Cushing’s Syndrome/Disease

Cushing's syndrome is a disorder caused by an excessive production of cortisol. It can also be caused by excessive use of cortisol or other similar steroid (glucocorticoid) hormones. When too much cortisol is produced in the adrenal glands, or an excess amount is taken as a treatment for other diseases, this affects all of the tissues and organs in the body. These effects together are known as Cushing's syndrome.

Cortisol is a normal hormone produced in the outer portion of the adrenal glands. When functioning normally, cortisol helps the body respond to stress and change. It mobilizes nutrients, modifies the body's response to inflammation, stimulates the liver to raise blood sugar, and helps control the amount of water in the body. Cortisol production is regulated by the adrenocorticotrophic hormone (ACTH), produced in the pituitary gland. Spontaneous overproduction of cortisol in the adrenals is divided into two groups – those attributed to an excess of ACTH and those that are independent of ACTH.

Incidence and Prevalence

- An estimated 10 to 15 of every million people are affected every year.
- Pituitary adenomas account for more than 70 percent of cases in adults and about 60-70 percent of cases in children and adolescents.
- Cushing’s syndrome most commonly affects adults aged 20 to 50, and is more prevalent in females, accounting for about 70 percent of all cases.

Underlying Causes

Pituitary Adenomas – Cushing’s disease

Pituitary adenomas are benign tumors of the pituitary gland which secrete increased amounts of ACTH, causing excessive cortisol production. Most patients have a single adenoma. First described in 1912 by neurosurgeon Harvey Cushing in his book *The Pituitary Body and its Disorders,* Cushing’s disease is the most common cause of spontaneous Cushing’s syndrome, accounting for 60 to 70 percent of cases.

Ectopic ACTH Syndrome

Some benign or malignant (cancerous) tumors that arise outside the pituitary can produce ACTH. This condition is known as ectopic ACTH syndrome. Lung tumors cause more than 50 percent of these cases. Other less common types of tumors that can produce ACTH are thymomas, pancreatic islet cell tumors, and medullary carcinomas of the thyroid.

Adrenal Tumors

An abnormality of the adrenal glands such as an adrenal tumor may cause Cushing's syndrome. Most of these cases involve non-cancerous tumors called adrenal adenomas, which release excess cortisol into the blood.

Adrenocortical carcinomas, or adrenal cancers, are the least common cause of Cushing's syndrome. Cancer cells secrete excess levels of several adrenal cortical hormones, including

cortisol and adrenal androgens. Adrenocortical carcinomas often cause very high hormone levels and rapid onset of symptoms.

Familial Cushing's syndrome

Most cases of Cushing's syndrome are not genetic. However, some individuals may develop Cushing's syndrome due to an inherited tendency to develop tumors of one or more endocrine glands. In Primary Pigmented Micronodular Adrenal Disease, children or young adults develop small cortisol-producing tumors of the adrenal glands. In Multiple Endocrine Neoplasia Type I (MEN I), hormone secreting tumors of the parathyroid glands, pancreas and pituitary occur. Cushing's syndrome in MEN I may be due to pituitary, ectopic or adrenal tumors.

Risk factors

Obesity, type 2 diabetes, poorly controlled blood glucose (blood sugar levels), and high blood pressure may increase the risk of developing this disorder.

Possible signs/symptoms of Cushing’s syndrome/disease:

- Weight gain in face (moon face)
- Weight gain above the collar bone (supraclavicular)
- Weight gain on the back of neck (buffalo hump)
- Skin changes with easy bruising, purplish stretch marks (stria)
- Red, round face (plethora)
- Excessive hair growth (hirsutism) on face, neck, chest, abdomen, and thighs
- Female balding
- Generalized weakness and fatigue
- Blurry vision
- Vertigo
- Muscle weakness
- Menstrual disorders in women (amenorrhea)
- Decreased fertility and/or sex drive (libido)
- Hypertension
- Poor wound healing
- Diabetes mellitus
- Severe depression
- Extreme mood swings

Diagnosis

Diagnosis of Cushing's syndrome is based on a review of medical history, physical examination and laboratory tests, which help to determine the existence of excessive levels of cortisol. In addition, it can be beneficial to compare old and recent photographs, because these often reveal classic changes in facial and body appearance associated with this disorder.

The following tests can help determine if there are excessive levels of cortisol:

- The **low-dose dexamethasone suppression test** measures the response of the adrenal glands to ACTH and has been widely utilized for four decades. It involves taking a small dose of a cortisol-like drug dexamethasone (1 mg) at 11 pm, then having blood

drawn for cortisol the following morning. In normal individuals, the levels of cortisol are typically very low in the blood, indicating that ACTH secretion is suppressed. In patients with Cushing's syndrome, cortisol is easily detected in the blood and may be increased. It is evident that normal individuals should suppress their cortisol level to a very low level (<1.8 mg/dl). Using this strict criterion, the test should provide an estimated 95 to 97 diagnostic accuracy rate. However, some patients with mild Cushing's syndrome will suppress their serum cortisol to even lower levels.

- The **24-hour urine test** measures the amount of urine produced over the course of an entire day and tests cortisol levels. Levels higher than 50 to 100 micrograms a day in an adult suggest the presence of Cushing's syndrome. Although the majority of patients with Cushing's syndrome have elevated levels of urine-free cortisol, it is becoming increasingly evident that many patients with mild Cushing's syndrome may also have normal levels of urine-free cortisol. Thus, a normal 24 hour urine-free cortisol does not exclude the diagnosis of Cushing's syndrome and additional testing is always required.

- **Late-night salivary cortisol**, a relatively new test, checks for elevated levels of cortisol between 11 pm and midnight. Cortisol secretion is usually very low late at night, but in patients with Cushing's syndrome, the level will always be elevated during this timeframe. Normal levels of late-night salivary cortisol virtually exclude the diagnosis of Cushing's syndrome. Collection of saliva requires special sampling tubes; however, this is an easy test for patients to perform and can be done multiple times. Administered correctly, this test should provide an estimated 93 to 100 percent diagnostic accuracy rate.

After a definitive diagnosis of Cushing's syndrome has been made, the source of the excessive cortisol must be determined. The first step in distinguishing the underlying cause is the measurement of ACTH. Patients with ACTH-secreting tumors will either have a normal or elevated level of ACTH. In contrast, patients with the adrenal form will have a subnormal level.

Distinguishing a pituitary from a non-pituitary ACTH-secreting tumor can be diagnostically challenging. The majority of patients with ACTH-secreting tumors have a pituitary lesion (often very small).

- **MRI** of the pituitary gland with gadolinium enhancement is a recommended approach. When an obvious pituitary tumor (>5 mm) is identified with MRI, further diagnostic evaluation may not be needed depending on the clinical presentation. However, about 10 percent of people have incidental tumors in the pituitary gland demonstrated on MRI. In such cases, the MRI will not provide a definitive diagnosis and additional tests will be required.

- **Petrosal sinus sampling** is a test used to distinguish the source of ACTH secretion and should only be performed after the diagnosis of Cushing's syndrome has been confirmed. ACTH and other pituitary hormones circulate through the system via veins called the inferior petrosal sinuses. During this procedure, blood is sampled from the inferior petrosal sinus veins that drain the pituitary. 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) and at 2, 5, and 10 minute intervals. This invasive study should be performed at a center with extensive experience in the

procedure. Administered correctly, this test should provide an estimated 95 to 98 percent diagnostic accuracy rate.

Treatment of Cushing's syndrome

Treatment depends on the underlying cause of excess cortisol and may include surgery, radiation, chemotherapy or the use of cortisol-inhibiting drugs. If the cause is long-term use of glucocorticoid hormones to treat another disorder, the physician will gradually reduce the dosage to the lowest dose adequate for control of that disorder. Once control is established, the daily dose of glucocorticoid hormones may be doubled and given on alternate days to lessen side effects.

Treatment of Cushing's disease

Microsurgical resection of ACTH-secreting pituitary adenomas is the optimum treatment for Cushing's disease, with cure rates of approximately 80 percent. Surgery is most often done through a transnasal approach, which will not leave a visible scar. Partial removal of the pituitary gland (subtotal hypophysectomy) may be used in patients without clearly identifiable adenomas.

Post surgery, the production of ACTH drops below normal. This decrease is natural and temporary, and patients are prescribed a synthetic form of cortisol such as hydrocortisone or prednisone to compensate. Most patients can discontinue this replacement therapy in 1 to 2 years, but others must take it for the rest of their lives. Patients who need adrenal surgery may also require steroid replacement.

Other treatment options are recommended in patients with incompletely resected pituitary macroadenomas or carcinomas, patients with multiple medical issues preventing surgery, and patients of childbearing age who wish to preserve fertility. Radiation therapy, which is administered over a 6-week period to the pituitary gland, has yielded improvement in 40 to 50 percent of adults and up to 85 percent of children.

Stereotactic radiosurgery has found to be an effective treatment for patients with ACTH-secreting pituitary adenomas. A recent study demonstrated endocrine remission in 54 percent of cases and tumor growth control in 96 percent of patients with Cushing's disease. However, ongoing observation is required to monitor for tumor growth, disease recurrence, the development of new hormone deficiencies, and damage to the optic pathways and brain.

Cushing's Resources

Cushing's Help and Support
Cushing's Support & Research Foundation
National Endocrine and Metabolic Diseases Information Service
Pituitary Network Association