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REVIEW

Evaluation and treatment of Cushing's syndrome

Lynnette K. Nieman, MD, Ioannis Ilias, MD, DSc

Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md.

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ABSTRACT: Cushing's syndrome results from sustained pathologic hypercortisolism caused by excessive corticotropin (ACTH) secretion by tumors in the pituitary gland (Cushing's disease, 70%) or elsewhere (15%), or by ACTH-independent cortisol secretion from adrenal tumors (15%). The clinical features are variable, and no single pattern is seen in all patients. Those features most specific for Cushing's syndrome include abnormal fat distribution, particularly in the supraclavicular and temporal fossae, proximal muscle weakness, wide purple striae, and decreased linear growth with continued weight gain in a child. Patients with characteristics of glucocorticoid excess should be screened with measurements of saliva or urine cortisol or dexamethasone suppression testing. The diagnosis of Cushing's syndrome should be followed by the measurement of plasma ACTH concentration to determine whether the hypercortisolism is ACTH-independent. In ACTH-dependent patients, bilateral inferior petrosal sinus sampling with measurement of ACTH before and after administration of ACTH-releasing hormone most accurately distinguishes pituitary from ectopic ACTH secretion. Surgical resection of tumor is the optimal treatment for all forms of Cushing's syndrome; bilateral adrenalectomy, medical treatment, or radiotherapy are sought in inoperable or recurrent cases. The medical treatment of choice is ketoconazole. The prognosis is better for Cushing's disease and benign adrenal causes of Cushing's syndrome than adrenocortical cancer and malignant ACTH-producing tumors.

Cushing's syndrome results from sustained pathologic hypercortisolism. It is caused by excessive cortisol secretion by adrenal tumors (15%) or by excessive corticotropin (ACTH) secretion from pituitary (Cushing's disease, 70%) or nonpituitary tumors (ectopic ACTH secretion, 15%), which increases cortisol production. It is a rare disorder, with an annual incidence of 2.5 cases per million inhabitants in Denmark.[1]

Requests for reprints should be addressed to Lynnette K. Nieman, MD, Building 10, CRC, 1 East, Rm 1-3140, 10 Center Dr, MSC 1109, Bethesda MD 20892-1109.

E-mail address: NiemanL@nih.gov.

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Establishing the diagnosis of Cushing's syndrome

Clinical features

The diagnosis of Cushing's syndrome often cannot be made on clinical grounds, because no single pattern of symptoms is seen in all patients (Table 1). The most characteristic features (increased supraclavicular fat, proximal muscle weakness, and purple striae wider than 1 cm) occur in a minority.

Clinical and laboratory features of Cushing's syndrome overlap with those of common entities that comprise pseudo-Cushing states including alcoholism, anxiety, depression, inadequately controlled diabetes, and morbid obesity. The dilemma is to identify patients most likely to have Cushing's

Table 1 Frequency of clinical signs and symptoms of Cushing's syndrome*

Sign	Percentage of individuals
Decreased libido	91%-100%
Facial rounding ("moon faces")	
Obesity	
Impaired glucose tolerance/diabetes	71%-90%
Menstrual changes	
Hirsutism	
Striae	
Muscle weakness	51%-70%
Osteopenia/osteoporosis/fractures	
Psychiatric disturbances (especially lethargy, depression)	
Atherosclerosis	
Easy bruising	
Impaired wound healing	
Headaches	21%-50%
Backache	
Recurrent infections	
Edema	
Hypokalemic alkalosis	
Acne	11%-20%
Hair loss	

*Modified from: Nieman LK. Diagnostic tests for Cushing's syndrome. *Ann N Y Acad Sci.* 2002;970:112-118, with permission.

syndrome. Screening is appropriate in hirsute women and poorly controlled diabetic patients, because up to 2% of these populations have Cushing's syndrome.[2-4] It is reasonable to screen patients with unusual features for their age (eg, nontraumatic fracture, hypertension, or cutaneous atrophy in young individuals), as well as patients who accrue additional Cushingoid features over time.

Screening tests

Measurement of 24-hour urine cortisol (urinary free cortisol) with high-performance liquid chromatography, gas chromatography coupled with mass spectrometry, or tandem mass spectrometry is currently the gold standard for verification of sustained endogenous hypercortisolemia (Figure 1). To exclude periodic hypercortisolism, 3 or more samples should be obtained, with creatinine measurement to assess completeness of the collection. Approximately 100% of patients with Cushing's syndrome have elevated values.[5-8] False-negative results occur in periodic Cushing's syndrome and with glomerular filtration rates less than 30 mL/min.[9] The specificity of the test is as low as 81% in healthy persons.[5-8] False-positive results occur in pseudo-Cushing states, sleep apnea, polycystic ovary syndrome, familial glucocorticoid resistance, and hyperthyroidism.[6,10,11]

Increased midnight plasma and salivary cortisol concentrations distinguish pseudo-Cushing states from Cushing's syndrome with 95% diagnostic accuracy.[5,8,12-15] Salivary cortisol is simpler to obtain,[5,12-15] but needs additional validation of diagnostic criteria. Both tests may have falsely abnormal results in those who do not usually sleep at night.

The 1-mg overnight dexamethasone suppression test (DST) exploits loss of sensitivity to glucocorticoid feedback.[10] With a cutoff point for cortisol suppression of less than 5 μg/dL, the sensitivity was 95% to 98%.[16,17] However, reports that 7 of 104 patients with Cushing's disease suppressed less than 2.0 μg/dL[16,18] suggests that Cushing's syndrome cannot be excluded by "complete" suppression. In healthy subjects, the specificity was 87%.[16,17] False-positive results occur in 30% to 58% of patients with depression, schizophrenia, Alzheimer's dementia, obsessive compulsive disorder, or alcoholism (during acute alcohol withdrawal)[19] and are seen in the context of old age, weight loss, sleep deprivation, malabsorption, elevated corticosteroid-binding globulin, or medications that enhance dexamethasone clearance. Thus, Cushing's syndrome may be diagnosed with certainty only when DST cortisol values are greater than 14.3 μg/dL (395 nmol/L).[20] The 2-mg 2-day DST has better diagnostic accuracy than the 1-mg test (~98%), but only if serum cortisol end points are used.[10]

The dexamethasone–corticotropin-releasing hormone (CRH) stimulation test distinguishes pseudo-Cushing syndrome from Cushing's syndrome with approximately 100% diagnostic accuracy,[21] but it is expensive and cumbersome.

Differential diagnosis of Cushing's syndrome

Identifying ACTH-dependent versus ACTH-independent hypercortisolism

Hypercortisolism suppresses normal corticotrope ACTH secretion so that plasma ACTH levels are low (<5 pg/mL; 1.1

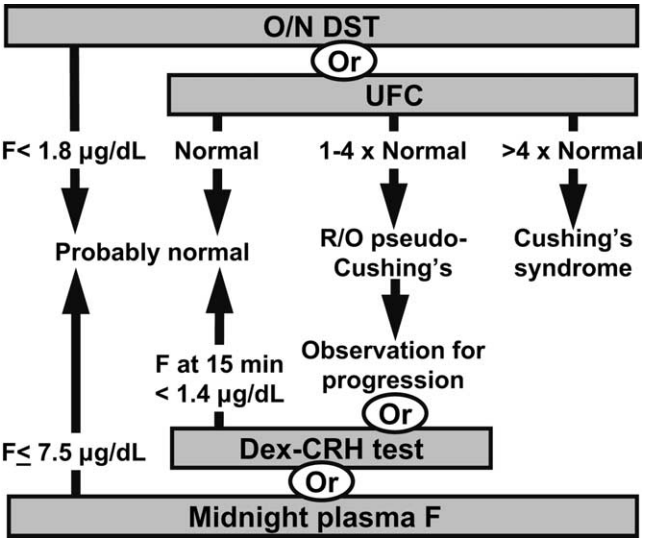

Figure 1 An algorithm for establishing the diagnosis of Cushing's syndrome. To calculate values in SI units (nmol/L) multiply by 27.59. O/N DST = overnight 1-mg dexamethasone suppression test; UFC = urinary free cortisol; F = cortisol; R/O = rule out; Dex-CRH = dexamethasone-corticotropin-releasing hormone test.

Table 2 Imaging modalities used in patients with Cushing's syndrome

	CT	MRI	Scintigraphy
Adrenal glands	Best modality Primary adrenal disorders: Inhomogeneous mass >10 HU with atrophic adjacent and contralateral tissue suggests functioning tumor; bilateral disorders show small (PPNAD) or large (MMAD) nodules ± hyperplasia. ACTH excess causes hyperplasia, superimposed nodules in 10%-15% of patients with Cushing's disease.	Adjunctive use for distinguishing adrenal adenoma from nonfunctioning or metastatic tumors.	[^{131}I]-6-iodomethyl norcholesterol (NP-59): Unilateral uptake indicates functioning adenoma; bilateral uptake indicates hyperplasia; no uptake indicates nonfunctional tumor or carcinoma.
Pituitary gland	CT not indicated	T1-weighted spin echo with gadolinium contrast is best modality. Spoiled gradient recalled acquisition technique improves sensitivity (40%-80%). Hypointense intrasellar masses <6 mm are present in 10% of healthy individuals. Microadenomas (<1 cm) are more common than macroadenomas (>1 cm).	Not indicated
Ectopic ACTH-secreting tumor	Indicated in all patients High resolution CT of chest (1- to 3-mm sections) and 1-cm sections in abdomen and neck may identify tumor.	Indicated in all patients Neuroendocrine tumors have high signal intensity on T2-weighted images.	[^{111}In]-pentetreotide (OctreoScan) is a useful adjunctive modality and may prompt additional review of conventional CT and MRI.

CT = computed tomography; MRI = magnetic resonance imaging; PPNAD = primary pigmented nodular adrenocortical disease; MMAD = massive macronodular adrenocortical disease; ACTH = corticotropin.

pmol/L) in patients with primary adrenal disorders and are inappropriately normal or high (>10 pg/mL) in patients with tumoral ACTH production, using a sensitive immunoradiometric assay with a detection limit of 2 to 5 pg/mL. There is very little overlap.[22]

Patients with primary adrenal disorders proceed to adrenal imaging. Computed tomography (CT) is the best modality because of its high structural resolution and the information derived from Hounsfield unit density measurements (Table 2). Unilateral tumors are most common and are equally likely to be benign or malignant; larger size, androgen and/or estrogen secretion,[23] aneuploidy, frequent mitoses, venous invasion, and abnormal gene expression suggest malignancy.[24]

Rare bilateral adrenocortical diseases include primary pigmented nodular adrenocortical disease (PPNAD) and massive macronodular adrenocortical disease (MMAD).[25] PPNAD is associated with Carney's complex and protein kinase A germline mutations.[26] The adrenal glands contain multiple pigmented cortical nodules (<1 cm) with atrophic internodular cortex.[27] MMAD affects older adults and is associated with the illicit expression of various G protein-coupled receptors.[28]

Distinguishing causes of ACTH-dependent Cushing's syndrome

Plasma ACTH levels overlap significantly in ectopic ACTH secretion and Cushing's disease,[22,29] and other tests are used to distinguish them (Figure 2).[30-34] Pituitary magnetic resonance imaging (MRI) with administration of gadolinium contrast detects approximately 40% to 52% of corticotrope tumors.[35] It should be performed before bilateral inferior petrosal sinuses sampling (IPSS), which is not necessary if MRI and noninvasive tests indicate Cushing's disease. Cushing's disease is suggested when 8 mg of dexamethasone suppresses cortisol, when corticotropin-releasing hormone increases plasma cortisol or ACTH levels,[30,31,36,37] or (for IPSS) when a sinus-to-peripheral vein plasma ACTH ratio is 2.0 or more before, or 3.0 or more after corticotropin-releasing hormone.[32-34,38,39]

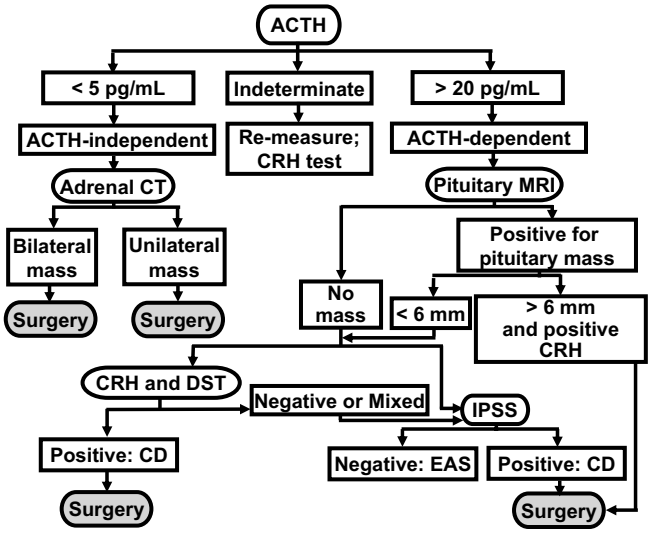

Figure 2 An algorithm for the differential diagnosis of Cushing's syndrome. ACTH = corticotropin; CT = computed tomography; CRH = corticotropin-releasing hormone; MRI = magnetic resonance imaging; NP-59 = [^{131}I]-6-iodomethyl norcholesterol scintigraphy; DST = 8-mg dexamethasone suppression test; IPSS = bilateral inferior petrosal sampling; CD = Cushing's disease; EAS = ectopic ACTH secretion.

The best test, IPSS, has a sensitivity and specificity for Cushing's disease of approximately 94%.[22,33,34,40-43] Its use is limited by the expertise necessary to perform it, the cost, and rare neurologic and thromboembolic complications. The sensitivity of the 8-mg DST for Cushing's disease is 81% to 82%, and the specificity is 67% to 79%,[44,45] whereas the corticotropin-releasing hormone test has a sensitivity of 70% to 93% and a specificity of 88% to 100%.[31,46,47]

Decision analysis showed that the 8-mg DST followed in selected cases by IPSS was a cost-effective approach.[48] However, the poor specificity of the 8-mg DST suggests that a corticotropin-releasing hormone test also should be performed. In 4 series, 98% of patients with positive results on both tests had Cushing's disease. However, 18% to 65% of patients with Cushing's disease lacked a response to one or both tests.[30,36,40,49,50] Patients with any negative response would require IPSS.

CT and MRI of the neck, chest, and abdomen are the primary imaging studies to localize tumors that produce ACTH ectopically,[51] including foregut carcinoids (pulmonary, thymus, pancreas), pheochromocytoma, poorly differentiated neuroendocrine tumors, small-cell lung cancer, and medullary thyroid cancer.[52] Scintigraphy with [^{111}In]-pentetreotide (OctreoScan; Mallinckrodt, St. Louis, MO) is a useful confirmatory modality[53,54] (Table 2).

Surgical treatment of Cushing's syndrome

Selective surgical excision of tumors producing ACTH or cortisol is the optimal treatment of Cushing's syndrome because it spares normal adjacent structures, and effects immediate remission and eventual recovery of normal adrenal function.

Worldwide, transsphenoidal resection for Cushing's disease has immediate postoperative cure rates of 78% to 97%,[55-59] with the best results obtained for microadenomas that are visualized by experienced neurosurgeons. Because macroadenomas may invade dura or bone, remission rates are lower, 50% to 80%.[60]

Unilateral resection is indicated for adrenal adenomas, whereas bilateral resection is needed for PPNAD or MMAD. Laparoscopic adrenalectomy, the procedure of choice for benign tumors, has less morbidity than laparotomy.[61,62]

Complete surgical resection of adrenal carcinoma may be achieved, but metastases to lymph nodes (68%), lungs (71%), liver (42%), and/or bone (26%) are common[63,64]; gross resection is possible in less than half.[65-69] Despite this, tumor debulking should be performed by staging laparatomy.[70,71] The effectiveness of adjuvant therapy is not established.

Resection of nonpituitary ACTH-secreting tumors should be attempted using a cancer-staging procedure.[72] Bilateral adrenalectomy is useful if medical treatment fails.

Postoperative considerations

Successful surgery results in hypocortisolism because the normal corticotrope is suppressed. Postoperative morning plasma cortisol levels, urinary free cortisol, the cortisol response to the 1-mg DST or the ACTH, and/or cortisol response to corticotropin-releasing hormone evaluate remission and may predict recurrence.[59,73-80] Although there is no consensus on criteria, curative surgery is most likely with lowest cortisol and urinary free cortisol values.[59,74-76,80] An abnormal postoperative 1-mg DST result may identify residual tumor.[73,81] Remission nearly always persists after resection of benign adrenal tumor(s), but not with other causes of Cushing's syndrome.

After adrenal-sparing curative surgery, glucocorticoid replacement is required (we recommend hydrocortisone at 12-15 mg/m^2) until pituitary-adrenal function recovers. This may take 2 years,[75] especially after resection of adrenal adenomas. Basal and ACTH-stimulated cortisol values gauge whether glucocorticoid replacement can be discontinued. Patients with bilateral adrenalectomy require lifelong glucocorticoid and mineralocorticoid (fludrocortisone, 0.5-0.2 mg daily) replacement. All patients need education regarding modification of glucocorticoid doses during illness and physiologic stressors.

Other treatment modalities for Cushing's disease

External beam radiotherapy to a pituitary tumor can be given either in conventional fractionated doses (with Co-

balt-60- or linear accelerator-based units) or with stereotactic modalities (radiosurgery/radiotherapy, with linear accelerator-based or gamma-knife units) that accurately deliver higher doses of radiation in one or a few settings.[82] The latter techniques may have fewer complications of panhypopituitarism and visual loss, although more experience is needed to ascertain this.[83] When used as initial treatment in children the remission rate was 85%.[84] Radiotherapy provides remission in 45% to 100% of patients with persistent hypercortisolism after transsphenoidal resection.[83,85-89]

Bilateral adrenalectomy provides immediate control of hypercortisolism but carries up to 47% risk of Nelson's syndrome.[90]

Medical treatment of Cushing's syndrome

Although the primary therapy for Cushing's syndrome is surgical, medical treatment often is required preoperatively or if surgery is not feasible. It should be considered before bilateral adrenalectomy for severe Cushing's syndrome to improve tissue healing and is used after radiotherapy until hypercortisolism remits. Medical agents include glucocorticoid receptor antagonists and compounds that modulate ACTH release or inhibit steroidogenesis. Ketoconazole is used most commonly because of its effectiveness as monotherapy and favorable side-effect profile. Serum hepatic aminotransferase levels increase in 5% to 10% of patients, and serious hepatic impairment occurs in 1 of 15 000 patients.[91] The side effects and therapeutic strategies for other agents, including metyrapone (currently difficult to obtain), aminoglutethimide, and mitotane, have been reviewed recently.[92]

Prognosis and survival

Hypercortisolism engenders visceral obesity, insulin resistance, and dyslipidemia. [87] Hypertension, hypercoagulability, and ventricular morphologic and functional abnormalities increase cardiovascular risk, and persist up to 5 years after resolution of hypercortisolism.[74,93,94] These complications should be treated aggressively. Treatment should be considered also for osteoporosis, psychiatric disease, growth hormone deficiency, hypogonadism, and hypothyroidism.[74]

Worldwide, the standardized mortality ratio of Cushing's disease and adrenal adenoma ranges from 0.98 to 3.80.[1,59,95,96] Cardiovascular disease is mainly responsible for increased mortality (standardized mortality ratio = 3.95-5.00).[1,96] Patients with adrenal cancer have a 5-year survival rate of 20% to 58%.[97-99]

The prognosis of patients with ectopic ACTH secretion depends on the underlying tumor. Nonpulmonary neuroendocrine tumors or small-cell lung cancer carry an ominous prognosis,[22,100] whereas pulmonary carcinoids have a better prognosis.[72]

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