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Patient information: Cushing's syndrome

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Cushing's syndrome is a condition that results from an excess of cortisol, a hormone produced by the adrenal glands. Cortisol has many important functions and is necessary for life; however, an excess of this hormone has well-known negative effects on the body. Cortisol, which is also called hydrocortisone, is classified as a glucocorticoid (because one of its effects is on glucose metabolism).

Normally, the adrenal glands' production of cortisol is carefully controlled by the hypothalamus and pituitary gland. Cushing's syndrome can result from several different conditions that affect this control system. Cushing's syndrome affects about three times more women than men.

People with Cushing's syndrome should learn as much as they can about this condition and the available treatment options, so that they can take an active role in decisions about treatment.

CAUSES OF CUSHING'S SYNDROME – The causes of Cushing's syndrome are usually divided into two broad categories, based upon whether the problem lies in the pituitary gland (a small structure at the base of the brain) or in the adrenal glands, which lie above the kidneys. Cushing's syndrome can also occur in individuals who take large doses of glucocorticoids (eg, prednisone) for diseases such as asthma and rheumatoid arthritis.

Cushing's syndrome that results from high blood corticotropin (ACTH) levels – Up to 70 percent of people with Cushing's syndrome have benign pituitary tumors (called adenomas) that produce excess amounts of ACTH, the hormone that stimulates the adrenal gland to produce cortisol. This condition is called Cushing's **disease**, which shouldn't be confused with Cushing's **syndrome**. Most of these tumors are very small, and they may be difficult to identify.

Other causes of high blood ACTH levels include non-pituitary tumors that produce ACTH. This form of Cushing's syndrome is called the ectopic ACTH syndrome. Many of these tumors occur in the lungs or elsewhere in the chest.

Cushing's syndrome that occurs in the presence of normal or low blood ACTH levels – Most people with Cushing's syndrome who have normal or low blood ACTH levels can be traced to the use of medications that contain glucocorticoids such as prednisone and therefore mimic the effects of cortisol.

Glucocorticoids have powerful anti-inflammatory actions and are used to treat autoimmune conditions, such as rheumatoid arthritis, and to prevent transplant rejection. Most forms of glucocorticoids, including inhaled and topical forms, can cause Cushing's syndrome.

Less common causes of Cushing's syndrome with normal or low ACTH levels include benign or malignant (cancerous) tumors of the adrenal gland that produce excess cortisol. Nodular hyperplasia (overgrowth) of the adrenal gland is an even less common cause of cortisol excess; some cases of nodular hyperplasia are hereditary.

SYMPTOMS OF CUSHING'S SYNDROME – The symptoms of Cushing's syndrome result from an excess of cortisol. Most patients develop at least a few of these symptoms, and the symptoms typically worsen over time. However, each person's symptoms depend not only on the degree and duration of cortisol excess, but also on the presence of high blood levels of other adrenal hormones and on the underlying cause of Cushing's syndrome. Age also plays a role: the symptoms of Cushing's syndrome may be very subtle in people over the age of 50 years.

Weight gain – Progressive weight gain is the most common symptom of Cushing's syndrome. This weight gain usually affects the face, neck, trunk, and abdomen; the limbs are usually thin. People with Cushing's syndrome often develop a rounded face and collections of fat on the upper back and at the base of the neck. Weight gain in children with Cushing's syndrome also involves the limbs and is usually associated with poor growth.

Skin changes – In Cushing's syndrome, the skin tends to become thin, fragile, and more susceptible to bruises and infections. Wounds heal poorly, and wide, reddish-purple streaks, called striae (also known as stretch marks), may occur in areas of weight gain.

Menstrual irregularities – Women with Cushing's syndrome may have a variety of menstrual problems, most typically infrequent or absent menstrual periods. They also are often infertile.

Symptoms of androgen excess – Women with adrenal gland tumors may have symptoms of male hormone (androgen) excess, such as hirsutism (growth of coarse body hair in a male pattern), oily skin, and acne.

Muscle loss and weakness – Prolonged Cushing's syndrome causes the muscles of the upper arms and legs to waste and become weaker. Some individuals notice that it becomes more difficult to get out of a chair or climb stairs because of the upper leg weakness.

Bone loss – Cushing's syndrome can lead to thinning of the bones (osteoporosis), which can eventually result in fractures of the ribs, long bones, and spinal vertebrae.

Glucose intolerance – Excess cortisol can cause an elevation of blood glucose levels. People with Cushing's syndrome may develop glucose intolerance, a prediabetic condition that can progress to diabetes mellitus.

Hypertension and cardiovascular disease – Excess cortisol raises blood

pressure and puts stress on the heart and vascular system.

Psychologic symptoms – Over half of all patients with Cushing's syndrome have psychologic symptoms that range from loss of emotional control and depression to panic attacks and paranoia. Insomnia is also common.

Infections – Cortisol suppresses the immune system, and people with Cushing's syndrome may develop infections more frequently.

CONFIRMING CUSHING'S SYNDROME – If your symptoms suggest that you have Cushing's syndrome, your doctor will ask about your use of any medications that contain glucocorticoid and will order tests to check your cortisol levels. Although other conditions share symptoms with Cushing's syndrome, they are not associated with high cortisol levels.

These tests may include measurements of cortisol in a 24-hour urine specimen; a blood or saliva test to check for the normal daily rise and fall of cortisol levels (this test may require collection of blood or saliva late at night); and a low-dose dexamethasone test, a potent glucocorticoid that suppresses cortisol production in healthy individuals but not in those with Cushing's syndrome.

DETERMINING THE CAUSE OF CUSHING'S SYNDROME – Once Cushing's syndrome has been diagnosed, other tests are used to find the exact location of the abnormality causing the excess cortisol production. The type and number of tests your doctor recommends will depend on the results of preliminary tests.

Blood tests – Blood tests can determine relative levels of cortisol and ACTH. Because these hormones are secreted episodically, your doctor will likely request that measurements be done on two or three separate days. The relative levels of cortisol and ACTH can help differentiate between the different causes of Cushing's syndrome.

Computed tomography (CT) and magnetic resonance imaging (MRI) scans – CT and MRI scans of the adrenal glands, pituitary gland, lungs, and abdomen can identify hormone-producing tumors.

High-dose dexamethasone suppression test – High doses of dexamethasone usually suppress ACTH production by pituitary adenomas (benign tumors) that cause Cushing's disease. As a result, blood and urine levels of cortisol should fall. If the excess ACTH is being produced by a non-pituitary tumor, this suppression is much less likely.

Scintigraphy – Scintigraphy, injection of a radiolabeled marker followed by a scan, is helpful for locating elusive tumors that cause the ectopic ACTH syndrome.

Petrosal sinus sampling – Blood draining from the pituitary gland collects in vascular spaces called sinuses; sampling of blood from these sinuses may reveal high levels of ACTH. This is accomplished by inserting catheters into a vein in the groin. Local anesthesia and mild sedation are used, and x-rays are done to make sure that the catheter is in the proper place near the pituitary gland.

Levels of ACTH in blood from the petrosal sinuses are measured and compared with ACTH levels in a forearm vein. ACTH levels higher in the petrosal sinuses than

in the forearm vein indicate the presence of a pituitary adenoma; similar levels at both locations suggest ACTH secretion by a non-pituitary tumor causing the ectopic ACTH syndrome.

TREATMENT OF CUSHING'S SYNDROME – The treatment of Cushing's syndrome is tailored to the underlying cause. Treatment can reverse most of the symptoms of Cushing's syndrome, but must be undertaken carefully to minimize the possibility of permanent hormone deficiency and treatment side effects. Be sure to discuss all of the pros and cons of treatment with your doctor before starting any treatment.

Treatment for medication-associated Cushing's syndrome – When Cushing's syndrome is caused by taking glucocorticoids for other medical conditions, discontinuing the treatment effectively resolves a person's symptoms. However, in most cases, the body has adapted to the presence of these medications, and they must therefore be tapered off gradually, so that the pituitary and adrenal glands can resume normal function. Furthermore, some conditions require prolonged glucocorticoid therapy, and it cannot be discontinued. It is therefore important not to discontinue treatment without consulting your doctor, and to ask about options if you have a condition that requires these medications long-term.

Treatment of Cushing's disease – When Cushing's syndrome results from an ACTH-producing tumor of the pituitary gland (Cushing's disease), treatment may include surgery, radiation, and medication to lower cortisol levels.

Surgery – Surgical removal of a small, well-defined pituitary adenoma is called transsphenoidal adenomectomy. Using special instruments, the surgeon reaches the pituitary gland via an incision in the gum above the upper front teeth or via the nose. Sometimes a tumor cannot be identified; in these cases, half of the pituitary gland may be removed (hemihypophysectomy) or 85 to 90 percent of the pituitary gland may be removed (subtotal hypophysectomy) to be certain that the tumor has been removed. Surgical removal of half or more of the pituitary gland can impair pituitary function, necessitating lifelong hormone replacement, and interfere with fertility, so be sure to discuss all of the benefits and risks with your doctor before selecting this option. These types of surgery permanently cure Cushing's syndrome in 60 to 70 percent of people.

Radiation – Radiation can be a useful treatment when pituitary tumors cannot be completely removed by surgery. Radiation of pituitary tumors reduces cortisol levels in about half of adults and most children with Cushing's disease. Because this cortisol-lowering effect takes time (3 to 12 months), doctors often prescribe medications that lower adrenal cortisol production while waiting for the effects of radiation to occur. These medications include ketoconazole, **metyrapone**, and aminoglutethimide (see below).

Adrenalectomy – Surgical removal of the adrenal glands (adrenalectomy) is a final measure for halting excess cortisol production. This is used only when all other measures fail in individuals with pituitary tumors.

Treatment of ectopic ACTH syndrome – In about 10 percent of people, ACTH-producing, non-pituitary tumors can be surgically removed, with resolution of the symptoms of Cushing's syndrome. These tumors are usually in the lung. When complete surgical removal is not possible, treatment with medications that reduce

adrenal cortisol production (ketoconazole, metyrapone, and aminoglutethimide) and surgical removal of the adrenal glands (adrenalectomy) may be necessary to lower cortisol levels.

Treatment of adrenal gland tumors – Adrenal tumors are usually treated by surgical removal of the affected adrenal gland, leaving the opposite adrenal gland for cortisol production. If the tumor is an adenoma (a benign tumor), surgery always cures the associated Cushing's syndrome. If the tumor is a carcinoma (a malignant tumor), radiation, chemotherapy, and treatment with mitotane (a medication that is toxic to cortisol-producing cells) are usually required to lower cortisol levels. After these treatments, daily adrenal hormone replacement is usually necessary. The prognosis of adrenal carcinoma is quite poor.

Treatment of nodular adrenal hyperplasia – Treatment of nodular adrenal hyperplasia usually requires surgical removal of both adrenal glands. Before surgery, medications that inhibit adrenal enzymes (ketoconazole, **metyrapone**, or aminoglutethimide) can lower cortisol levels.

Treatment of Cushing's syndrome during pregnancy – Cushing's syndrome is rare during pregnancy. The excess cortisol production is usually caused by an adrenal tumor, most often an adenoma (a benign tumor), but some patients have a pituitary tumor (Cushing's disease).

Although most of the excess cortisol doesn't cross the placenta and affect the fetus, untreated Cushing's syndrome poses a risk to pregnant women because it can lead to maternal complications such as hypertension and gestational diabetes, and it is associated with spontaneous abortion and premature delivery.

When Cushing's syndrome is caused by an adrenal tumor or a benign pituitary tumor (Cushing's disease), surgical removal of the adrenal or pituitary gland can lower the abnormal cortisol levels without affecting the pregnancy.

EFFECTIVENESS OF TREATMENT – If treatment removes the source of excess cortisol, most of the symptoms of Cushing's syndrome disappear over 2 to 12 months. Osteoporosis begins to improve within six months and continues to improve over several years. Some hypertension and glucose intolerance may persist. And although psychiatric symptoms usually improve, some conditions may linger even after cortisol levels have been lowered. With successful treatment, children with Cushing's syndrome regain much of their lost bone density and growth.

PROGNOSIS – Today, virtually all people with Cushing's syndrome can be treated effectively, and most can be cured. Because Cushing's syndrome is potentially fatal if untreated, people with this condition should have regular medical care and should follow their treatment plan closely.

WHERE TO GET MORE INFORMATION – Your doctor is the best resource for finding out important information related to your particular case. Not all patients with Cushing's syndrome are alike, and it is important that your situation is evaluated by someone who knows you as a whole person.

This discussion will be updated as needed every four months on our web site (www.uptodate.com). Additional topics as well as selected discussions written for

health care professionals are also available for those who would like more detailed information.

A number of other sites on the internet have information about Cushing's syndrome. Information provided by the National Institutes of Health, national medical societies, and some other well-established organizations are often reliable sources of information, although the frequency with which their information is updated is variable.

- National Library of Medicine
(<http://www.nlm.nih.gov/medlineplus>)
- The Hormone Foundation
(<http://www.hormone.org>)
- National Adrenal Diseases Foundation
(NADF, (516)487-4992)
(<http://www.medhelp.org/nadf/>)
- Pituitary Tumor Network Association
(<http://www.pituitary.com>)
- Cushing's Support & Research Foundation
(617) 723-3674
csrf@world.std.com
(<http://world.std.com/~CSRF/>)

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