Diagnostic Testing For Cushing's Syndrome

By James Findling, MD

A screening laboratory evaluation for Cushing's syndrome should be considered in any patient with signs and symptoms of excessive cortisol secretion. Abnormal weight gain, particularly in the central part of the body, accompanied by hypertension, diabetes, or hyperlipidemia should signal the possibility of Cushing's syndrome. Many patients with this disorder will also have facial rounding with the so-called "moon facies." Accumulations of fat above the clavicles or behind the neck are also common features of excessive cortisol secretion. Some patients will also present with osteoporosis and some have muscle weakness. The presence of wide purplish striae (stretch marks) in the abdomen or elsewhere can also be a symptom of Cushing's syndrome. The majority of patients with Cushing's syndrome have some type of neuropsychiatric problem (particularly depression) or even some cognitive impairment. Fatigue is almost always present in patients with Cushing's usually related to very poor sleep quality. Mild Cushing's syndrome is sometimes detected in patients in whom an adrenal nodule is incidentally discovered during CT imaging of the abdomen.

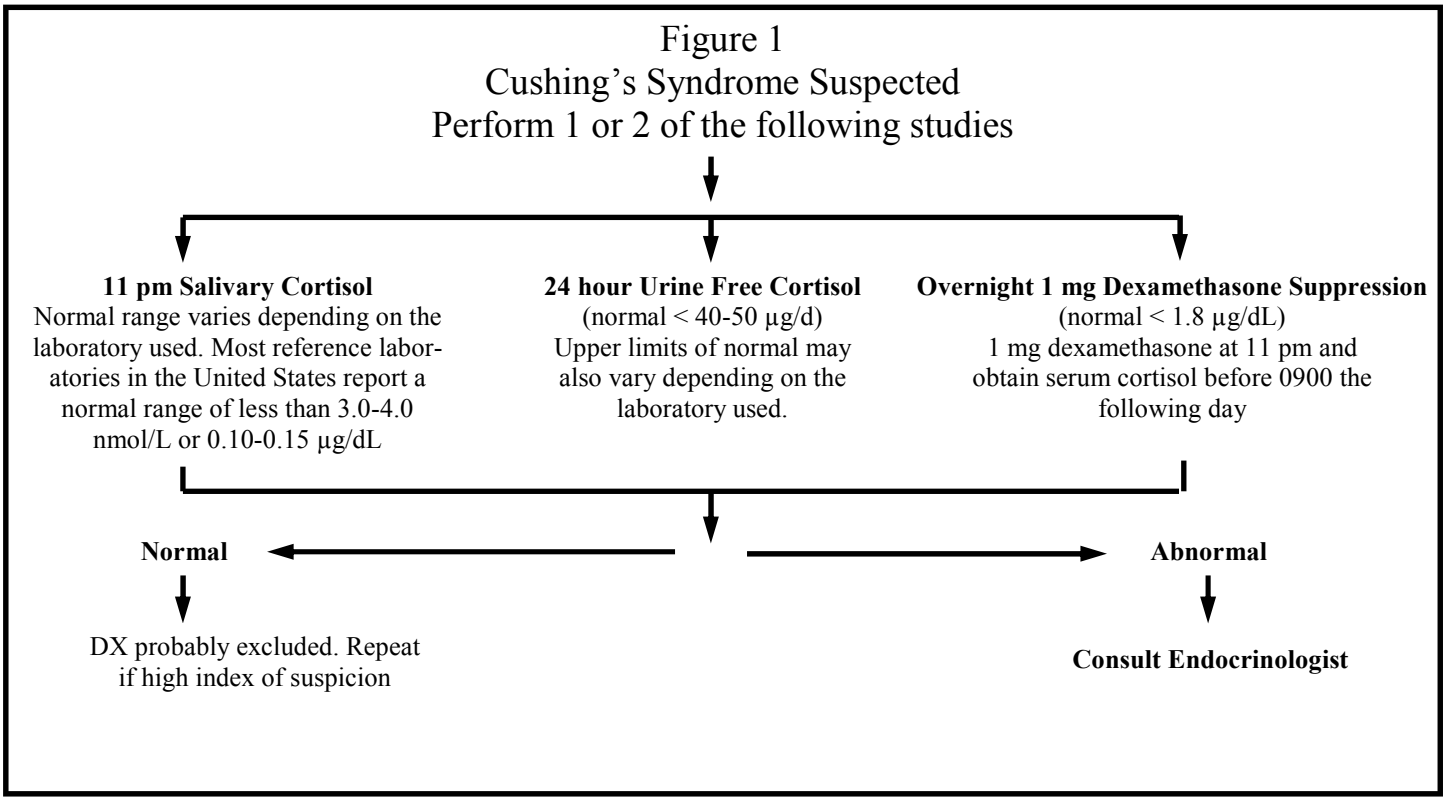
The diagnostic approach to patients with suspected Cushing's syndrome has been published in an evidence-based guideline by the Endocrine Society. Three diagnostic studies are currently recommended: late-night salivary cortisol, 24 hour urine free cortisol, low-dose dexamethasone suppression. If any of these tests is abnormal, a referral to an endocrinologist is strongly encouraged. These three tests are summarized in Figure 1.

Late-Night Salivary Cortisol

Late-night salivary cortisol is one of the most sensitive diagnostic tests for Cushing's syndrome. Elevated cortisol between 11:00 p.m. and midnight appears to be the earliest detectable abnormality in many patients with this disorder. Cortisol secretion is usually very low at this time of the day, but in patients with Cushing's syndrome, the value is usually elevated. It is the most widely studied single test for the diagnosis of Cushing's syndrome with many studies from all over the world demonstrating a sensitivity of 93-100% for the diagnosis of Cushing's syndrome; however, like all the tests for Cushing's syndrome there are many things which may cause a false positive result and additional testing is always needed. Collection of saliva requires special sampling tubes; however, this is a very easy test for patients to perform and can be done on multiple occasions. Salivary cortisol is very stable at room temperature and the samples can actually be mailed to a reference laboratory. This test is now widely available. Normal levels of late-night salivary cortisol usually exclude the diagnosis of Cushing's syndrome due to an ACTH secreting tumor; however, some patients with Cushing's caused by an adrenal tumor will have normal late-night salivary cortisol levels.

Urine Free Cortisol

Urine free cortisol has been used for many years for the diagnosis of Cushing's syndrome. A 24 hour urine free cor-



tisol level does reflect the cortisol secretion throughout an entire day. Although the majority of patients with Cushing's have elevated levels of urine free cortisol, it is becoming increasingly evident that many patients with mild Cushing's syndrome will actually have normal levels of urine free cortisol. It is estimated that 20-25% of patients with Cushing's syndrome may have a normal urine cortisol. In other words, a normal 24 hour urine free cortisol does not exclude the diagnosis of Cushing's syndrome and additional testing is usually needed. In addition, there are many conditions which may increase urine free cortisol that are not Cushing's syndrome including depression, chronic alcoholism, and eating disorders.

Low-Dose Dexamethasone Suppression Testing

The low-dose dexamethasone suppression testing has been used for four decades as a diagnostic tool in the evaluation of patients with suspected Cushing's syndrome. Dexamethasone is a synthetic steroid that should suppress the cortisol production in normal subjects to a very low level. Currently, the most widely used test is the administration of a small dose of dexamethasone (1 mg) at 11:00 p.m. followed by a measurement of serum cortisol early the following morning. Normal subjects should suppress their cortisol level to a very low level (<1.8 µg/dl) after dexamethasone. This test provides approximately 95-97% sensitivity in the diagnosis of Cushing's syndrome; however, there are many things that may cause false-positive testing. This is the preferred screening test in patients with suspected Cushing's from a primary adrenal gland disorder.

DIFFERENTIAL DIAGNOSTIC TESTING

Once the diagnosis of Cushing's syndrome has been established, its cause must be identified. The majority of patients with Cushing's syndrome have an ACTH-secreting tumor usually from the pituitary gland (Cushing's disease) or a non-pituitary tumor (ectopic ACTH syndrome). Some patients may have Cushing's syndrome due to a solitary or multiple tumors in their adrenal glands secreting excessive cortisol.

ACTH Levels

The first step in distinguishing the type of Cushing's syndrome is a blood test for the measurement of ACTH obtained in the morning. Patients with ACTH-secreting tumors will either have a normal or elevated level of ACTH. In contrast, patients with adrenal Cushing's will have a subnormal level.

MRI Pituitary

Distinguishing a pituitary from a non-pituitary ACTH-secreting tumor may be a diagnostic challenge. Since the majority of patients with ACTH-secreting tumors have a pituitary lesion (often very small), a MRI of the pituitary gland with gadolinium enhancement is always the initial approach. When an unequivocal pituitary tumor is identified with MRI, further diagnostic evaluation may not be needed depending on the clinical presentation. In such a case, referral to a skilled pituitary neurosurgeon may be recommended; however, it should be noted that at least 10% of the population have incidental tumors in the pituitary gland demonstrated on MRI. This means that at least 10-15% of patients with the ectopic ACTH syndrome also have an abnormal MRI of the pituitary gland.

Inferior Petrosal Sinus Sampling

For patients with an ACTH secreting tumor causing Cushing's syndrome and a normal pituitary MRI, the single best test to confirm the presence or absence of an ACTH-secreting pituitary tumor is a procedure called inferior petrosal sinus sampling. This procedure requires a skilled invasive radiologist who can sample blood from the veins (inferior petrosal sinuses) that drain the pituitary. ACTH as well as other pituitary hormones reach the blood stream through veins called the inferior petrosal sinuses. A catheter can be placed in both of these veins at the same time and blood sampled for ACTH before and after the administration of CRH (which stimulates ACTH). This invasive study should be performed at a center with extensive experience in the procedure. If properly executed, this study has excellent diagnostic accuracy and will reliably establish the presence or absence of an ACTH-secreting pituitary tumor.

Computed Tomography of the Adrenal Glands

In patients who do not have an ACTH-secreting tumor and thereby low ACTH levels, the problem usually resides within the adrenal gland. CT scanning of the adrenal glands will be helpful in identifying whether this represents a solitary cortisol-producing tumor from the adrenal gland or whether there are large nodules in each adrenal gland resulting in cortisol excess.

Summary

The diagnosis of Cushing's syndrome is the most challenging problem in endocrinology and may be difficult for even experienced endocrinologists. Patients need to appreciate that all the currently available tests have pitfalls and none are perfect. Repeated testing may often be needed when the results are not straightforward. The Endocrine Society guidelines recommend that one of the screening tests be performed (my personal preference is late-night salivary cortisol and/or the dexamethasone suppression test). If any test is abnormal, patients should be referred to an endocrinologist to perform confirmatory studies.

Editor's Note: Dr. Findling is an endocrinologist and Professor of Medicine at the Medical College of Wisconsin. Dr. Findling has been dedicated to the clinical evaluation and care of patients with Cushing's syndrome for over thirty years. He has over 100 publications and was a co-author of the Endocrine Society guidelines for the diagnosis of Cushing's syndrome.

