Cushing’s syndrome is characterized not only by excess cortisol production but also by a loss in the diurnal rhythm of cortisol secretion.

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Cushing’s syndrome is the clinical manifestation of glucocorticoid excess. When the most common cause, exogenous glucocorticoid intake, is excluded, one is left with a group of disorders in which a tumor (or rarely hyperplastic tissue) either produces excess cortisol or stimulates excess cortisol production indirectly through overproduction of either adrenocorticotropic hormone (ACTH) or corticotrophin-releasing hormone (CRH).1-4

CHALLENGE OF THE DIAGNOSIS

Although essential to mammalian life, cortisol at supraphysiologic doses provokes symptoms and signs such as decreased libido (100%), weight gain (90%), moon facies (88%), hypertension (85%), glucose intolerance, plethoric facies (80%), reddish striae (65%), hirsutism (65%), among others.5 Growth retardation is frequently seen in children. On routine screening, Cushing’s syndrome is found in 2% to 5% of patients with poorly controlled type 2 diabetes.6 Cushing’s disease predominates in young women (8:1 vs men) from age 20 to 40 years, whereas ectopic ACTH-producing tumors are seen in older males aged between 40 and 60 years.7,8 A faster onset of hypercortisolemic symptomatology is often witnessed in the setting of ectopic ACTH-producing neoplasms such as small-cell lung carcinoma.

Confirming hypercorticolism. It is extremely important that true hypercortisolism be confirmed (Cushing’s syndrome) before any attempt to try to localize the source of overproduction is made. The order of testing is crucial, as premature confirmatory testing can lead to false-positive and false-negative readings. Individual test results are often equivocal, and it remains the onus of the multidisciplinary team to weigh the supporting clinical, radiologic, and biochemical evidence before recommending surgery.

Cortisol secretion is controlled by ACTH, which is released from the anterior pituitary gland in a pulsatile fashion. Cushing’s syndrome is characterized by excess cortisol production and a loss in the diurnal rhythm of cortisol secretion. Isolated serum cortisol is not reliable for the diagnosis of Cushing’s syndrome. The recommended screening tests include two or more 24-hour urinary-free cortisol (UFC) measurements, two or more late-night salivary cortisols, the 1-mg overnight low-dose dexamethasone suppression test (LDDST), or the 2-day low-dose dexamethasone suppression test.1,3,9,10

Recent Endocrine Society guidelines recommend that one of these four initial screening tests should be done, and the type of screening test should be chosen based on the performance characteristics of each test in certain clinical situations to avoid false results. Each of these tests can have false results under certain clinical conditions. If one of the initial screening tests shows abnormal readings, then one of the other screening tests should be performed. Concordantly positive results on two or more different screening tests support Cushing’s syndrome diagnosis and is sufficient to proceed with tests to identify the source of Cushing’s syndrome.
PITUITARY, GONAD, AND ADRENAL CONDITIONS

when suspicion is high.10

Other screening tests include midnight plasma cortisol and a combined dexamethasone suppression-corticotropin-releasing hormone (DS-CRH) test, which should be used in certain cases if the previous results are discordant. Patients with normal results on two different screening test do not require further investigation if suspicion is low.10

24-hour UFC. Excess cortisol is excreted in the urine, so cortisol overproduction is reliably reflected by the 24-hour UFC measured by high-performance liquid chromatography (HPLC). Two or more collections are recommended to enhance the test's sensitivity.10 Urine creatinine is typically measured concomitantly to ensure a complete collection. False negatives can occur in patients with severe renal failure (glomerular filtration rate <30 mL/min). The normal range for UFC measured by HPLC is <50 µg/day.1 Drugs such as carbamazepine, fenofibrate, and digoxin can falsely elevate cortisol on HPLC due to cross-reactivity. The UFC test is very sensitive but cumbersome, and compliance can be difficult with pediatric patients. Stress can also cause modest elevations of the UFC, which decreases its specificity.

A fourfold increase in 24-hour UFC above normal (>250 to 300 µg/day) establishes Cushing's syndrome.1 If 24-hour UFC is <90 µg/day on three consecutive samples, Cushing's syndrome is unlikely. If clinical suspicion is high and the UFC is nondiagnostic, other screening tests should be pursued. Pregnant women tend to have elevations on 24-hour UFC testing (90 to 300 µg/day).

LDDSTs. The powerful glucocorticoid dexamethasone normally suppresses cortisol production via the hypothalamic-pituitary-adrenal (HPA) inhibitory feedback loop. The LDDST exploits the loss of sensitivity to glucocorticoid feedback observed in Cushing's syndrome. The test is performed overnight or over 2 days. The overnight test is easier and is used more frequently. The 2-day test is more difficult, but has improved specificity.10

Overnight LDDST requires ingesting 1 mg of dexamethasone at night (between 11 PM and 12 AM) and measuring fasting plasma cortisol the next morning (between 8 AM and 9 AM). A morning plasma cortisol level <1.8 µg/dL effectively rules out Cushing's syndrome.1 Reducing the cut-off from 5 to 1.8 µg/dL improved the sensitivity of this test for Cushing's syndrome from 82% to 95%. There are reports of occasional patients with Cushing's syndrome who have demonstrated cortisol suppression <2 µg/mL.2

False-positive results (no suppression) can be seen with increased hepatic metabolism of dexamethasone (CYP3A4), which is common in patients taking drugs such as phenytoin and carbamazepine. Pregnancy and exogenous estrogen intake increase plasma levels of cortisol-binding globulin and may also result in a false-positive test. The level of dexamethasone should be measured in these situations to verify adequate plasma levels and oral estrogens should be stopped at least 6 weeks before performing the LDDST.

The 2-day LDDST consists of giving 0.5 mg dexamethasone orally every 6 hours for 48 hours. Urine is collected for UFC on the second day, and serum cortisol is measured at 48 hours after the first dose of dexamethasone. The normal suppression response engenders UFC values <10 µg over 24 hours and serum cortisol levels <1.8 µg/dL on the morning after the last dose of dexamethasone. Initial studies indicated that the 2-day LDDST had the highest specificity (95%) of all the screening tests, and therefore, it was traditionally used as a confirmatory test for Cushing's syndrome.1

Pooled results from four studies demonstrated a lower specificity of 70%, but unlike earlier studies, these recent studies did not obtain dexamethasone levels. It is possible that inadequate dexamethasone levels may explain the higher false-positive rate. The Endocrine Society's recent guidelines recommend this test as an initial screening test. It may have higher specificity than the 1-mg overnight LDDST to establish the diagnosis of Cushing's syndrome.

The DS-CRH test combines the 2-day LDDST with CRH administration. Two hours after the last dose of dexamethasone is given in the 2-day LDDST, 1 µg/kg of intravenous (IV) CRH is given at 8 AM. Plasma cortisol is measured 15 minutes later, and the cut-off of >1.4 µg/dL distinguishes patients with true Cushing's syndrome from those with pseudo-Cushing's syndrome.1 The advantage of the DS-CRH test over the traditional 2-day LDDST is its greater sensitivity of 98% to 100% in identifying patients with Cushing's disease who occasionally have false-negative results on the 2-day LDDST. Pooled results from four recent studies have shown a lower specificity of 60%, which is in contrast to the 100% specificity found in Yanovski's initial studies. As with the 2-day LDDST, dexamethasone levels were not obtained in these recent studies, which may explain the higher rate of false-positive results. This test should be reserved for patients with a high clinical suspicion for Cushing's syndrome but who have a normal result on the 2-day LDDST.10

Late-night salivary cortisol. The late-night salivary cortisol test is the newest screening test for hypercortisolism.1,7,10 Salivary cortisol mirrors serum cortisol levels, and a 10 PM sampling has been shown to have a 92% to 100% sensitivity and a 93% to 100% specificity for the diagnosis of Cushing's syndrome.10,11 The late-night (10 PM to 11 PM) target time represents the physiologic nadir for serum cortisol levels. Advantages of this test include ease of collection, which facilitates its use in children, and the impressive stability (1 week) of salivary cortisol at room temperature. Renal failure becomes insignificant because salivary cortisol excretion is not influenced by renal function. Salivary cortisol is unaltered by variations in the level of cortisol-binding globulin. A late-night salivary cortisol level >4.3 nmol/L suggests
Cushing’s syndrome, as healthy individuals usually have levels <4.0 nmol/L. False results are seen in shift workers, the elderly, and those with diabetes and hypertension. Two or more collections should be done to enhance the sensitivity of the test, as some patients with Cushing’s syndrome demonstrate intermittent hypercortisolism.10

**Midnight plasma cortisol.** The midnight plasma cortisol is often abnormally elevated in Cushing’s syndrome because of derangement in the circadian rhythm of plasma cortisol levels; midnight levels in hospitalized sleeping patients with Cushing’s syndrome tend to have levels of >1.8 µg/dL or an awake value of >7.5 µg/dL, for midnight plasma cortisol increases probability of Cushing’s syndrome.10 This test remains somewhat unreliable and impractical, outside of a research setting, because it requires hospitalization to collect the plasma, and the stress of hospitalization or illness can raise the patient’s plasma cortisol level. Nonetheless, a midnight serum cortisol <1.8 µg/dL excludes Cushing’s syndrome, whereas values >20 pg/mL point to ACTH-dependent Cushing’s syndrome.1,3 ACTH secretion from ectopic tumors, however, with the exception of differentiated neuroendocrine tumors such as carcinoid tumors of the bronchus, thymus, and pancreas, generally fails to respond to high-dose dexamethasone. HDDST will usually not influence the autonomous cortisol production seen with adrenal tumors. The HDDST requires that dexamethasone be taken over 2 days (2 mg every 6 hours for eight doses), as an 8-mg single overnight dose, or as a single 4- to 7-mg IV dose. Urinary cortisol or serum cortisol levels are determined at baseline and after high-dose dexamethasone administration. A 90% or greater suppression of urinary cortisol levels is highly suggestive of Cushing’s disease but has low sensitivity. Furthermore, the specificity of the HDDST is not high enough to permit this to be the only differentiator between Cushing’s disease and ectopic ACTH-producing tumors.13

**CRH-stimulation test.** The CRH-stimulation test is useful in the differential diagnosis of ACTH-dependent Cushing’s syndrome. Although some patients may fail to respond to CRH, its administration generally raises both plasma ACTH and plasma cortisol levels in patients with Cushing’s disease. In adrenal Cushing’s syndrome and most ectopic ACTH-secreting tumors, there is no such response. The test is performed by injecting 1 µg/kg of synthetic bovine or human CRH; a cut-off of either >35% or >50% increase in plasma ACTH from baseline supports a diagnosis of Cushing’s disease. There is no consensus yet as to which cut-off (35% vs 50%) should be used. This test has higher diagnostic accuracy than the HDDST.1 Accuracy is improved when CRH administration accompanies ACTH sampling from peripheral blood and blood within the inferior petrosal sinuses in the brain.14

**MRI of the sella.** In ACTH-dependent Cushing’s syndrome, an MRI of the sella will find a pituitary adenoma in about 60% of cases.13,15-17 If biochemical tests correlate with Cushing’s disease and a significant size pituitary adenoma of >6 mm is visualized on the MRI, the diagnosis of Cushing’s disease is established.1,3,17 On the other hand, autopsy and imaging studies have found a 15% to 20% prevalence of incidental pituitary adenomas, usually <5 mm in size.18 Tests of higher specificity such as bilateral inferior petrosal sinus sampling with CRH are needed in cases with negative or equivocal (<6 mm) pituitary MRI results.1 Pathologic analysis is always necessary to confirm that the resected pituitary tumor is an ACTH-secreting pituitary adenoma and not an incidental lesion such as a Rathke’s cleft cyst or any other
type of adenoma. Traditional MR pituitary protocols have focused on identifying microadenomas via fine-cut coronal T1 sequences with gadolinium, which has improved with spoiled gradient recalled acquisition MRI.

**Bilateral inferior petrosal sinus sampling (BIPSS).** BIPSS is the most invasive confirmatory test for Cushing’s disease. Patients with ACTH-dependent Cushing’s syndrome who have discordant or equivocal biochemical or radiologic studies should undergo this procedure. Ideally, an elevated 24-hour UFC is documented the day before BIPSS to maximize the diagnostic validity of the procedure. Endovascular catheters are placed in both inferior petrosal sinuses. Timed samples of ACTH are drawn from the bilateral catheters and from a peripheral vein before and after CRH is administered at a dose of 1 µg/kg. The threshold criteria for declaring a pituitary source has been defined as a basal inferior petrosal sinus ACTH concentration to a peripheral blood ACTH concentration ratio of ≥2:1 without CRH administration. A ratio of ≥3:1 after CRH stimulation strongly supports a diagnosis of Cushing’s disease. When the ratio is <3:1, the physician should search for an ectopic source of ACTH with imaging studies.

Only patients with a well-established diagnosis of ACTH-dependent Cushing’s syndrome should undergo BIPSS because a central-to-peripheral ACTH gradient of 3:1 with CRH stimulation may be found in healthy individuals. Therefore, this test should only be used to differentiate ectopic sources of ACTH production from a pituitary source in patients where there is certainty about the diagnosis of ACTH-dependent Cushing’s syndrome. It is almost 100% sensitive, false negatives with BIPSS have been described, usually due to difficulty with catheterization of the petrosal sinuses. On the other hand, it is less successful as a lateralizing tool; correct lateralization of ACTH secretion with BIPSS occurs only in about 70% of cases. Perioperative management. Once the critical biochemical obstacles of Cushing’s disease have been triumphed, the definitive treatment remains surgical extirpation of the pituitary tumor. Glucocorticoids are not given preoperatively or intraoperatively, as resultant cortisol suppression may cloud the evaluation of remission.

**SURGICAL RESECTION**

For the neurosurgeon, regardless of the technique used for resection of pituitary adenomas, if a microscope or endoscope is used, there are two different scenarios: (1) A pituitary adenoma is seen on the MRI or (2) the MRI reading is normal or equivocal. The surgery for the situation in which the target is seen on the MRI is much less stressful for the neurosurgeon. It allows a direct approach to the adenoma, and remission is more often seen after an adenomectomy. Even in cases when the pituitary gland needs to be explored, we believe that an extracapsular resection of the adenoma should be uniformly attempted to permit a well-controlled resection of the functional adenoma with margin, as the pseudocapsule is a compact normal gland. Occasionally, the medial wall of the cavernous sinus must be resected to increase the chance of remission in more invasive adenomas.

We perform practically all surgeries for the treatment of Cushing’s disease using a pure endoscopic endonasal approach. The entire procedure is performed by a head and neck surgeon and a neurosurgeon. In our experience, as there are no data to support a significant difference in the literature, the visualization allowed by the endoscope is far superior to that from the operating microscope. The illumination and image captured by the endoscope are closer to the target, whereas with the microscope, the image is captured from a greater distance. This is important considering that the surgeon’s hands are always blocking the sight of view during microscopic surgery. The wide field of visualization provided by the endoscope allows dissection in the parasellar area, which is crucial in order to resect invasive pituitary adenomas to the cavernous sinus and extensive

Figure 1. A, B, and C are intraoperative views with a 0º endoscope during an endoscopic endonasal transsellar approach for resection of a pituitary adenoma in a patient with Cushing’s disease. (A) Pituitary gland exposure, (B) identification of the adenoma, (C) removal of the pituitary adenoma extracapsularly, and (D) specimen removed en bloc and sent to pathology.
suprasellar projections of tumor, always under direct visualization without the use of blind curettage.

**POSTOPERATIVE CARE**

Several postoperative management strategies have been applied.\(^{24,28}\) Although there is little evidence that withholding glucocorticoids postoperatively after adenoecotony for Cushing’s disease is dangerous, many clinicians prefer to prevent hypocortisolism and its accompanying symptoms of fatigue, headache, and myalgias and choose to give perioperative steroids.\(^{24}\) In our center, steroid replacement is withheld until hypocortisolism is manifested either clinically or biochemically. We obtain cortisol levels immediately after surgery and then every 6 hours without any steroid administration perioperatively; when serum cortisol levels fall below 2 µg/dL and/or the patient shows clinical symptoms of hypocortisolism, remission is assumed and hydrocortisone is administered. The postoperative fall in serum cortisol may be quite rapid owing to chronic suppression of CRH by previously high circulating levels of ACTH and cortisol. Most patients experience a serum cortisol nadir within 48 hours of surgery. Thus, a successful surgery that has eliminated the source of excess ACTH production should engender a state of secondary adrenal insufficiency. There is a subset of patients, particularly young patients with mild disease or those who received steroidogenesis inhibitors preoperatively, whose serum cortisol levels remain within the normal range after surgery despite achieving remission; nevertheless, a lack of postoperative hypocortisolism in Cushing’s disease has been associated with a high recurrence rate of up to 67%.\(^{29}\) The HPA axis recovers slowly over the next 11 to 18 months until normal cortisol levels are achieved and steroid replacement can be discontinued.\(^{17}\) Replacement corticosteroids are necessary during this phase, and the dose should be multiplied two- to fourfold in the setting of acute illness to prevent Addisonian crisis.

Supraphysiologic dosing (40 mg hydrocortisone in morning and 20 mg in evening) is often initiated and tapered to a more physiologic dose (20 mg of hydrocortisone in the morning and 10 mg in the evening). Remission is ascertained in a delayed fashion by confirming a low morning serum cortisol value 24 to 48 hours after the last glucocorticoid dose.

Recovery surveillance is often performed by measuring morning plasma cortisol every 3 months, 24 to 48 hours after the last glucocorticoid dose. Replacement therapy can be discontinued once a morning plasma cortisol >18 µg/dL is confirmed. Alternatively, once the morning plasma cortisol is >10 µg/dL, stimulation of cortisol to >18 µg/dL after 250 µg of cosyntropin (or to >20 µg/dL after insulin-induced hypoglycemia) indicates resolution of secondary adrenal insufficiency. Surgery for Cushing’s disease often necessitates exploring a large portion of the sella to find a corticotroph microadenoma. The surgeon must anticipate deficiencies of other pituitary hormones and comprehensively exclude any hypopituitarism postoperatively.

**Criteria for remission.** Undetectable plasma cortisol or values less than 2 to 3 µg/dL 24 to 72 hours after surgery herald a remission.\(^{1,17,24,28}\) In patients who receive postoperative corticosteroid replacement, the evaluation of remission must be initiated in a delayed manner, typically after 7 to 10 days; hypocortisolism screening tests such as UFC and LDDST may be repeated at this time. A persistently elevated postoperative serum cortisol level and the absence of secondary adrenal insufficiency at 4 to 6 weeks must be interpreted as residual disease or a failure to achieve remission. CRH may be administered to interrogate the sella for resid-
ual disease. Surgical reexploration is an option and may be especially warranted when intraoperative pathology confirms an ACTH-secreting pituitary adenoma.

Multimodality management. When repeat surgery is not feasible, other treatment options such as radiosurgery, medications, and bilateral adrenalectomy may be considered. In cases where remission is not obtained, the possibility of tumor invasion into the dural membranes around the sella including the cavernous sinus, ectopic parasellar locations, needs to be considered. In most series, gamma-knife radiosurgery (GKRS) resulted in remission in 50% to 80% of patients with persistent Cushing's disease within 3 to 5 years. GKRS allows delivery of highly focused radiation to the sellar region while sparing surrounding critical structures. When treatment directed at the sella fails, bilateral adrenalectomy is highly effective in controlling hypercortisolism. Medical therapy with ketoconazole can be pursued while the patient waits for a response to GKRS. All patients who have achieved remission from Cushing's disease remain at risk for relapse and must undergo lifelong monitoring. Thus, patients must be educated about the possibility of recurrence so that “cure” is appropriately construed and compliance with follow-up is maintained. A relapse rate of 25% to 40% at 7 years after surgery has been estimated.

Uncontrolled Cushing's syndrome is among the most morbid and life-threatening diseases. Most patients with Cushing's syndrome have Cushing's disease and can greatly benefit from surgical intervention. The confirmation of the diagnosis, however, can be very challenging and requires patience and a conscious utilization of the screening tests. Endoscopic endonasal transsellar surgery has proved to be an excellent surgical tool allowing better visualization and consequently better identification and resection of pituitary adenomas generating a potential for better results in terms of disease control, shorter hospital stay, and less morbidity that still remains to be appropriately confirmed. Once surgery is performed, confirming remission can also be demanding, and further treatments can be necessary. Thus, it is extremely important that a collaborative effort among neurosurgeons, otolaryngologists, endocrinologists, and endocrinologists is present to adequately manage this complex disease. Every patient with Cushing's disease considered in remission should be enrolled in a program of dedicated surveillance.

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