

# CUSHING'S SYNDROME

## • THE FACTS YOU NEED TO KNOW •

Written by: Paul Margulies, MD, FACE, FACP,  
Medical Director, NADF.  
Clinical Associate Professor of Medicine,  
Zucker School of Medicine at Hofstra/Northwell.

### WHAT IS CUSHING'S SYNDROME?

Cushing's Syndrome is a disease caused by an excess of cortisol production or by excessive use of cortisol or other similar steroid (glucocorticoid) hormones.

Cortisol is a normal hormone produced in the outer portion, or cortex, of the adrenal glands, located above each kidney. The normal function of cortisol is to help the body respond to stress and change. It mobilizes nutrients, modifies the body's response to inflammation, stimulates the liver to raise the blood sugar, and it helps control the amount of water in the body. Another adrenal cortex hormone, aldosterone, regulates salt and water levels which affects blood volume and blood pressure. Small amounts of androgens (male hormones) are also normally produced in the adrenal cortex. Cortisol production is regulated by adrenocorticotrophic hormone (ACTH), made in the pituitary gland, which is located just below the brain.

When too much cortisol is produced in the adrenal glands, or an excess is taken in treating other diseases, significant changes occur in all of the tissues and organs of the body. All of these effects together are called Cushing's Syndrome.

Cushing's disease is the name given to a type of Cushing's Syndrome caused by too much ACTH production in the pituitary. Dr. Harvey Cushing first described a woman with signs and symptoms of this disease in 1912, and in 1932 he was able to link the adrenal overproduction of cortisol to an abnormality in the pituitary.

### WHAT CAUSES CUSHING'S SYNDROME?

When cortisol or other glucocorticoid hormones (such as hydrocortisone, prednisone, methylprednisolone or dexamethasone) are taken in excess of the normal daily requirement for a prolonged period of time, it causes Cushing's syndrome. This "iatrogenic" (caused by the treatment) form is unfortunately a necessary side effect when high doses of these steroid hormones must be used to treat certain life-threatening illnesses, such as asthma, rheumatoid arthritis, systemic lupus, inflammatory bowel disease, some allergies, and others.

Spontaneous overproduction of cortisol in the adrenals is divided into two groups - those due to an excess of ACTH and those that are independent of ACTH. A pituitary tumor producing too much ACTH, stimulating the adrenals to grow (hyperplasia) and to produce too much cortisol, is the most common type, and this is called Cushing's disease. It is the cause of 70% of spontaneous Cushing's

syndrome. ACTH can also be produced outside the pituitary in a benign or malignant tumor in the lung, thymus gland, pancreas, or other organ. This is called "ectopic" ACTH production.

When the source of excess cortisol production is a tumor of the adrenal gland itself, then it is not dependent on ACTH. The tumor makes cortisol on its own, and the other adrenal gland shrinks because ACTH production is suppressed. Adrenal cortex tumors can be benign (an adenoma), or malignant (a carcinoma) and are usually found on only one side. A very rare type is caused by multiple benign adenomas on both sides. An inherited form of this is called Carney complex.

Although almost all types of spontaneous Cushing's Syndrome are ultimately caused by one type of tumor or another, little is known about what makes these tumors occur. Aside from the genetic cause of Carney complex, we still have limited understanding about the factors that cause most forms of Cushing's Syndrome.

## **HOW COMMON IS CUSHING'S SYNDROME?**

Iatrogenic Cushing's Syndrome from taking steroid medication is extremely common because of the widespread use of these medicines in treating many illnesses.

Spontaneous Cushing's Syndrome and Cushing's disease can occur in children and adults. Pituitary Cushing's disease generally occurs after puberty with equal frequency in boys and girls. In adults, it has a greater frequency in women than men, with most found at age 25 to 45. The total incidence is about 5 to 25 cases per million people per year. Ectopic ACTH as a cause of Cushing's Syndrome is more common because of the high rate of lung cancer (about 660 per million per year), but it often goes unrecognized. The incidence increases with age. Adrenal tumors are relatively rare, and cause Cushing's Syndrome in only 2 people per million per year for both adenomas and carcinomas. Both are also 4 to 5 times more common in women than men.

## **WHAT ARE THE SYMPTOMS AND SIGNS OF CUSHING'S SYNDROME?**

Cortisol excess produces significant and serious change in the appearance and health of affected individuals. Depending on the cause and duration of the Cushing's Syndrome, some people may have more dramatic changes, some might look more masculinized, some may have more blood pressure or weight changes.

General physical features include a tendency to gain weight, especially on the abdomen, face (moon face), neck and upper back (buffalo hump); thinning and weakness of the muscles of the upper arms and upper legs; thinning of the skin, with easy bruising and pink or purple stretch marks (striae) on the abdomen, thighs, breasts and shoulders; increased acne, facial hair growth, and scalp hair loss in women; sometimes a ruddy complexion on the face and neck; often a skin darkening (acanthosis) on the neck. Children will show obesity and poor growth in height.

On physical examination, a physician will notice these changes and will also usually find high blood pressure and evidence of muscle weakness in the upper arms and legs, and sometimes some enlargement of the clitoris in females. Symptoms usually include fatigue, weakness, depression, mood swings, increased thirst and urination, and lack of menstrual periods in women.

Common findings on routine laboratory tests in people with Cushing's Syndrome include a higher

white blood count, a high blood sugar (often into the diabetic range), and a low serum potassium. These will often reinforce a physician's suspicion about Cushing's Syndrome. Ectopic Cushing's Syndrome tends to present with less impressive classic features, but more dramatic hypertension and loss of potassium, sometimes in the setting of weight loss from the underlying cancer.

If untreated, Cushing's Syndrome will cause continued weakness of the muscles, fatigue, poor skin healing, weakening of the bones of the spine (osteoporosis), and increased susceptibility to some infections including pneumonia and TB.

## **HOW IS CUSHING'S SYNDROME DIAGNOSED?**

Most people who appear to have some of the classic physical features of Cushing's Syndrome (Cushingoid appearance) do not actually have the disease. After iatrogenic Cushing's is excluded, other causes of this appearance can be polycystic ovary syndrome (androgen excess from the ovaries), ovarian tumors, congenital adrenal hyperplasia, ordinary obesity, excessive alcohol consumption, or just a family tendency to have a round face and abdomen with high blood pressure and high blood sugar.

Because Cushing's Syndrome is a rare but serious disorder, it is very important to carefully exclude (rule out) other disorders and then separate the different types, leading eventually to a specific cause that can be treated. This process of testing and excluding usually takes days to weeks and requires a lot of patience and cooperation by the person being tested.

After the initial history, physical exam and routine blood tests, the first step is to prove cortisol excess with specific blood and 24 hour urine tests for cortisol. Inappropriate cortisol production will then be evaluated by doing a dexamethasone suppression test. Dexamethasone (steroid) pills are given by mouth, then blood and urine are collected for cortisol and other adrenal hormones. A screening test might be done initially with an overnight test, but if it is abnormal, usually a 4 day test divided into low and high dose dexamethasone is needed. To separate ACTH dependent from independent types, a blood test for ACTH in the morning is done. Blood and urine tests for adrenal androgens are useful. Testing with other drugs, such as metyrapone and CRH (corticotropin releasing hormone) may also be needed.

Once all of the blood and urine results are analyzed, they will establish whether some type of Cushing's Syndrome is present, and should indicate whether the disease is ACTH dependent (pituitary or ectopic) or independent (an adrenal tumor). Localizing techniques such as CT or MRI are then used to find the tumor. Often a pituitary tumor is tiny and hard to find, so a special test of the release of ACTH from both sides of the pituitary (petrosal sinus sampling) might be needed. Small tumors producing ectopic ACTH are also sometimes difficult to localize and require repeated scans and x-rays.

## **HOW IS CUSHING'S SYNDROME TREATED?**

If the Cushing's Syndrome is a side effect of taking high doses of steroid hormones (iatrogenic), withdrawing these medicines will allow the body to go back to normal. The ability to taper or stop the steroids, however, depends on the type of disease being treated and the pattern of response. Sometimes, steroids cannot be totally stopped or may be reduced only to a limited degree because the illness being treated would worsen. In that case, some degree of persistent Cushing's Syndrome

would remain as an unwanted side effect. Treatment of the effects of steroid excess would include management of high blood sugar with diet and medications, replacement of potassium, treatment of high blood pressure, early treatment of any infections, adequate calcium intake and appropriate adjustments in steroid doses at times of acute illness, surgery or injury.

Cushing's disease is best treated with the surgical removal of the pituitary tumor, usually with a technique called transsphenoidal resection (behind the nose) by a neurosurgeon.

Occasionally, the entire pituitary gland will need to be removed or injured in order to cure the Cushing's disease, leaving the person with a deficiency of ACTH and the other pituitary hormones. This can be treated by giving replacement hormones for cortisol, thyroid and gonadal (sex) hormones. Fertility can be restored with special hormonal therapies. If the pituitary tumor cannot be removed, radiation therapy to the pituitary can be used, but the improvement in the Cushing's Syndrome is much slower.

Before transsphenoidal surgery became available, the surgical removal of both adrenal glands was common, but this always produced adrenal insufficiency and sometimes caused large ACTH producing pituitary tumors to grow (called Nelson's syndrome). That is why pituitary surgery rather than adrenal surgery is usually preferred for Cushing's disease.

Ectopic ACTH producing tumors are usually malignant (cancer). Removing this cancer or treating it with radiation or chemotherapy may help in improving the Cushing's Syndrome. If the tumor is benign, or it can be completely removed, surgery may be a cure. Most of the time, reduction of the cortisol production from the adrenals with medications such as metyrapone, amino-gluthethimide or ketoconazole is useful while the ACTH-producing tumor is treated.

Adrenal adenomas are always treated by surgically removing the tumor with either an abdominal or side (flank) incision. The other adrenal is left in, and will grow back to normal size or function. After the surgery, replacement steroid hormones are given and slowly tapered over a few months as the remaining adrenal responds to the normal ACTH production from the pituitary.

Adrenal carcinomas (cancer) can be cured if removed early. Unfortunately, they are usually discovered after they have already spread beyond the adrenal gland and are then not curable. Chemotherapy including o, p'DDD and other medicines are often used to try to control the tumor but do not cure it. The excess cortisol production can be controlled with o, p'DDD or by other medications like those mentioned for ectopic ACTH production: metyrapone, aminogluthethimide and ketoconazole. These medicines can be used to treat any form of inoperable or incurable Cushing's Syndrome, including Cushing's disease, but they can have serious side effects and require very careful monitoring and balancing with steroid hormone replacement therapies. Surgical cure of the primary cause of the Cushing's Syndrome is always the best, if possible.

## **HOW NORMAL IS A CUSHING'S PATIENT'S LIFE?**

The symptoms, disabilities and life-style of a person with Cushing's Syndrome depend on the degree of cortisol excess, the duration of the disease, the basic health of the person, but especially the type and curability of the Cushing's Syndrome. If it is cured, all of the features of the disease can resolve, but this may take as long as 2 to 18 months. During that time, most people get annoyed and frustrated by the slow improvements in physical changes and the combination of Cushing's and adrenal insufficiency signs and symptoms (dizziness, weakness, nausea, loss of appetite) as

replacement steroid hormones are tapered and adrenal hormone production slowly improves toward normal. Frequent calls and visits to physicians are necessary.

If the Cushing's Syndrome is incurable, or if iatrogenic Cushing's Syndrome must remain, these individuals will have to cope with persistent fatigue, muscle weakness, abdominal and facial weight gain, depression, mood swings, and all the other signs and symptoms mentioned earlier. Regular visits to a physician for examinations, blood tests, and treatments of infections and complications will be necessary and are often viewed as a severe burden.

## **WHY CONSULT AN ENDOCRINOLOGIST?**

Iatrogenic Cushing's Syndrome is generally managed by the physician prescribing the steroid hormones for the primary illness, such as asthma, arthritis, or inflammatory bowel disease. Sometimes physicians are able to decrease steroid doses by using other drugs in the treatment of these diseases.

All of the types of spontaneous Cushing's Syndrome should be carefully evaluated by an endocrinologist (a specialist in hormonal disease) who has the knowledge and experience in choosing the correct diagnostic studies and evaluating the results. Finding the correct diagnosis often requires prolonged testing and even repetition of tests. Quick shortcuts can be misleading. Referrals for surgery or radiation should be coordinated by the endocrinologist, who will also be directly involved in managing the patient afterwards.

## **NEW TREATMENTS**

If Cushing's disease is not cured by surgery; or if there is persistent elevation of cortisol from ectopic ACTH production, or a residual adrenal tumor or cancer, then medical management is needed. Several medications have been used for many years, including: ketoconazole, metyrapone, etomidate, and mitotane. Each of these medications, or combinations of them, can reduce cortisol levels, but the medications can have significant side effects.

Two new treatments are now available. Pasireotide (Signifor) suppresses ACTH in persistent pituitary Cushing's disease. Mifepristone (Korlym) blocks the cortisol receptor and reduces the effect of persistent high cortisol. These new treatments have a range of side effects, so patients must be carefully monitored. Both treatments potentially offer significant benefits and can be used in combination with older therapies.

## **ADDITIONAL RESOURCES FOR CUSHING'S SYNDROME**

Cushing's Support and Research Foundation  
<http://www.csrf.net/index.htm>

National Institutes of Health  
<http://www.nih.gov>

## **ADDITIONAL RESOURCE FOR CUSHING'S DISEASE**

Pituitary Disorders Education & Support  
<http://pituitarydisorder.net/>

Supplied as a service by:



The National Adrenal Diseases Foundation  
is a non-profit organization providing  
information, education and support  
to all persons affected by adrenal disease.

For more information on joining NADF, or  
to find a support group in your area, contact:

National Adrenal Diseases Foundation  
P.O. Box 566  
Lake Zurich, IL 60047  
(847) 726-9010  
[www.nadf.us](http://www.nadf.us)  
e-mail: [NADFMail@nadf.us](mailto:NADFMail@nadf.us)