

The OHSU Pituitary Unit

Cushing's Disease

Cushing's disease is a form of Cushing's syndrome that is caused by an ACTH secreting pituitary adenoma. About 10% of pituitary adenomas secrete excess ACTH. This elevated ACTH in turn stimulates the adrenal glands to produce excess cortisol. This disease process is called Cushing's disease (named after the famous neurosurgeon, Harvey Cushing).

Signs and Symptoms

Cushing's disease has a myriad of signs and symptoms, many of which are listed in Table 1 (below). Cushingoid features are often pronounced but may be subtle in some cases. ACTH secreting pituitary adenomas are often small (less than 10 mm) at the time of discovery but, if large, may manifest with "mass effects" (visual field disturbances, headaches, pituitary hormone deficiencies, etc). Cortisol influences virtually every cell in the body and Cushing's patients often complain of severe dysfunction due extreme fatigue and weakness. Many of the features of Cushing's disease are common to other diseases (non-specific symptoms) and thus Cushing's patients often suffer for years prior to appropriate diagnosis. Insights into how a patient can work with their primary care provider can be found in the section: [How Do I Work With My Doctor To Find Out if I have a Pituitary Disorder?](#)

Table 1 - Features of Cushing's Disease

- Rounding of the face (moon face)
- Facial redness (facial plethora)
- Hump on back of neck (dorsocervical fat deposition)
- Weight gain around the belly with thinner arms and legs (truncal obesity)
- Purple stretch marks (violaceous stria)
- Facial hair growth (hirsutism)
- Acne
- Muscle weakness
- Easy bruising
- Bone thinning (osteoporosis - sometimes with recurrent fractures)
- Recurrent infections
- Sleep disturbances
- Fatigue
- High blood pressure
- Diabetes mellitus

Diagnosis

Biochemically confirming the presence of Cushing's disease can be very difficult in some cases since there is no "gold standard" for making the diagnosis. Stated otherwise, virtually every test available for diagnosing Cushing's disease will sometimes falsely diagnose a "normal" person with the disease and conversely will sometimes fail to diagnose the disease in those who have it. However, a thorough history and physical exam combined with multiple tests can correctly rule in or rule out the disease in most cases.

The diagnosis of Cushing's is often made by measuring free cortisol in a 24-hour urine collection (UFC). Most clinicians consider a level of more than four times the upper limit of normal as diagnostic. For example, a urine cortisol of more than 300 mcg/24 hours with the normal being 8-70 is diagnostic of Cushing's. If the UFC is elevated but less than four times the upper limit of normal, more tests are necessary. This is because other entities can lead to small elevations in urine cortisol (e.g., depression, alcoholism, chronic and severe stress, etc). Conversely, a "normal" 24hour UFC suggests the absence of Cushing's but does not rule it out (i.e., there is a population of surgically proven Cushing's disease patients who had a "normal" UFC as part of their evaluation).

There are many other tests available for evaluating a patient for Cushing's disease. This author primarily uses two additional tests. The first is the sampling of serum cortisol over a 24-hour period. Normal individuals typically have serum cortisol levels of 18 ug/dl or higher around 8:00 a.m. The serum cortisol level steadily drops through the day and is typically undetectable around midnight. This is referred to as diurnal variation. Cushing's tumors typically do not follow this pattern and serum cortisol levels greater than 5 ug/dl at midnight are very suggestive of Cushing's. A second useful test is the "low dose" dexamethasone suppression test followed by CRH stimulation. ACTH secreting pituitary adenomas are typically less sensitive to suppression by dexamethasone than are normal pituitary cells but are typically more sensitive to stimulation by CRH (normally released by the hypothalamus). Therefore, a serum cortisol that is not suppressed (i.e., greater than 1.4 ug/dl) 15 minutes after CRH stimulation is suggestive of Cushing's. A multitude of other tests for evaluating Cushing's are also available (e.g., salivary cortisol measurements, "high dose" dexamethasone suppression test, etc.) As with virtually all tests for the evaluation of Cushing's disease, there can be false positive and false negative results.

Once the diagnosis of Cushing's has been made, the second step is to confirm that the serum ACTH level is not suppressed. This is important so as to rule out other causes of Cushing's syndrome (i.e., confirm that an ACTH secreting tumor is driving the disease). Third, it is important to localize the tumor to a pituitary versus a non-pituitary (or "ectopic") source. If a pituitary tumor (greater than 4mm) is clearly seen on MRI, many clinicians will proceed with surgery to treat ACTH dependant

Cushing's. Alternatively cavernous or petrossal sinus sampling may be helpful to clearly localize the ACTH source. In this procedure, a catheter is placed in the vein of each leg and fed up past the heart up into the blood sinuses around the pituitary. Blood is then sampled from either side. This test not only confirms whether the tumor is in the pituitary, but helps the surgeon know which side of the pituitary to look for the tumor. In the hands of a good interventional radiologist experienced in the procedure, this process is relatively straightforward. Bad patient experiences with the procedure usually result from having it performed by an interventional neuroradiologist inexperienced in the procedure. The dexamethasone suppression test is also sometimes used for tumor localization but it is not as reliable as sinus sampling.

Treatment

The treatment of choice for Cushing's disease is pituitary surgery. A good surgeon will most often be able to cure Cushing's with one attempt. More details on the process of selecting a qualified neurosurgeon are available in the section: [I Have Been Diagnosed with a Pituitary Tumor - What Should I Do Next?](#). Alternate treatments include stereotactic radiosurgery, adrenalectomy, and medications. All of these alternate treatments have potential complications making surgery in the hands of an expert pituitary surgeon the treatment of choice. In the case of large ACTH producing tumors (macroadenomas), deficiencies of other pituitary hormones may be present due to the damaging "mass effect" of the tumor. Patients with pituitary macroadenomas should be evaluated for pituitary hormone deficiencies as discussed in the section: [How Do I Work With My Doctor To Find Out if I have a Pituitary Disorder?](#) Pituitary hormone replacement therapy is discussed in the section: [Pituitary Hormone Deficiency and Replacement](#).

The experience of cortisol withdrawal during the first several months after being cured of Cushing's can be very unpleasant. During this period, cortisol must be given back to the patient and then tapered off over time. Classic symptoms of this withdrawal process include fatigue, aching, and depression. Abdominal pain, nausea and vomiting, and dizziness are indicators that the cortisol withdrawal is occurring too quickly (adrenal insufficiency is occurring) and the hydrocortisone taper should be slowed.

There are two main phases that a cured patient will go through after surgery. The first is the cortisol withdrawal phase. The features of Cushing's disease are due to cortisol excess and the body reacts to having the cortisol withdrawn. To make the process tolerable (and safe), large doses of glucocorticoids are given to the postoperative patient and then tapered over a month or so as symptoms allow. This can be an awful experience for the patient marked by fatigue, depression, and body aches. Headache may be present but if severe (especially if accompanied by nausea and

dizziness) may indicate that the taper is happening too quickly. After the initial withdrawal phase, the second phase is marked by the temporary need for continued glucocorticoid replacement (typically 20 mg hydrocortisone or 5 mg prednisone) until the hypothalamic/pituitary/adrenal (HPA) axis awakens. This phase may last many months and may last over a year. Until this axis awakens, the patient is adrenally insufficient and should be treated accordingly.

Assessment of Cure

Just as the initial diagnosis of Cushing's disease can be difficult to make, "proving" someone has been cured of Cushing's can be very challenging as well. One early indicator of biochemical cure is the measurement of very low (or undetectable) post-operative morning cortisol levels (typically measured 72 hours after surgery). In this post-operative setting, morning cortisol levels are typically low because normal ACTH producing cells in the pituitary have been suppressed by elevated serum cortisol levels. Therefore, the removal of the ACTH secreting tumor leaves no source of ACTH, the adrenal glands are no longer stimulated and cortisol levels plummet. It is important to note that as high as 30% of patients with long term cure of Cushing's disease do not have a history of undetectable 72 hour post-operative serum cortisol levels. Therefore, if 72-hour post-operative cortisols are not below 5 ug/dl, further evidence should be obtained to confirm the presence or absence of cure.

After a patient has been tapered off replacement glucocorticoids post-operatively, it is important to demonstrate the normalization of the tests that were initially used to diagnose Cushing's disease. For example if a patient had a significantly elevated 24-hour UFC pre-operatively, it should normalize if a cure was obtained. Other evidence of cure is the dramatic resolution of the features of Cushing's disease. For example, many patients note a dramatic weight reduction in the first few months after surgery. By contrast, even in the context of a biochemical cure, features may resolve slowly. Even in the context of a biochemical cure, the symptoms of fatigue and depression can persist for many months since they are also the symptoms of cortisol withdrawal. It is important to note that even with an incomplete cure (i.e., not all the pituitary tumor was removed), many symptoms will begin to resolve at first but they usually return over time.

In general, when a cure is obtained, most of the features of Cushing's disease will reverse over time. Some of these changes can be dramatic. Some may take years. Of note, the need for medical treatment for high blood pressure and diabetes should be evaluated closely and will likely need to be tapered.

Finally, even in the hands of an excellent neurosurgeon, there is a recurrence rate of about 10% over time for Cushing's disease. Therefore, even in the context of a "biochemical cure", Cushing's patients should be monitored by history, physical, and biochemistry over time for possible recurrence of their disease. Work up and treatment are similar to those done at initial presentation.

Long-term Course and Potential Complications

Cured Cushing's are typically delighted with the resolution of most of their Cushing's symptoms. This can, however, take from months to even years to fully happen. As stated above, recurrence does occur and should be watched for by the patient and their clinician. Associated diseases such as diabetes mellitus, hypertension, and osteoporosis should be followed (and treated if necessary) although each may resolve fully over time as well.

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