Series Editor: Bernard M. Karnath, MD

Cushing's Syndrome

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Cushing's syndrome was first described by Harvey Cushing in 1910 in a woman with central obesity, abdominal striae, hirsutism, amenorrhea, hypertension, proximal muscle weakness, thinning hair, and purpura.[1,2] Cushing's syndrome is now known to be associated with hypercortisolism, either endogenous or exogenous in origin. Endogenous causes of Cushing's syndrome are classified as either dependent or independent of adrenocorticotropin hormone (ACTH), determined by assessing serum ACTH level in relation to serum cortisol level. Exogenous hypercortisolism is most often caused by excessive use of pharmacologic glucocorticoids.

Cushing's syndrome is rare, with a prevalence of 2 to 5 cases per million.[3,4] Although several signs and symptoms are suggestive of Cushing's syndrome (eg, weight gain, central obesity, moon facies, abdominal striae, buffalo hump), no single physical finding is pathognomonic. The diagnosis is confirmed through biochemical testing, and treatment is dependent on the cause of hypercortisolism. This article describes some of the more common manifestations of Cushing's syndrome and discusses the differential diagnoses and work-up of suspected Cushing's syndrome.

CUSHING'S SYNDROME

- Signs suggestive of Cushing's syndrome include central obesity, facial plethora, moon facies, and violaceous striae (> 1 cm).
- Rapid weight gain is the most common presenting manifestation.
- Available screening tests for hypercortisolism include the overnight (1-mg) dexamethasone suppression test, 24-hour urinary free cortisol measurement, and/or a midnight salivary cortisol measurement.
- After confirming hypercortisolism, serum adrenocorticotropin hormone (ACTH) should be measured—if elevated or normal, the patient has ACTH-dependent Cushing's syndrome; if ACTH is low, the patient has ACTH-independent Cushing's syndrome.
- Treatment is dependent on the underlying cause of hypercortisolism.

CLINICAL FEATURES

Excessive cortisol production leads to numerous systemic effects, and the frequency of these effects varies by case series (**Figure 1**).[4–11] Most patients with Cushing's syndrome present because of rapid weight gain,[4] which is the most striking feature of this disorder, resulting in central adiposity, round or "moon" facies, and a dorsocervical fat pad, or "buffalo hump" (**Figure 2**).

Skin

Dermatologic manifestations of Cushing's syndrome include violaceous striae, ecchymoses, hyperpigmentation, oily skin, acne, and facial plethora. Violaceous striae and ecchymoses are caused by deficient collagen synthesis, resulting in thin and fragile skin. Striae are the result of scarring from dermal tears, and they appear purple because the underlying vasculature becomes apparent as the skin becomes increasingly thin (Figure 2). Although most often found on the abdomen and lower flank, striae can occur on the breasts, hips, buttocks, shoulders, upper thighs, upper arms, and axillae.[8] Some experts consider the presence of multiple violaceous striae wider than 1 cm on the abdomen pathognomonic of Cushing's syndrome.[12,13]

Patients often report easy bruising, which is caused by weakness of vessel walls and the surrounding connective tissue. In cases of excess ACTH production (ie, Cushing's disease, ectopic ACTH-producing tumors),

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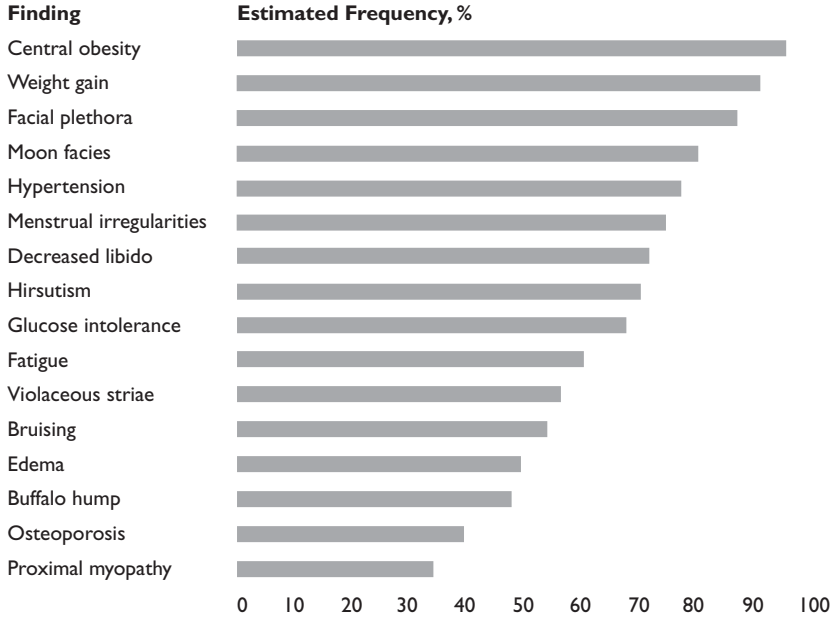

Figure 1. Approximate frequency of findings in Cushing's syndrome. (Data compiled from references 4 to 11.)

ACTH binds to melanocyte-stimulating hormone, causing hyperpigmentation. The duration and degree of ACTH hypersecretion influence the severity of hyperpigmentation. Patients are also at risk for cutaneous infections from the immunosuppressive effects of glucocorticoids.

Musculoskeletal

Excess glucocorticoids can suppress muscle protein synthesis, which atrophies the muscles.[14] Patients may report weakness as a result of proximal myopathy. Proximal muscle weakness is similar in presentation to that of polymyositis and dermatomyositis, such that patients report difficulty climbing stairs or rising from a chair. Osteoporosis can also develop with long-standing Cushing's syndrome, and fractures, including vertebral fractures, may result. Osteoporosis results from inhibition of bone formation and suppression of calcium absorption from the intestine, both of which are effects of excess glucocorticoids.[14]

Gonadal Dysfunction

Hypogonadism results from the inhibitory effect of cortisol on gonadotropin-releasing hormone, follicle-stimulating hormone, and luteinizing hormone. Increased androgen production causes hirsutism, oily skin, acne, and menstrual irregularities (eg, amenorrhea, oligomenorrhea) in women, impotence in men, and loss of libido in both sexes.

Psychiatric

Emotional changes in Cushing's syndrome may be profound. Changes in mood include irritability, anxiety, and depression. Confusion and psychosis are possible. Depression is the most common psychiatric complication of endogenous Cushing's syndrome, whereas mania is more common with exogenous Cushing's syndrome.[6,15,16]

Common Comorbidities

Increased hepatic gluconeogenesis and insulin resistance can cause impaired glucose intolerance, ultimately leading to the development of diabetes mellitus. Glucose intolerance is more common than overt diabetes in patients with Cushing's syndrome.[6] Hypertension is also common, resulting from increased extracellular volume.[14] Obesity, hypertension, osteoporosis, and diabetes are nonspecific findings and are less helpful in making a diagnosis of Cushing's syndrome.

DIFFERENTIAL DIAGNOSIS

The causes of endogenous hypercortisolism are categorized as ACTH-dependent or ACTH-independent. Approximately 80% of all cases of Cushing's syndrome can be classified as ACTH-dependent, with 70% caused by an ACTH-secreting pituitary adenoma (ie, Cushing's disease) and 10% occurring in the setting of a paraneoplastic syndrome caused by small cell lung cancer and carcinoid tumors.[17–19] The distinction between Cushing's syndrome and Cushing's disease is important. Cushing's

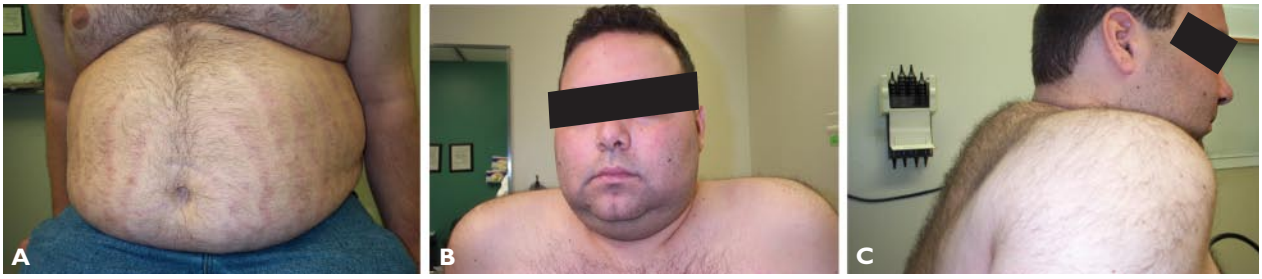

Figure 2. Signs of Cushing's syndrome. (**A**) Abdominal striae, (**B**) facial plethora, and (**C**) dorsocervical fat pad (ie, buffalo hump).

syndrome is the constellation of signs associated with hypercortisolism, whereas Cushing's disease is specific to an ACTH-secreting pituitary tumor that results in Cushing's syndrome.

The most common cause of ACTH-independent Cushing's syndrome is long-term exogenous glucocorticoid administration.[14,20] ACTH-independent Cushing's syndrome is caused by adrenal tumors (eg, a benign adenoma or malignant adrenal cell carcinoma) in approximately 10% of cases. Cushing's syndrome is more commonly due to administration of supraphysiologic doses of corticosteroid drugs rather than spontaneous production of corticosteroids by an adrenal neoplasm.[18,20]

Conditions That Mimic Cushing's Syndrome

Pseudo-Cushing's syndrome. In pseudo-Cushing's syndrome, patients have all or some of the clinical features of true Cushing's syndrome, but hypercortisolism is due to activation of the hypothalamic-pituitary-adrenal axis by an underlying illness. Differentiating true Cushing's syndrome from pseudo-Cushing's syndrome can be challenging and requires a careful history and physical examination as well as biochemical testing. Pseudo-Cushing's syndrome usually occurs in patients with chronic severe depression, chronic alcoholism, morbid obesity, and poorly controlled diabetes.[13] Treatment of the underlying primary condition resolves the symptoms of the Cushing's-like state.[5] The dexamethasone suppression/corticotropin-releasing hormone (CRH) stimulation test can be used to differentiate Cushing's syndrome from pseudo-Cushing's states (*see* Localizing the Cause).

Polycystic ovary syndrome (PCOS). Another disease that can closely mimic Cushing's syndrome is PCOS. PCOS is the most common endocrine disorder of women of childbearing age, and Cushing's syndrome is relatively uncommon when compared with the high prevalence of PCOS in this patient population (4%–8%).[21,22] The clinical phenotype of PCOS is the result of hyperandrogenism. Signs of hyperandrogenism that overlap with Cushing's syndrome include hirsutism, obesity, acne, glucose intolerance, menstrual dysfunction, and hypertension. Menstrual irregularities, hirsutism (ie, excessive hair in androgen-dependent areas of a woman's body), and weight gain are common manifestations of both PCOS and Cushing's syndrome, present in 80% to 90% of women with Cushing's syndrome according to 1 study.[6] In another study, clinical symptoms of Cushing's syndrome occurred in 25% of hirsute women, yet only 10% had proven hypercortisolism.[23] Some authors have suggested that Cushing's syndrome be considered in a patient with a PCOS clinical phenotype, especially if hypertension is present.[21] This emphasizes the diagnostic dilemma that can occur between 2 somewhat phenotypically similar diseases.

DIAGNOSTIC EVALUATION

Confirming Hypercortisolism

To confirm the diagnosis of Cushing's syndrome and elicit a potential cause, the presence of hypercortisolism must first be determined using 1 of 3 available screening tests: the overnight (1-mg) dexamethasone suppression test, 24-hour urinary free cortisol (UFC) measurement, and/or a midnight salivary cortisol measurement. It should be noted that there is no perfect test for Cushing's syndrome, as hypercortisolism can be cyclical or episodic.[24,25] The overnight 1-mg dexamethasone suppression test is the easiest to perform and involves administering dexamethasone 1 mg at 11:00 PM and measuring serum cortisol at 8:00 AM the next morning. In a healthy patient, baseline serum cortisol levels should be between 5 and 25 μg/dL and will suppress to less than 5 μg/dL. Failure to suppress cortisol is indicative of Cushing's syndrome.

A positive initial dexamethasone suppression test (serum cortisol > 5 μg/dL) should be followed by a confirmatory 2-day low-dose dexamethasone suppression test. Dexamethasone 2 mg is administered daily (0.5-mg doses every 6 hr) over 48 hours, and serum cortisol is then measured at 8:00 AM on the morning of day 3. A serum cortisol level below 5 μg/dL on day 3 essentially rules out Cushing's syndrome (**Table**). Of note, the sensitivity and negative predictive value of the

Table. Evaluation of Cushing's Syndrome Using Dexamethasone Suppression Testing

	ACTH-Dependent		ACTH-Independent
	Cushing's Disease (Excess Pituitary ACTH)	**Ectopic ACTH**	**Cortisol-Secreting Adrenal Adenoma**
ACTH level	Normal or elevated	Elevated	Low
Dexamethasone			
Low-dose (2 mg/day administered as 0.5 mg every 6 hr × 48 hr)	Urinary or serum cortisol will not decrease	Nonsuppressible cortisol levels	
High-dose (8 mg/day administered as 2 mg every 6 hr × 48 hr)	Urinary or serum cortisol decreases		

Note: normal ACTH levels = 9–52 pg/mL; normal cortisol values at 8 AM = 5–25 µg/dL; and normal urinary cortisol excretion = 20–100 µg/24 hr. ACTH = adrenocorticotropin hormone.

low-dose dexamethasone suppression test are limited. Findling and colleagues[26] noted false-negative results in 18% of patients with the use of the overnight 1-mg dexamethasone suppression test and in 38% with the 2-day low-dose dexamethasone suppression test.

The 24-hour UFC measurement is the most widely used screening test for Cushing's syndrome and is considered the gold standard test for evaluating the presence of hypercortisolism.[7,17] Because UFC levels are not valid with glomerular filtration rates less than 30 mL/min, renal function should be assessed before the 24-hour urine collection. Normal urinary cortisol excretion is 20 to 100 µg per 24 hours, whereas most patients with Cushing's syndrome excrete more than 250 µg of urinary cortisol per 24 hours. However, false-positive results can occur in obese patients and patients with polycystic ovaries, in which case UFC measurement may be between 100 and 150 µg per 24 hours.[5,21]

The midnight salivary cortisol measurement is a relatively new option in screening for hypercortisolism. A single salivary cortisol measurement is obtained at 11 PM; a level greater than 8.6 nmol/L is highly suggestive of Cushing's syndrome, whereas a salivary cortisol level less than 4.3 nmol/L makes Cushing's syndrome unlikely. If results are equivocal, the test should be repeated.[12] However, it is important to note that validation of established diagnostic criteria for this screening test is pending.[12,17]

Localizing the Cause

Once hypercortisolism is established, the next step is to determine the cause. To localize the cause, the serum ACTH level should be measured. Normal ACTH levels range from 9 to 52 pg/mL. An elevated or normal ACTH level in the presence of elevated serum cortisol indicates a pituitary or ectopic source (ie, ACTH-dependent Cushing's syndrome). Low ACTH levels indicate an adrenal source (ie, ACTH-independent Cushing's syndrome). For ACTH-dependent Cushing's syndrome, a high-dose (8-mg) dexamethasone suppression test (2 mg every 6 hr for 2 days) can differentiate between a pituitary adenoma and an ectopic source. In cases of pituitary adenomas, cortisol levels will be suppressed more than 50% with high-dose dexamethasone, whereas with an ectopic source of ACTH production, cortisol levels will be unchanged.[27,28] The Table outlines the use of the low-dose and high-dose dexamethasone test.

If ACTH levels are normal or elevated in the presence of hypercortisolism and serum cortisol is suppressed with a high-dose dexamethasone test, then magnetic resonance imaging of the pituitary is warranted.[28] Bilateral inferior petrosal sinus sampling (IPSS) is useful in differentiating a pituitary source from an ectopic source of ACTH. A central-to-peripheral ACTH gradient greater than 2 has a high specificity for an ACTH-secreting pituitary tumor.[7] If neuroimaging is normal or reveals a pituitary microadenoma and ACTH-dependent Cushing's disease is suspected, the patient can undergo bilateral IPSS to confirm a pituitary source.[29] Compared with neuroimaging, bilateral IPSS is an accurate method for establishing a diagnosis of Cushing's disease.[30] The sensitivity and positive predictive value of IPSS can be increased with ovine CRH stimulation.[31]

A CRH stimulation test can also be used to differentiate ACTH-dependent causes of Cushing's syndrome.[32] In patients with pituitary ACTH secretion, intravenous CRH causes a rise in plasma ACTH and cortisol levels, whereas levels remain unchanged in patients with an ectopic source of ACTH secretion. The most likely cause of ectopic ACTH secretion is a pulmonary tumor,[11] in which case computed tomography of the chest is warranted. Computed tomography of the adrenals is needed to evaluate the cause of hypercortisolism in the presence of low ACTH values.[32]

The dexamethasone suppression/CRH stimulation test is a second-line test used to differentiate mild cases

of Cushing's syndrome from pseudo-Cushing's states.[33] Ovine CRH 100 µg is administered as an intravenous bolus within 2 hours of the last 0.5-mg dexamethasone tablet in the 2 mg/day (low-dose) suppression test. In patients with Cushing's syndrome, low doses of dexamethasone are insufficient to prevent the rise in cortisol that follows CRH stimulation. Conversely, in patients with pseudo-Cushing's syndrome, serum cortisol is unaffected by CRH stimulation due to suppression by dexamethasone.

TREATMENT

Treatment depends on the source of hypercortisolism. Surgical resection of the tumor is often curative. For pituitary tumors (ie, Cushing's disease), transsphenoidal resection is the standard of care.[18] For adrenal adenomas, removal with unilateral adrenalectomy is the best option.[18] When surgery is not an option (eg, ectopic sources of ACTH such as small cell lung cancer), control of hypercortisolism may be attempted with medication. Glucocorticoid inhibitors, such as metyrapone, ketoconazole, and aminoglutethimide can be used. Metyrapone and ketoconazole block cortisol synthesis, and aminoglutethimide inhibits production of adrenal glucocorticoids, mineralocorticoids, aldosterone, estrogens, and androgens.

CONCLUSION

Cushing's syndrome is characterized by a constellation of manifestations caused by chronically elevated cortisol. Diagnosis requires strong clinical suspicion, given that many signs and symptoms of Cushing's syndrome are nonspecific and no 1 physical finding is pathognomonic for the disorder. Confirmation of Cushing's syndrome begins with measurement of UFC, and once confirmed, investigation of the underlying cause requires measurement of serum ACTH levels, dexamethasone suppression testing, and imaging studies. **HP**

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