CLINICAL REVIEW: Cushing's Syndrome: Important Issues in Diagnosis and Management

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Context: The diagnosis, differential diagnosis, and treatment of Cushing's syndrome are challenging problems in clinical endocrinology. We focus on critical questions addressing screening for Cushing's syndrome, differentiation of Cushing's subtypes, and treatment options.

Evidence Acquisition: Ovid's MEDLINE (1996 through April 2006) was used to search the general literature. We also relied on previously published reviews and a recent monograph and cite a mix of primary articles and recent reviews.

Evidence Synthesis: Although this article represents our opinion, it draws heavily on a recent consensus statement from experts in the field and a recent monograph on Cushing's syndrome.

Conclusions: We concluded that: 1) measurement of late-night or bedtime salivary cortisol is a useful approach to screen for Cushing's syndrome; 2) measurement of suppressed plasma ACTH by immunometric assay is useful to differentiate ACTH-dependent and -independent Cushing's syndrome; 3) inferior petrosal sinus sampling for ACTH should be performed in patients with ACTH-dependent hypercortisolism in whom a pituitary magnetic resonance imaging is normal or equivocal (in the absence of a pituitary ACTH gradient, prolactin levels should be measured to confirm the integrity of venous sampling); 4) computed tomography of the chest and abdomen and somatostatin receptor scintigraphy should be performed in patients with the occult ectopic ACTH syndrome; and 5) patients with Cushing's disease should be referred to a neurosurgeon with extensive experience operating on corticotroph microadenomas. Bilateral laparoscopic adrenalectomy should be considered in patients with Cushing's disease who fail therapies directed at the pituitary. (*J Clin Endocrinol Metab* 91: 3746–3753, 2006)

THE DIAGNOSIS, DIFFERENTIAL diagnosis, and treatment of Cushing's syndrome (hypercortisolism) are challenging problems in clinical endocrinology. One of the many manifestations of the obesity epidemic is the increase in the number of patients with the Cushing's phenotype. This makes the use of an accurate but simple screening test vital if one is to find the relatively unusual patient with true endogenous Cushing's syndrome among the many patients who have some of the manifestations of hypercortisolism. Once the diagnosis is made, the accurate differentiation of Cushing's syndrome into its subtypes is essential so that the appropriate treatment option can be selected. For the purposes of this brief review, we will focus on endogenous hypercortisolism with the acknowledgment of the existence of iatrogenic Cushing's syndrome due to widespread use of pharmacological glucocorticoid therapy (1).

We, and others, have extensively reviewed Cushing's syndrome as a diagnostic and treatment dilemma (2–8). The reader is encouraged to consult a recent in-depth monograph published on this topic for detailed expositions on each aspect of Cushing's syndrome (9). This review will focus on major issues confronting the clinical endocrinologist when considering the diagnosis, differential diagnosis, and treat-

ment of Cushing's syndrome. We will use a Socratic approach in which we pose questions addressing the most critical clinical problems associated with Cushing's syndrome and then provide a focused answer to each question.

Question 1: Who Should Be Screened for Cushing's Syndrome, and What Is the Best (*i.e.* Reliable and Simple) Approach?

Question 1A: Who should be screened?

Endogenous Cushing's syndrome is a relatively unusual condition that resembles many of the phenotypic features of modern life: obesity, hypertension, and depression (2, 4, 6–8). Accordingly, it is important to identify those signs and symptoms that warrant a screening test for Cushing's syndrome. A common complaint is weight gain with redistribution of adipose mass centrally (face, neck, trunk, and abdomen). This weight gain can occur at a wide range of rates and sometimes can occur over more than a decade. Significant dorsocervical fat accumulation and, more specifically, supraclavicular and temporal fossa fullness are examples of findings warranting a screening test for Cushing's syndrome.

Endogenous cortisol excess also leads to fairly specific catabolic effects. These include thinning of the skin with easy bruising, abdominal striae (usually in younger patients), poor wound healing, immune suppression (opportunistic and fungal infections), rib fractures, hirsutism in women, acne, and muscle wasting leading to proximal muscle weakness. Finally, decreased growth velocity in children with Cushing's syndrome is a common finding (10, 11).

Mood changes (usually depression) are also a common

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finding, although mania, anxiety, and cognitive dysfunction can also be found (12, 13). In its extreme, psychosis and suicidal tendencies can occur.

Diagnostic testing for spontaneous Cushing's syndrome should also be considered in patients with clinical disorders caused or aggravated by hypercortisolism. There is a 2–5% prevalence of unsuspected Cushing's syndrome in patients with poorly controlled diabetes mellitus (14, 15). A preliminary study also found that as many as 3% of patients with osteoporosis have mild hypercortisolism (16). Because the clinical features of polycystic ovary syndrome may overlap with those of hypercortisolism (17), it would seem prudent to screen the majority of women with polycystic ovary syndrome. It is also appreciated that up to 9% of patients with incidental adrenal nodules (>2 cm) have evidence of hypercortisolism (18).

Question 1B: How should patients be screened?

Because it is clear from the above that many patients should be screened for Cushing's syndrome, it is imperative that the tests chosen have an adequate sensitivity and specificity, ease of use, and reasonable cost.

Late-night/midnight serum or salivary cortisol. One of the earliest biochemical abnormalities in Cushing's syndrome of any cause is the failure to fully suppress plasma cortisol at or near its late-night circadian nadir (5). Obtaining a stress-free, sleeping midnight blood sample for serum cortisol sample is not feasible under all but the most controlled clinical environments, making it suboptimal for most clinicians (19–22). It has now been convincingly demonstrated in 10 studies in adults and children that an elevated late-night or bedtime salivary cortisol sampling is an excellent surrogate for increased midnight serum cortisol in the diagnosis of Cushing's syndrome (23–32). There does not appear to be a difference in performance between bedtime (2300 h) and midnight salivary cortisol sampling (26, 28, 32). Of course, one should always verify that the patient has a typical sleep/wake cycle and that the sampling was done at the proper time (5).

Late-night salivary cortisol has also been shown to be useful to identify patients with pseudo-Cushing's syndrome, *i.e.* the presence of the Cushingoid habitus associated with alcohol intake, type 2 diabetes, and major depression (28, 32). There are several conditions such as hypertension, advanced age, and psychiatric diagnoses that may lead to false-positive late-night salivary cortisol results (33). However, repeat testing is often normal in these false-positive situations, whereas it is usually not in true endogenous Cushing's syndrome (29, 33). As with any hormone, different assay methodologies have different sensitivities, specificities, and reference ranges. Despite these caveats, we conclude that this is the best approach: it is simple, can be performed on patients with a very wide age range, has a sensitivity and specificity of greater than 90–95%, is now available at many reference laboratories,[1] and can be measured by a Food and Drug Administration-cleared ELISA available internationally (35).

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[1] www.acllab.com; www.aruplab.com; www.esoterix.com; www.questdiagnostics.com; www.mayoreferenceservices.org.

Its usefulness to the practicing endocrinologist is indisputable (36).

Urine free cortisol (UFC) and low-dose dexamethasone suppression testing (LDDST). Although late-night or midnight assessment of cortisol appears to be the most sensitive and specific screening test, UFC and LDDST continue to be used to screen for endogenous hypercortisolism. UFC depends on the notion that increases in the daily release of cortisol from the adrenal cortex will be reflected in the free cortisol filtered in the kidney. Morning cortisol levels are not elevated in many patients with Cushing's syndrome, whereas late-night cortisol is usually increased (26). Therefore, we theorize that small increases in cortisol production at the circadian nadir may not be detected as an increase in UFC (4). Furthermore, differences in assay methodology may make interpretation of the data very challenging (37–40). It is clear that the sensitivity of UFC for Cushing's syndrome may be only 45–71% at 100% specificity (20, 21, 24, 31). Furthermore, pseudo-Cushing's states may have false-positive UFC testing (20, 28). Therefore, although UFC may be useful to confirm Cushing's syndrome (Fig. 1), its sensitivity and specificity are not optimal as an initial screening test (4).

The LDDST depends on the notion that just the correct dose of dexamethasone will suppress ACTH, and hence cortisol release in normal subjects, whereas patients with corticotroph adenomas will not suppress below a specified cutoff. Because of the significant variability of the biological behavior of corticotroph adenomas, neither the overnight nor 2-d LDDST test appears to be able to reliably rule out Cushing's syndrome using standard cutoffs for serum cortisol (41–43). The consensus of experts in the field is that, to be reliable, the cutoff for serum cortisol in the overnight LDDST should be less than 1.8 μg/dl (<50 nmol/liter) (2), which should improve the sensitivity to 95% or greater but
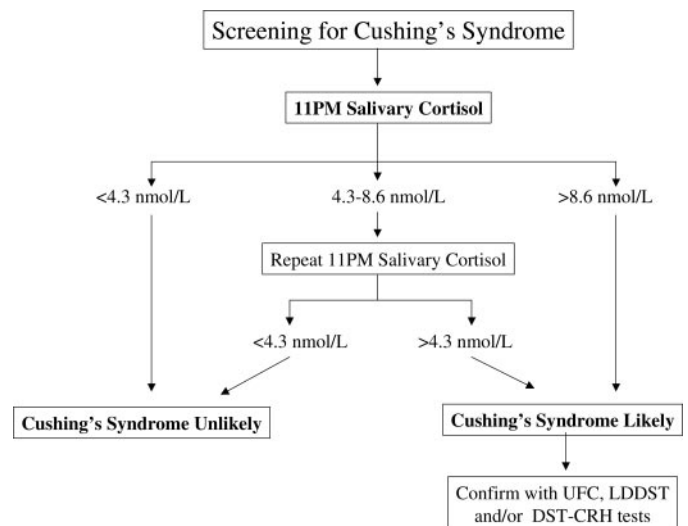

FIG. 1. A simplified paradigm for screening patients for Cushing's syndrome using late-night salivary cortisol (cutoffs for salivary cortisol from Ref. 5). This approach takes advantage of the excellent sensitivity of the test. Confirmatory tests: UFC, 24-h; DST-CRH, combined dexamethasone suppression-CRH stimulation test. [Figure reprinted with permission from J. W. Findling and H. Raff. *Endocrinol Metab Clin North Am* 34:385–402, 2005 (4). © Elsevier.]

will greatly reduce the specificity. We recently reported that approximately 8% of patients with Cushing's disease can have false-negative results [serum cortisol < 2.0 μg/dl (< 55.2 nmol/liter)], indicating that no cutoff can reliably rule out Cushing's syndrome (42). Adding to the problem is that, at the low levels of serum cortisol achieved after LDDST in normal subjects *vs.* those with mild Cushing's disease, differences in assay performance add significant error to the approach (44).

The three commonly performed diagnostic studies for Cushing's syndrome (late-night salivary cortisol, UFC, and LDDST) are complementary. In patients with mild or intermittent hypercortisolism, any of these tests may yield normal results and be misleading. Because of the high sensitivity and ease with which repeated measurements can be performed, late-night salivary cortisol appears to be the most useful screening test. UFC and LDDST should be performed to provide further confirmation of the diagnosis (Fig. 1).

Dexamethasone/CRH test. There are occasional patients in whom the screening tests described above are equivocal (Fig. 1). This is particularly so when trying to distinguish mild pituitary Cushing's disease from the pseudo-Cushing's syndrome (6, 8, 45, 46). The dexamethasone/CRH test has been advocated as the final arbiter of this diagnosis (45, 46). The concept is that the abnormal corticotroph will still respond to CRH, even under dexamethasone suppression. There have been only a handful of studies to verify the use of this expensive and time-consuming test. Furthermore, abnormal dexamethasone/CRH testing has been found in patients with anorexia nervosa (47), raising concerns that other, non-Cushing's related increases in hypothalamic-pituitary adrenal axis activity will lead to false-positive results.

Figure 1 summarizes a suggested approach to screening for Cushing's syndrome. Two late-night (usually 2300 h) salivary cortisol samples are obtained. If they are both normal, Cushing's is ruled out with greater than 95% certainty (4, 29). If they are both greater than twice the upper limit of the reference range, the diagnosis is made with greater than 93% certainty (4, 29, 36). If the results are equivocal, the salivary cortisol tests can be repeated to rule out false-positive tests (33). If they are still abnormal or equivocal, additional testing is warranted to confirm or exclude the diagnosis as indicated in Fig. 1. To confirm the biochemical diagnosis of Cushing's syndrome, we perform repeated measurement of late night salivary cortisol. Levels consistently above the high end of the reference range strongly suggest the diagnosis of Cushing's syndrome. LDDST and UFC should help to provide further diagnostic certainty. If these studies are equivocal or discordant, repeated testing several months later should be recommended in patients in whom there is a reasonable index of clinical suspicion.

Question 2: Is the Diagnosis of ACTH-Independent (Adrenal) Cushing's Excluded if Plasma ACTH Is Not Suppressed below the Reference Range?

Endogenous ACTH-independent Cushing's syndrome is caused by an increased release of cortisol from the adrenal gland not dependent on stimulation by ACTH and has two general causes. The first is autonomous cortisol production due to an adrenal adenoma or, less commonly, carcinoma (48, 49). Second, ACTH-independent increases in cortisol can be secondary to stimulation of the adrenal gland by secretagogues other than ACTH (50). This group of conditions can be lumped into a classification called bilateral nodular adrenal hyperplasia and can be due to adrenocortical expression of receptors for a variety of circulatory factors (*e.g.* glucose-dependent insulinotropic peptide, catecholamines, vasopressin, gonadotropin) (50). Micronodular adrenal hyperplasia, which is often radiologically occult, can be a component of the Carney complex, or may be sporadic, is also a potential and often difficult-to-diagnose cause of ACTH-independent Cushing's syndrome (5, 8). There are also other relatively rare causes of adrenal Cushing's (5, 8). Regardless of the etiology, ACTH is usually suppressed due to glucocorticoid negative feedback (5).

The diagnosis is important because some form of adrenal surgery is the primary therapy for ACTH-independent Cushing's syndrome. The development of the two-site immunometric assay for ACTH has greatly facilitated the diagnosis of adrenal Cushing's syndrome (51, 52) in a manner analogous to the diagnosis of Graves' disease with a suppressed TSH. If morning plasma ACTH is suppressed below the reference range, patients should undergo adrenal imaging by computed tomography or magnetic resonance imaging (MRI) (6, 49).

Klose *et al.* (53) performed an interesting analysis of 34 patients with ACTH-dependent and 22 patients with ACTH-independent Cushing's syndrome. They found one patient with ACTH-independent (adrenal) Cushing's syndrome with one plasma ACTH measurement within but at the low end of the reference range. A second morning ACTH measurement was below the reference range (Fig. 2). Of course, excluding one of two plasma ACTH measurements introduces potential bias and a larger number of patients would have to be studied to prove this approach. It has been shown that a single plasma ACTH at the lower end of the reference range does not exclude adrenal Cushing's, particularly if there is mild or occult disease (14). Therefore, a peripheral CRH test should be performed in patients with Cushing's syndrome whose plasma ACTH is at the low end of the reference range (54, 55). The ACTH response to CRH should be blunted in adrenal Cushing's syndrome due to negative feedback and is usually exaggerated in Cushing's disease if the pituitary tumor expresses the CRH receptor.

Question 3: Under What Circumstances Should the Inferior Petrosal Sinus Be Sampled for an ACTH Gradient to Distinguish between Cushing's Disease and Occult Ectopic ACTH Syndrome?

The vast majority (90–95%) of patients with ACTH-dependent Cushing's syndrome have a pituitary corticotroph microadenoma. Because the pretest probability of Cushing's disease is so high, any differential diagnostic test must be very accurate. Actually, simple clinical measures have been shown to have good predictive value in establishing the presence of Cushing's disease (56). A woman with mild to moderate hypercortisolism, a normal or slightly elevated plasma ACTH, and normokalemia has at least a 95%
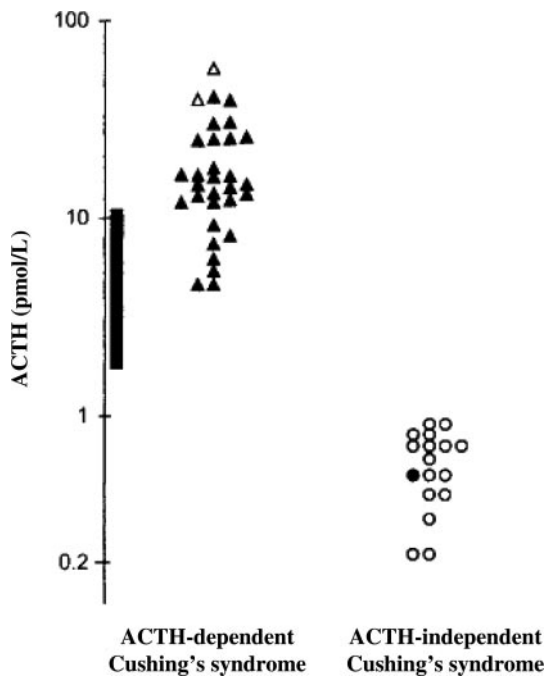
FIG. 2. Basal morning ACTH concentrations measured by immunoradiometric assay in patients with ACTH-dependent Cushing's syndrome (▲, Cushing's disease; △, ectopic ACTH syndrome) and ACTH-independent Cushing's syndrome (○, adrenal adenoma; ●, adrenal carcinoma). *Bar*, Normal range at 0800–1000 h. ACTH concentrations were obtained by selecting the higher of two independent measurements in the ACTH-dependent group and the lower of two in the ACTH-independent group. Multiply by 4.5 to convert to pg/ml. [Figure reprinted with permission from M. Klose, A. Kofoed-Enevoldsen, L. Ostergaard Kristensen. *Scand J Clin Lab Invest* 62:33–38, 2002 (53). © Taylor, Francis AS.]
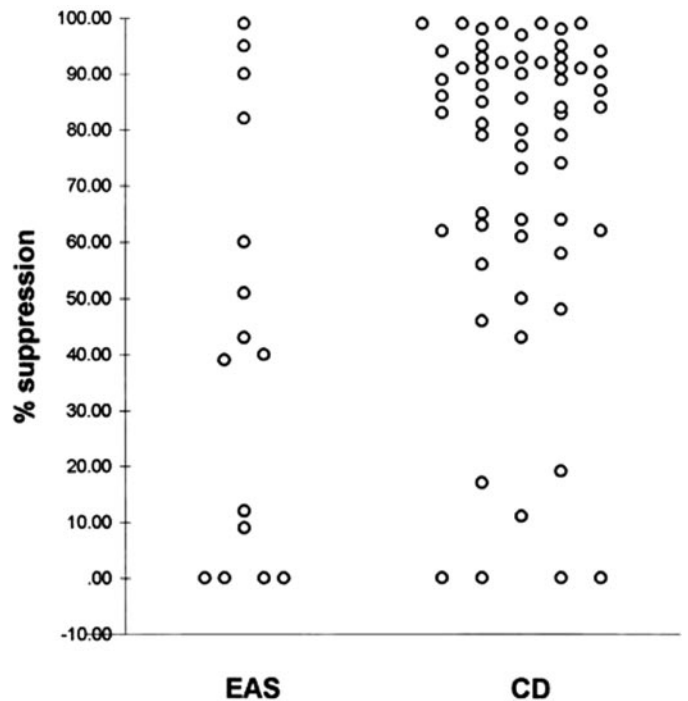
FIG. 3. Percent suppression of serum or urine cortisol with high-dose dexamethasone in patients with Cushing's disease (CD; n = 61) *vs.* ectopic ACTH syndrome (EAS; n = 15). Note that maximum suppression (100%) is at the *top of the graph* and the extensive overlap between the two groups. Three patients with EAS suppressed to more than 90% of baseline, and four patients with CD had no suppression with high-dose dexamethasone. [Figure reprinted with permission from D. C. Aron, H. Raff, and J. W. Findling. *J Clin Endocrinol Metab* 82:1780–1785, 1997 (56). © The Endocrine Society.]

likelihood of having Cushing's disease. In contrast, a patient with prodigious hypercortisolism, hypokalemia, and marked elevations of plasma ACTH may be more likely to have an occult ectopic ACTH-secreting tumor.

Pituitary imaging with MRI is the initial study required. Unfortunately, 40–50% of corticotroph microadenomas causing Cushing's syndrome in adults are not visible with this technique (57). The use of dynamic MRI (with iv gadolinium) with spoiled gradient sequences may increase the sensitivity (58); however, all of this must be weighed against the 10% rate of pituitary incidentalomas in the normal population (59). Nonetheless, the presence of an unequivocal pituitary lesion greater than 6 mm with MRI in the patient without clinical features suggesting an ectopic ACTH secreting tumor (3, 56) is sufficient to proceed with pituitary microsurgery.

We and others have clearly shown that there is little difference between the results of high-dose dexamethasone suppression test in patients with Cushing's disease and those with the ectopic ACTH syndrome (6, 56, 60) (Fig. 3). The continued use of this approach is not justified.

Inferior petrosal sinus ACTH sampling with CRH stimulation is the only study having the potential to yield a diagnostic sensitivity and specificity for Cushing's disease higher than its pretest probability. Clearly, this study must be performed in an experienced center dedicated to per-

forming it safely and correctly. In the presence of documented hypercortisolism (*e.g.* obtaining a salivary cortisol the night before the procedure), the presence of an unequivocal pituitary ACTH gradient [peak dominant inferior petrosal sinus to peripheral ACTH ratio (IPS:P-ACTH) > 2.0 in the basal state and/or > 3.0 after CRH] yields a diagnostic sensitivity of nearly 100% (61, 62). However, the absence of a pituitary ACTH gradient may reflect a false-negative result rather than a true occult ectopic ACTH-secreting tumor. False-negative results with inferior petrosal sinus sampling (IPSS) have been attributed to technical problems during catheterization as well as anomalous venous drainage (63). Recently it has been shown that use of prolactin as an index of the fidelity of pituitary venous sampling may help to identify patients with Cushing's disease, even in the absence of a pituitary ACTH gradient during IPSS (64). This approach may work because prolactin is produced in large quantities by the pituitary gland (64). The establishment of a normalized ACTH to prolactin petrosal sinus to peripheral ratio will help to identify patients with Cushing's disease who fail to have a peak IPS:P-ACTH ratio greater than 3.0 after CRH. Therefore, any patient without a significant pituitary ACTH gradient during IPSS should have samples retrospectively evaluated for a prolactin gradient to ensure that adequate pituitary venous effluent was obtained.

Question 4: What Are the Best Approaches to Search for an Occult ACTH-Secreting Tumor?

The occult ectopic ACTH syndrome reflects the presence of hypercortisolism due to a radiographically and clinically inapparent nonpituitary, ACTH-secreting neoplasm. The majority of occult ectopic ACTH-secreting neoplasms are either bronchial or thymic carcinoids or other neuroendocrine tumors (*e.g.* islet cell, medullary carcinoma of the thyroid, or pheochromocytoma) (3, 65). A radiological search for an occult ACTH-secreting tumor should be instituted only after the diagnosis of Cushing's disease has been excluded by IPSS. Extensive imaging without performing IPSS may result in false-positive studies and lead to surgical misadventures.

Imaging of the thorax and abdomen with computed tomography will yield the highest detection rate in searching for an occult ACTH-secreting neoplasm. MRI of the chest may also provide some additional benefit because some bronchial carcinoids have a central location and may be mistaken on CT scanning for a blood vessel (66).

If these studies fail to yield a positive finding, further studies are usually not helpful. The use of somatostatin receptor scintigraphy may be used because many of the neuroendocrine tumors express somatostatin receptors; however, these tumors may be quite small and the resolution of somatostatin receptor scintigraphy is often not adequate (3, 6). Because of the low metabolic activity of occult ectopic ACTH-secreting neoplasma, an initial study found that positron emission tomography with 18-fluorodeoxyglucose was of little value (67); however, a recent report in three patients suggested some potential benefit particularly as camera techniques are refined (68). The use of C-5-hydroxytryptophan with positron emission tomography scanning has been studied as a universal imaging technique for neuroendocrine tumors, but there are not enough data with ectopic ACTH-secreting tumors to warrant its current use (69). Although tumor markers such as plasma calcitonin, gastrin, glucagon, or somatostatin may often be elevated in patients with ectopic ACTH syndrome, they are rarely helpful in identifying the source of the neoplasm (3). Extensive multiorgan venous sampling for ACTH and even bronchial lavage for ACTH have been reported but seem to have very limited indications (3).

Question 5: What Are Approaches to the Patient with Cushing's Disease Who Has Had Unsuccessful Pituitary Surgery or in Whom Cushing's Disease Has Recurred?

The most important treatment recommendation that an endocrinologist makes to a patient with Cushing's disease is referral to a neurosurgeon with extensive experience in operating on patients with corticotroph microadenomas. Even under the best circumstances, remission rates after transsphenoidal pituitary microsurgery range from 42 to 86% (70). It has been shown that centers performing a large number of pituitary operations have better outcomes and less morbidity and mortality (71).

Immediate postoperative assessment of cortisol secretion provides good prognostic information regarding the outcome in patients with Cushing's disease. Patients whose cortisol levels decrease to less than 2–3 μg/dl (55.2–82.8 nmol/liter) (preferably undetectable) within 24–72 h after surgery usually have a clinical and biochemical remission (70, 72, 73). The absence of secondary adrenal insufficiency 4–6 wk postoperatively suggests that the patient either has persistent hypercortisolism or most likely will have a recurrence. Some neurosurgeons have even advocated reoperation and more complete hypophysectomy within a few days of the initial surgery in patients whose basal cortisol levels fail to suppress satisfactorily (74). Although this may be successful, there are not yet many published data regarding this aggressive approach. Furthermore, even in patients who clearly have a clinical and biochemical remission (preceded by secondary adrenal insufficiency), there is a recurrence rate of 5–25% (70). Consequently, there are many patients with Cushing's disease who either fail initial pituitary surgery or have a recurrence.

The increase morbidity and mortality in patients with Cushing's disease is related to the hypercortisolism and rarely the ACTH-secreting pituitary tumor *per se*. Therefore, the most important treatment goal must be ameliorating the excessive cortisol secretion. In many patients with recurrent or persistent Cushing's disease, offering a repeat pituitary operation may be a reasonable approach, particularly in those with abnormalities on pituitary MRI. Again, there are very few published data on reoperation in Cushing's disease, but the remission rates are clearly less than those in the initial operation (74, 75).

Pituitary radiation (conventional or gamma knife) has been recommended as a means to treat Cushing's disease when surgery fails. Although remission rates of 53–100% have been reported with conventional radiotherapy and as high as 76% in patients using gamma knife radiotherapy, the normalization of cortisol secretion takes 12–36 months mandating adrenostatic therapy to attenuate hypercortisolism in the interim (76, 77). Side effects of pituitary radiation, although uncommon, may be quite serious (77) and include development of a second tumor (astrocytoma), temporal lobe necrosis, and temporal lobe epilepsy. Not surprisingly, the majority of patients who undergo pituitary radiation eventually develop other anterior pituitary hormone deficiencies.

Pharmacological management of Cushing's disease is usually directed at decreasing adrenal steroid secretion. Adrenostatic therapies, including ketoconazole, metyrapone, and aminoglutethimide, all competitively inhibit adrenal enzyme activity and decrease cortisol secretion (78). These drugs must be used two to three times daily, and the doses are usually titrated to maintain a eucortisolemic state. In addition to their individual side effects, these drugs frequently lose effectiveness when the decrease in cortisol secretion results in enhanced ACTH secretion leading to escape from the competitive blockade on adrenal steroid biosynthesis. Mitotane, a drug often used in adrenal carcinoma, has several mechanisms of action that include adrenolytic activity, modification of steroid peripheral metabolism, and direct inhibition of steroidogenesis (78). Acute control of severe hypercortisolism may be achieved with the parenteral administration of the hypnotic agent etomidate that will immediately decrease adrenal steroid production (79).

Drugs acting at the hypothalamic-pituitary level have little

clinical utility. Dopamine agonist therapy (cabergoline and bromocriptine) may be useful in the unusual patient whose tumor cosecretes prolactin (80). Recently a new multiligand somatostatin analog (SOM 230; Pasireotide) has shown some promise in phase II clinical studies (81). High doses of the peroxisomal proliferator-activated receptor-γ agonist rosiglitazone have been shown to reduce ACTH and cortisol levels in animal models (82), but the effectiveness of this treatment in humans is not consistent, and it does not appear to be predictable in individuals (83). Finally, mifepristone is the first potent glucocorticoid receptor antagonist, but its use has been reported in only a few patients with Cushing's disease and, because of its long half-life and lack of biochemical markers to monitor response, may be associated with significant adrenal insufficiency (84).

The widespread availability of laparoscopic adrenal surgery has now made bilateral adrenalectomy an attractive choice in patients with Cushing's disease who fail pituitary surgery (34). This procedure is well tolerated with very little morbidity and a nearly 100% cure rate in patients with ACTH-dependent hypercortisolism. With comprehensive educational efforts and careful clinical monitoring, lifelong adrenal insufficiency requiring glucocorticoid and mineralocorticoid replacement can be managed safely with minimal morbidity. The development of Nelson's syndrome is always a concern in these patients, but with periodic MRI of the pituitary and measurement of basal ACTH, the potential development of Nelson's syndrome poses minimal risk to the patient. Because of the significant increase in morbidity and mortality in patients with untreated Cushing's disease, we strongly urge clinicians to use laparoscopic bilateral adrenalectomy in patients with significant hypercortisolism who have failed interventions directed at the pituitary.

Summary

The best diagnostic approach to patients with suspected hypercortisolism is a work in progress. An appreciation of the clinical subtleties and protean manifestations of endogenous hypercortisolism has stimulated more frequent testing. The use of late-night salivary cortisol testing has provided clinicians with a simple, sensitive, and specific means to screen for the presence of hypercortisolism. A specific and sensitive immunometric assay for ACTH, pituitary imaging with MRI, and inferior petrosal sinus ACTH sampling has streamlined the differential diagnosis of Cushing's syndrome. Finally, pituitary microsurgery and laparoscopic adrenalectomy have given all patients with Cushing's syndrome a chance for a gratifying clinical remission.

Acknowledgments

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