Neurosurgical Treatment of Cushing Disease

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KEYWORDS

• Cushing syndrome • Cushing disease • Transsphenoidal surgery • Adrenocorticotropin • Hypercortisolism

KEY POINTS

- Cushing syndrome (CS) refers to the clinical and metabolic effects of excess systemic glucocorticoids; Cushing disease (CD), or adrenocorticotropin (ACTH) overproduction by an adrenal adenoma or carcinoma, is the most common cause of endogenous CS.
- CD is largely a surgical disease, with microscopic and endoscopic transsphenoidal surgery enjoying similar success rates and relatively low complication rates.
- Remission rates following surgery are 70% to 95%, although the literature demonstrates significant variability in the definition of remission.
- Recurrence following surgery occurs 2% to 20% of the time, after 2 to 10 years.
- Recurrences may be treated with reoperation, radiosurgery, or radiation therapy; interim medical therapy is required in the latter 2 cases.

INTRODUCTION

Cushing syndrome (CS) refers to the constellation of physiologic effects of excess systemic glucocorticoids, including impaired glucose tolerance, skin and bone fragility, compromised immunity, and cardiovascular complications, to name a few. Untreated CS is associated with mortality rates greater than 5 times that of matched controls,[1–4] whereas proper treatment normalizes mortality risk.[5]

Whereas the most common cause of CS is the administration of exogenous steroids, endogenous CS is a consequence of adrenocorticotropin (ACTH) overproduction by a pituitary adenoma or an ectopic tumor, or cortisol overproduction by autonomous adrenal abnormalities. Overproduction of ACTH by a pituitary adenoma (or, rarely, carcinoma) is the most common of these, and is known as Cushing disease (CD).

DIAGNOSIS

Patients who should be considered for evaluation of possible CS/CD include those with unusual features for their age (including early-onset hypertension, low bone mineral density for age, fractures after minimal trauma, oligomenorrhea in premenopausal-aged women, to name a few), those who manifest multiple features suggestive of cortisol excess over time (including central adiposity, hyperglycemia, spontaneous ecchymoses, wide or darkly pigmented striae, proximal muscle weakness, edema, hypokalemia, thromboembolic events, psychiatric manifestations, and recurrent, opportunistic, or atypical

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infections), children with delay in linear growth, and patients with incidentally found adrenal or pituitary masses.

Once the diagnosis of CS/CD is considered, laboratory testing is aimed at establishing (or refuting) the presence of pathologic hypercortisolism (Fig. 1). After the diagnosis of CS is established on a biochemical basis, a thorough, systematic approach is required to identify the underlying cause (pathologic lesion) with the goal of curative resection, if possible.[6,7]

Establishing the Diagnosis of Cushing Syndrome

Laboratory testing is needed to confirm the presence of CS, and distinguish it from other conditions (Box 1).[8,9] The physiologic principles underlying laboratory testing for CS include excessive cortisol secretion leading to increased cortisol excretion in the urine (24-hour urine free cortisol [UFC]), blunting of the normal circadian rhythm of cortisol secretion leading to high nocturnal (nadir) cortisol levels (measured in the blood or saliva), and decreased sensitivity of the hypothalamic-pituitary-adrenal axis to negative feedback exerted by glucocorticoids, leading to lack of suppression of early-morning serum cortisol after the oral administration of dexamethasone (dexamethasone suppression testing).[8,9]

Measurement of UFC is optimally performed using liquid chromatography followed by tandem mass spectrometry or high-performance liquid chromatography, and provides a reliable estimate of endogenous cortisol secretion in patients with normal kidney function.[8,10] Several (at least 2–3) specimens should be collected to achieve adequate (95%) sensitivity.[8,10] Measuring urine creatinine excretion in the specimen is recommended to ensure adequacy of collection. In addition, urine volume should be recorded and high fluid intake (>5 L daily) discouraged during collection, as high urine volume is associated with high UFC.[11] A 4-fold or greater UFC above the upper end of the normal range is

Box 1
Conditions associated with clinical and/or biochemical evidence of hypercortisolism

- Cushing syndrome (endogenous or exogenous)
- Pregnancy
- Psychiatric conditions (including major depression)
- Severe obesity
- Poorly controlled diabetes mellitus
- Alcohol dependence
- Familial glucocorticoid resistance
- Physical illness, including trauma or surgery[a]
- Strenuous regular exercise[a]
- Anorexia nervosa[a]
- Excessive serum cortisol binding globulin levels (including women taking oral contraceptives)[a]

[a] Clinical features of Cushing syndrome are generally absent.

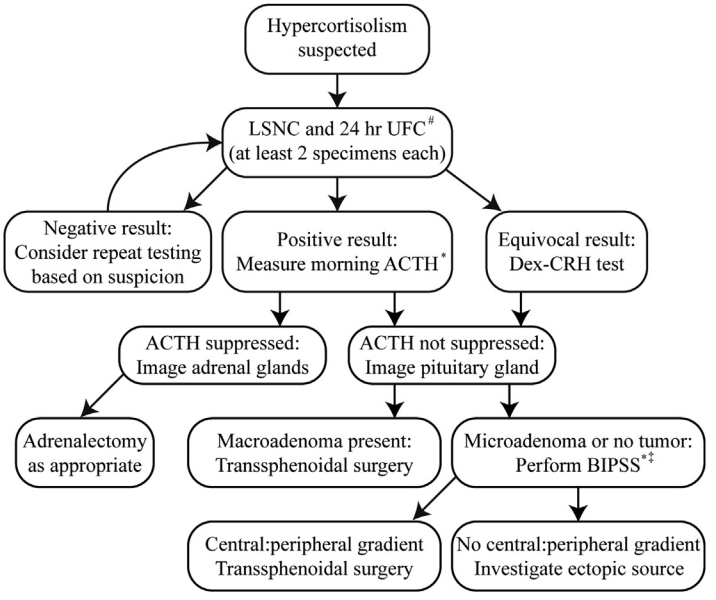

Fig. 1. An approach to the diagnosis of suspected Cushing syndrome and Cushing disease. A flow chart depicting a suggested diagnostic algorithm for determining the etiology of hypercortisolism is presented. # The 1-mg dexamethasone suppression test may also be considered (see text for details). * Testing to be conducted during periods of biochemical hypercortisolism. † Patients whose plasma ACTH levels are not fully suppressed may undergo a (peripheral) CRH stimulation test to fully establish if Cushing syndrome is ACTH dependent. ‡ The 8-mg dexamethasone suppression test and the (peripheral) CRH stimulation test may be helpful in some patients (see text for details). *Abbreviations:* ACTH, adrenocorticotropin; BIPSS, bilateral inferior petrosal sinus sampling; Dex-CRH test, dexamethasone-suppressed corticotropin-releasing hormone stimulation test; LNSC, late-night salivary cortisol; UFC, urine free cortisol.