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June/July 2010

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Cushing's Syndrome

Definition

Cushing's syndrome refers to hypercortisolism of any cause. Whereas Cushing's disease refers to hypercortisolism due to a corticotropin (ACTH)-producing pituitary adenoma.

Overview

The incidence of Cushing's disease is 5 to 25 per million patients per year. Other causes of Cushing's syndrome are much less common.

Common causes

Cushing's syndrome may be either ACTH-dependent or ACTH-independent.

1. ACTH-dependent Cushing's syndrome

- A. Cushing's disease is the most common cause of Cushing's syndrome and comprises 65-70% of the cases. Almost all patients with Cushing's disease have a pituitary adenoma. The adenomas are frequently small, and even a gadolinium-enhanced, high-resolution MRI of the sella identifies only 50% of them. pituitary adenoma cells have a higher than normal set point for cortisol feedback inhibition. This feature is clinically important because it permits the use of dexamethasone suppression to distinguish between pituitary and ectopic ACTH secretion; the latter is usually very resistant to glucocorticoid negative feedback.



Photo: Kevin Vance

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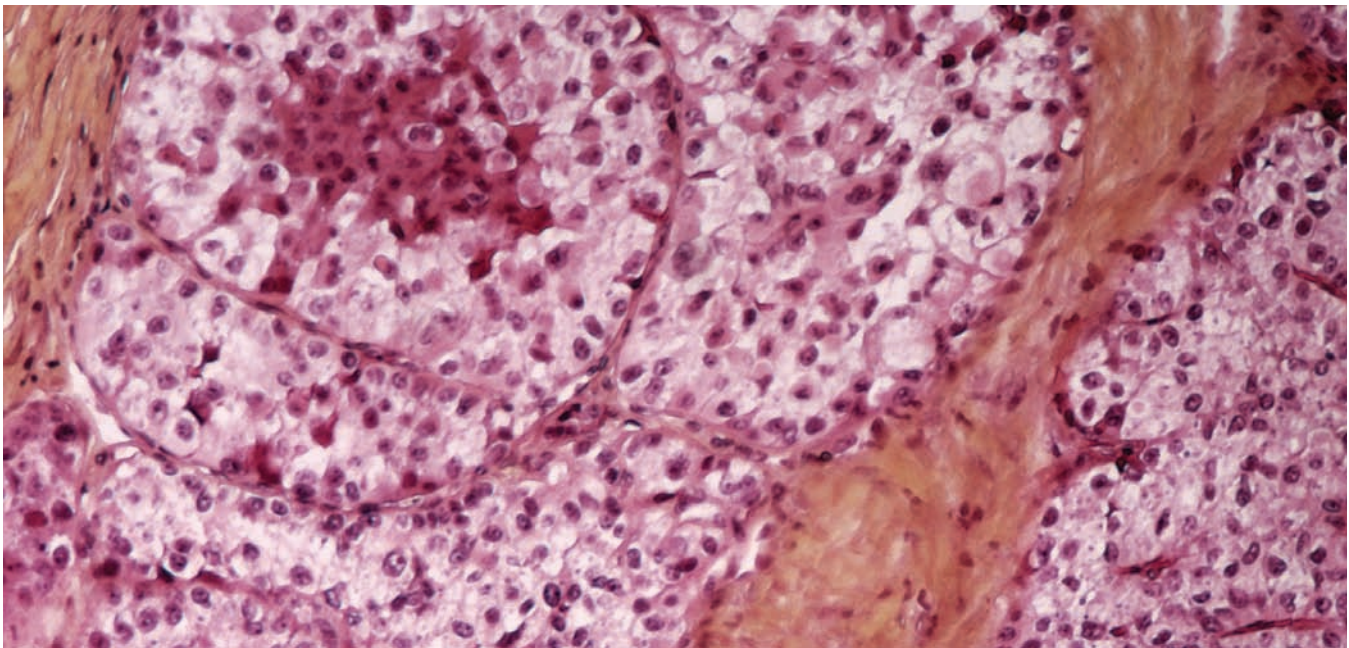
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- B. Ectopic ACTH secretion by non-pituitary tumors accounts for 10-15% of the cases of Cushing's syndrome. A wide variety of tumors, usually carcinomas rather than sarcomas or lymphomas, have been associated with the ectopic ACTH secretion. The most common causes are small cell carcinomas of the lung, bronchial or pulmonary carcinoid tumors, and pancreatic islet cell tumors, and thymic tumors. Ectopic secretion of ACTH causes bilateral adrenocortical hyperplasia and hyperfunction.
- C. Ectopic corticotropin-releasing hormone (CRH) syndrome constitutes less than 1% of Cushing's syndrome. CRH secretion by nonhypothalamic tumors causes pituitary hyperplasia, hypersecretion of ACTH, and bilateral adrenal hyperplasia.

2. ACTH-independent Cushing's syndrome

- A. Adrenal tumors account for 18-20% of the cases of Cushing's syndrome. It is important to be sure of the biochemical diagnosis prior to performing any adrenal imaging since 4% of patients have an adrenal incidentaloma.
- B. Iatrogenic or factitious Cushing's syndrome is usually caused by the use of prednisone, or potent inhaled, injected, and topical glucocorticoids, such as beclomethasone and flucocinolone. Exogenous glucocorticoids inhibit CRR and ACTH secretion, leading to bilateral adrenocortical atrophy. Plasma ACTH, serum cortisol, and urinary cortisol excretion are all low.

Who should be suspected?

Symptoms and signs of Cushing's syndrome include hypertension, type 2 diabetes mellitus, and menstrual and psychiatric disorders. Physical examination findings include central obesity, proximal muscle weakness, wide purple striae, spontaneous ecchymoses, and facial plethora (moon face).

Laboratory findings

The diagnosis of Cushing's syndrome involves three steps. The first step is to suspect Cushing's syndrome based on the symptoms and signs. The second step is to confirm the presence of excess cortisol production by biochemical testing. The third step is to determine if the hypercortisolism is ACTH dependent, and if so, the source of the ACTH.

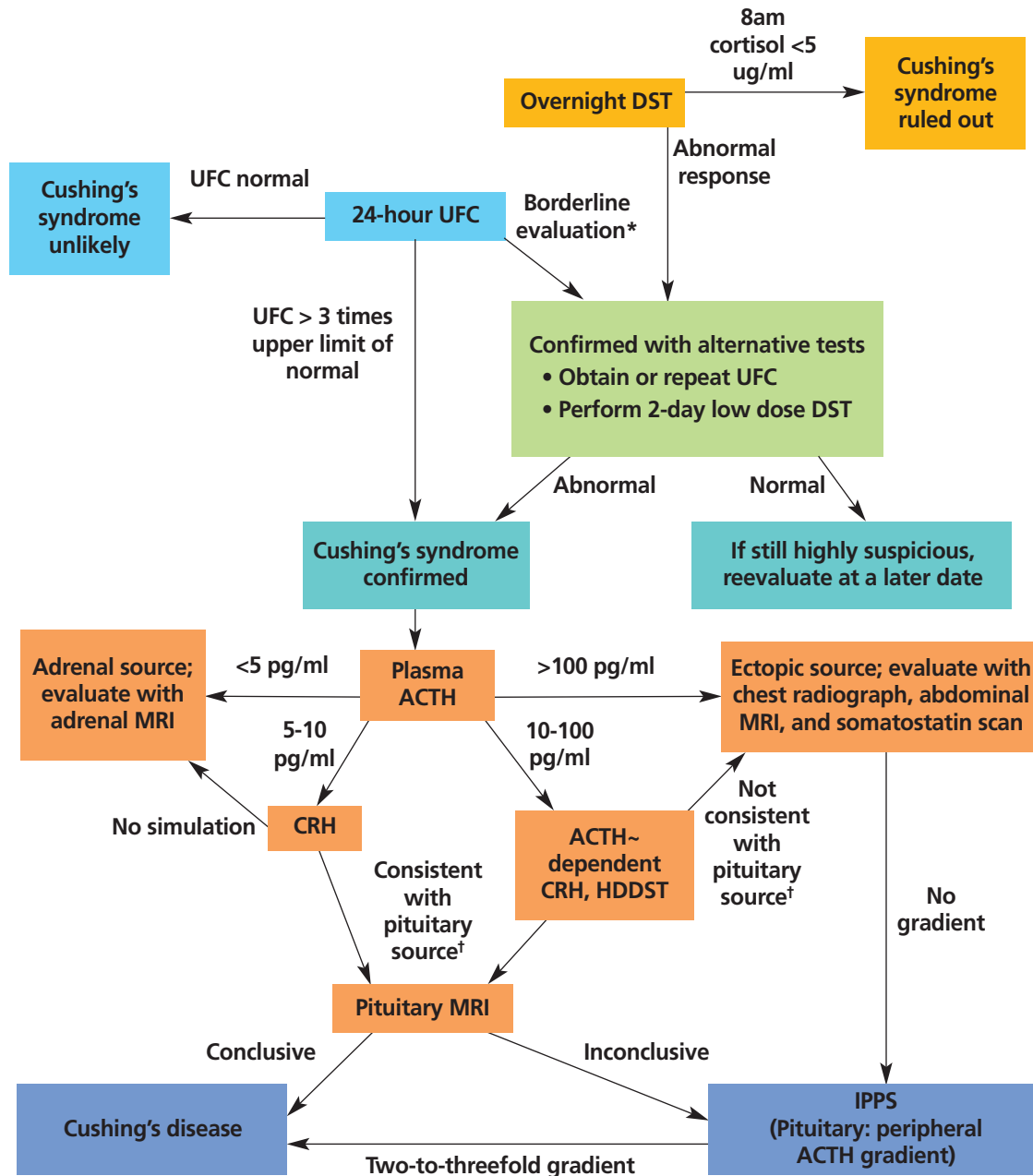
1. Tests used to establish the diagnosis of Cushing's syndrome are listed in the table on page 4. Urinary cortisol late night salivary cortisol, and low-dose dexamethasone suppression tests are now recommended as first line tests. At least two first-line tests should be unequivocally abnormal to establish the diagnosis of Cushing's syndrome. Urinary and salivary cortisol measurements should be obtained at least twice.
 - A. 24-hour urinary cortisol excretion provides a direct and reliable practical index of cortisol secretion. It is an integrated measurement of plasma free cortisol; as cortisol secretion increases, the binding capacity of cortisol binding globulin is exceeded and results in a disproportionate rise in urinary free cortisol. The two most important factors in obtaining a valid result are collection of a complete 24-hour specimen and a reliable reference laboratory.

Common Tests Used to Establish the Diagnosis of Cushing's Syndrome

Test	Normal Results	Diagnostic
24-hr urinary free cortisol (UFC)	<90 µg cortisol per 24-hr period	> 3 times the upper limit of normal
1 mg overnight dexamethasone suppression test (DST) given at 11 -12pm	8AM plasma cortisol <5µg/dL	Cushing's syndrome unlikely if cortisol suppresses normally
Low-dose DST (0.5 mg dexamethasone given every 6hr for 2 days)	UFC < 10 µg and 17-OHS < 2.5 mg in a 24-hr urine collected on second day	UFC > 36 µg/d 17-OHS > 4 mg/d
12 midnight cortisol	< 5.0 µg/dl	> 7.5 µg/dl
12 midnight salivary cortisol	<2.0 ng/dl	> 2.0 ng/dl



Algorithm for the Evaluation of Cushing's Syndrome



*Patients with alcoholism or depression may have pseudo-cushing's syndrome and require a CRR test for further evaluation.

† With a pituitary source, ACTH should increase with CRR, and cortisol production should decrease with HDDST.

ACTH = adrenocorticotrophic hormone; CRR = corticotrophin-releasing hormone;

DST = dexamethasone suppression test; HDDST = high-dose dexamethasone suppression test;

MRI = magnetic resonance imaging; IPPS = inferior petrosal sinus sampling; UFC = urinary free cortisol.

Figure 1



- B. Late night or midnight salivary cortisol concentration can also be used. Saliva is easily collected and cortisol is stable in saliva for several days even at room temperature. The criteria used to interpret salivary cortisol results vary among different studies. Midnight salivary cortisol is an accurate diagnostic test. A cortisol value greater than 2.0 ng/ml has 100% sensitivity and 96% specificity for diagnosing Cushing's syndrome.
 - C. Low-dose dexamethasone suppression tests include overnight 1mg test and standard two-day test. In normal patients, the administration of glucocorticoid results in suppression of ACTH and cortisol secretion. Whereas in Cushing's syndrome of whatever cause, there is a failure of this suppression and the cortisol concentration remains elevated.
 - D. Midnight serum cortisol is based on the fact that the normal evening or night nadir in serum cortisol is preserved in obese and depressed patients (pseudo-Cushing's syndrome) but not in those with Cushing's syndrome. The test needs to be repeated on at least two nights. Accuracy of midnight cortisol requires an indwelling catheter and it is clearly not convenient in an outpatient setting.
2. Tests used to localize the source hormone excess (Figure 1, Page 5). Once the diagnosis of Cushing's syndrome is confirmed, the next step is to distinguish among the three most common causes: a pituitary tumor, ectopic ACTH secretion,

and an adrenal tumor. Determining whether elevated cortisol is ACTH-dependent (due to an ACTH-secreting tumor) or whether it is ACTH-independent (due to a primary adrenal disorder⁴) is based primarily on measuring plasma ACTH level.

3. Imaging studies

- A. Adrenal imaging is indicated when plasma ACTH levels are $<5\text{pg/ml}$. Thin section CT or MRI is the next step in evaluating the adrenals. Bilateral adrenal hyperplasia may be present in ACTH-dependent disease.
 - B. Somatostatin scanning. Ectopic sources of ACTH are notoriously difficult to identify. Because many of these tumors are carcinoids and have somatostatin receptors, scintigraphy with the somatostatin analogue indium-111-pentetreotide can sometimes localize tumors not found by conventional techniques.
 - C. Because both incidental pituitary and adrenal tumors are common, biochemical evaluation should be completed before any imaging studies.
4. Petrosal sinus sampling is used when the anatomical localization fails to identify an unequivocal lesion as suggested by the biochemical testing. This test allows confirmation of the pituitary source of ACTH and identifies the side of the ACTH-secreting lesion. ACTH is measured simultaneously in samples from catheters placed in the left and right inferior petrosal sinuses and compared to peripheral levels. A gradient of two- to threefold is consistent with a pituitary source of ACTH. CRH can also be given during the procedure to enhance its accuracy.

Reference: Dr. Hongbo Yu

Suggested reading

Nieman LK. "Establishing the diagnosis of Cushing's syndrome". *Uptodate 2009*, Rose B, editor, Uptodate, Inc. Waltham, MA

Nieman LK. "Establishing the cause of Cushing's syndrome". *Uptodate 2009*, Rose B, editor, Uptodate, Inc. Waltham, MA

Nieman LK. "Clinical manifestations of Cushing's syndrome". *Uptodate 2009*, Rose B, editor, Uptodate, Inc. Waltham, MA

Nieman LK. "Causes and pathophysiology of Cushing's syndrome". *Uptodate 2009*, Rose B, editor, Uptodate, Inc. Waltham, MA

Khan F, Sachs H, Pechet L, and Snyder LM. *Guide to Diagnostic Testing*. Lippincott Williams & Wilkins, 2002

Kronenberg HM, Melmed S, Polonsky KS, and Larsen PR. *Williams Textbook of Endocrinology. Ed 11.*, Saunders, Elsevier Inc., 2008

Two-Patient Identifiers and Specimen Labeling

In our continuing effort to improve quality and in compliance with the College of American Pathologists (CAP) and the Joint Commission's 2009 National Patient Safety goals (1A), UMass Memorial Laboratories will soon require all specimens to be properly and adequately labeled to assure positive identification. All specimen containers must be labeled with two person-specific identifiers. Person-specific identifiers may include patient's full first and last names, date of birth, or unique other identifying number (e.g., medical record number or accession number).

When a specimen is received at UMass Memorial Laboratories the patient's first and last names and date of birth, or alternate ID numbers are verified by comparing the information on the specimen container with the electronic order, requisition, or manifest that accompany the specimen to be tested. To use the patient's name as one form of identification, the patient's full first and last names must be used on the specimen containers and order. Specimens are considered mislabeled when there is a discrepancy between the person-specific identifiers on the specimen and the electronic order, requisition, or manifest that accompany the specimen.

This fall, when name discrepancies or insufficient person-specific identifiers on the specimen container are identified, UMass Memorial Laboratories Customer Service Department will contact the client to verify discrepant information to ensure that we are performing the correct testing for the correct patient. Verification of specimen identification may



require completion and submission of a patient/specimen identification correction form and corrected requisition before results can be released.

UMass Memorial Laboratories appreciates your assistance as we continue our on-going efforts to provide the highest quality of care for you and your patients.

Requisitions for Specialized Testing

UMass Memorial Laboratories now offers customized requisitions for specialized testing. The new requisitions include:

Cytopathology Requisition for ordering PAP testing with accompanying testing such as HPV, Chlamydia, and GC. Cervical biopsies may also be ordered using this form. This form is available now. (Form #3433 Cytopathology).

Molecular Diagnostics Requisition & Consent is used for ordering tests from our Molecular Diagnostics laboratory. For added convenience; the necessary consents for physicians and patients are built into the form. The physician consent can be found at the bottom of the top copy. The patient consent can be found on page 3 of the 3-part requisition. This form will be available mid-June (Form # NS 142).

Cytogenetics Requisition & Consent is used for ordering tests from our Cytogenetics laboratory. As with the Molecular Diagnostics form, the physician's and patient's consents are incorporated into the requisition. This form will be available mid-June (Form # NS 144).

Maternal Screening Requisition for ordering the Maternal Quad screen and other prenatal testing such as AFP. This form is available now. (Form #NS 130).

All four of these requisitions also include space for the patient information that is required to provide results and interpretation. Please contact your Customer Service at 800-476-4431 for additional information or to order these forms.

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- To be a leading provider of laboratory services throughout New England, meeting the needs of patients and providers in the region, and
- To be one of the top ten academic medical center-based laboratories in the United States



Benefit Street PSC **139 Benefit Street** **Pawtucket, Rhode Island**

Benefit Street PSC is located at 139 Benefit Street, Pawtucket, Rhode Island. The hours are Monday, Tuesday, Wednesday and Friday, 8:30am-4:00pm, closed 12:00-1:00pm. Open Thursday 10:00am-5:30pm. The phone number at Benefit St. PSC is 401-729-7425.