical cure show improvement in mood but no change in cognitive function, with a concomitant increased, but not normalization, of brain volume. Longer follow-up periods are needed to determine whether cognitive, emotional, and anatomical abnormalities are fully reversible (65, 66).

Physicians should advise patients and their families about the persistent psychosocial and cognitive abnormalities after surgical remission. Counseling and the use of written educational materials that detail the expected postoperative course may reduce demoralization and psychological distress after CS remission.

Alterations of other endocrine systems

Somatotropic axis. The somatotropic axis is negatively affected by exogenous or endogenous (54, 67) hypercortisolism, which reduces spontaneous GH secretion as well as the GH response to various stimuli, although with apparently minor changes in circulating IGF-I.

The impairment of somatic growth, observed in children, is primarily due to the ability of glucocorticoids to inhibit directly the development of epiphyseal cartilage in the growing long bones of children. After normalization of cortisol, children with a retarded linear growth rate should be evaluated and treated with GH as soon as possible, because there is a limited window of opportunity to promote an increase in linear growth and attain a normal adult height (68, 69). If a delay of epiphyseal closure is judged necessary, the puberty of the patients can be arrested with GnRH analogs, although the success of this strategy has not been established.

On the other hand, there is no agreement regarding the utility of GH replacement therapy in adults. An impaired GH response to GH secretagogues may persist in adult patients as long as 2 yr after successful treatment (70). GH replacement may be considered in such cases, because GH promotes an increase in muscle mass, a decrease in fat mass, and an increase in BMD, as well as a general feeling of well-being.

Gonadal axis. Reproductive function is often altered in CS; men usually exhibit features of hypogonadotropic hypogonadism, whereas women of reproductive age have oligo- or anovulation. Women with CS may have gonadal dysfunction reminiscent of polycystic ovary syndrome, including: oligomenorrhea or amenorrhea, adrenal hyperandrogenism with acne, and/or hirsutism and the metabolic syndrome. In some cases, mild hyperprolactinemia may also be present (71, 72).

Hormone replacement therapy during the active phase of the disease is not usually recommended in women, because of the high thromboembolic risk.

There are no data about restoration of gonadal axis function after treatment. However, men and premenopausal women should be evaluated 3 months after successful treatment, and if gonadal function has not recovered, gonadal steroid replacement should be considered. In women, transdermal estrogen replacement should be considered to reduce the effects of estrogens on liver function and perhaps the risk of thromboembolic disease.

Thyroid axis. Hypercortisolism suppresses thyroid function, probably through inhibition of TRH and TSH secretion and suppression of the 5′-deiodinase enzyme that converts T_4 into active T_3. Central hypothyroidism usually persists for at least 3 months after surgical cure of hypercortisolism. During this time, central hypothyroidism may contribute to fatigue and other postoperative symptoms. The time-course of recovery of the hypothalamo-pituitary-thyroid axis is not well known. Patients with persistently subnormal free T_4 values should receive T_4 replacement therapy, using free T_4 and not TSH plasma levels as the therapeutic end point. In addition, successful cure of hypercortisolism may unmask a preexisting primary autoimmune thyroid disease, which may present either as hypothyroidism or transient hyperthyroidism (73, 74).

Effects of subclinical hypercortisolism. Subclinical hypercortisolism (minimal autonomous cortisol hypersecretion) is present in at least 10% of adrenal incidentalomas (75). A recent case-controlled analysis showed that subclinical CS of adrenal adenomas may be associated with features of the metabolic syndrome such as impaired glucose tolerance, insulin resistance, increased blood pressure, high triglyceride levels, and increased visceral fat mass. These subjects also demonstrated an adverse cardiovascular and metabolic risk compared with controls matched for gender, age, and body mass index (76).

For these reasons, patients with adrenal incidentalomas with a small degree of cortisol oversecretion should be enrolled in a

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program of regular and careful follow-up to detect and treat all features of the metabolic syndrome.

Finally, although abnormalities in biochemical markers of bone function have been described in patients with incidentalomas, data on BMD in this condition are discordant.

Part II conclusions

Most patients with CS develop some manifestations of the metabolic syndrome or syndrome X, which may persist a long time after remission of the hypercortisolism. The metabolic syndrome contributes to the increased cardiovascular risk observed in these patients and should be treated according to common standard practice. The possibility of a prothrombotic tendency also should be considered in these patients.

Osteoporosis is a frequent complication in CS. Considering the high prevalence of fractures, it is reasonable to measure BMD, with lumbar spine DEXA, and to consider antiresorptive therapy if osteoporosis is present.

Normalization of cortisol is the mainstay for prevention and treatment of nearly all complications of hypercortisolism. This is also true for depression, the major psychiatric complication of CS, and for cognitive impairment that is associated with apparent loss of brain volume. Although conventional antidepressants may treat major depression in the postoperative period, there is no general agreement in their effectiveness in hypercortisolemic patients. Physicians should counsel patients and their families about the persistent psychosocial and cognitive abnormalities after surgical remission.

Other endocrine abnormalities of this syndrome include impairment of somatotropic, gonadal, and thyroid function. Children with treated CS, retarded linear growth, and biochemical evidence of GH deficiency should be evaluated and treated with GH replacement as soon as possible. GH replacement may be considered in adults. Reproductive function is often altered in CS, and gonadal steroid replacement should be instituted in men and women with persistent hypogonadism after correction of hypercortisolism. Patients with central hypothyroidism should receive T_4 replacement therapy, using free T_4, not TSH, as the therapeutic end point.

In conclusion, the complications of CS may significantly alter life expectancy as well as life quality even in patients apparently cured by surgery. Therefore, particular efforts should be made by clinicians to diagnose and appropriately treat complications of this disorder. Appropriate laboratory and clinical examinations are required, with strenuous attempts to control hypercortisolism as well as the use of standard pharmacological treatment for any specific complications as necessary.

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