PATIENT RESOURCES

Cushing's Syndrome and Cushing Disease

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Cushing syndrome (also sometimes called Cushing's syndrome) is a disorder with physical and mental changes that result from having too much cortisol in the blood for a long period of time. There are two types of Cushing syndrome:

exogenous (caused by factors outside the body) and endogenous (caused by factors within the body). The symptoms for both are the same. The only difference is the causes.

Cushing disease is a rare condition, only affecting 10 to 15 people per million every year. It is more common in women and occurs most often in people between the ages of 20 and 50.

A pituitary adenoma is the most common cause of Cushing disease. An adenoma is a **pituitary tumor** that is almost always benign. The tumors can be hard to diagnose because they are quite small. Having an endocrinologist help with the diagnostic process can improve the chances of a prompt, successful diagnosis for patients who have symptoms of Cushing disease.

Endocrine Connection

Cortisol is a hormone produced by the adrenal glands that is directly connected to the body's stress response. Most cells within the body have cortisol receptors. Secretion of the hormone is controlled by the hypothalamus, the pituitary gland, and the adrenal gland, a combination gland often referred to as the HPA axis. In a healthy individual, it releases adrenocorticotropic hormone (ACTH), a hormone produced in the pituitary gland, and stimulates the production and release of cortisol by the adrenal glands. In normal amounts, cortisol helps the body:

- Manage blood sugar levels
- Regulate metabolism
- Reduce inflammation
- Assist with memory formulation
- Maintain blood pressure and cardiovascular function

- Develop the fetus during pregnancy (in women)
- Balance salt and water intake
- Convert fat, carbohydrates, and proteins into energy

When an individual faces a stressful situation, the body releases more cortisol. Sometimes the body is not able to properly regulate the production of cortisol and too much cortisol is produced. When too much cortisol is produced, it contributes to the development of Cushing syndrome.

Low cortisol levels can cause a condition known as primary adrenal insufficiency or Addison disease. While rare, primary adrenal insufficiency is an autoimmune disease that causes damage to the adrenal glands. Symptoms may start slowly, but they can be quite serious.

Exogenous Cushing Syndrome: The most common cause of exogenous Cushing syndrome is due to people taking cortisol-like medications such as prednisone. These drugs are used to treat inflammatory disorders such as asthma and rheumatoid arthritis. They also suppress the immune system after an organ transplant. This type of Cushing syndrome is temporary and goes away after the patient has finished taking the cortisol-like medications.

Endogenous Cushing Syndrome: Endogenous Cushing syndrome, in which the adrenal glands produce too much cortisol, is uncommon. It usually comes on slowly and can be difficult to diagnose. This type of Cushing syndrome is most often caused by hormone-secreting tumors of the adrenal glands or the pituitary, a gland located at the base of the brain. In the adrenal glands, the tumor (usually non-cancerous) produces too much cortisol. Most tumors that produce ACTH originate in the pituitary gland but sometimes non-pituitary tumors, usually i e lungs, can also produce too much ACTH and cause ectopic Cushing syndrome.

Cushing Disease: Cushing disease is a form of Cushing syndrome. Cushing disease occurs when a benign tumor in the pituitary gland causes the pituitary gland to produce too much ACTH, the hormone responsible for cortisol production. Too much ACTH in the body causes the adrenal glands to produce cortisol in high levels. Cushing disease can also occur with diffuse growth of the pituitary gland, also called pituitary hyperplasia. Pituitary hyperplasia can lead to the release of too much ACTH, which then leads to over-production of cortisol by the adrenal glands.

▸ Diagnosis and Prevention

Three tests are commonly used to diagnose Cushing syndrome and Cushing Disease. Diagnosing Cushing disease can be difficult because the symptoms can have many different causes and the elevated cortisol levels can happen in cycles. As a result, cortisol levels may not be elevated at the time of testing. These tests include:

Saliva Test: One of the most sensitive tests measures cortisol levels in the saliva between 11:00 p.m. and midnight. A sample of saliva is collected in a small plastic container and sent to the laboratory for analysis. In healthy people, cortisol levels are very low during this period of time. In contrast, people with Cushing's syndrome/Cushing Disease have high levels.

Urine Test: Cortisol levels can also be measured in urine that has been collected over a 24-hour period.

Steroid Test: In another screening test, people with suspected Cushing

syndrome have their cortisol levels measured the morning after taking a late-night dose of dexamethasone, a laboratory-made steroid. Normally, dexamethasone causes cortisol to drop to a very low level, but in people with Cushing's syndrome/Cushing Disease, this doesn't happen.

If these tests show high cortisol levels, the doctor will then measure the ACTH level in the blood. In Cushing disease, the cortisol levels are high, and the ACTH levels are normal or high. If these results are seen, the doctor will schedule MRI of the pituitary gland to pinpoint the location of any tumors.

▸ **Symptoms and Risk Factors**

Cushing Syndrome

Symptoms of Cushing's Syndrome include:

- Weight gain, especially in the upper body
- Rounded face and extra fat on the upper back and above the collarbones
- High blood sugar (**diabetes**)
- High blood pressure (**hypertension**)
- Thin bones (**osteoporosis**)
- Muscle loss and weakness
- Thin, fragile skin that bruises easily
- Purple-red stretch marks (usually over the abdomen and under the arms)
- Depression and difficulties thinking clearly
- Too much facial hair in women

Cushing Disease

Cushing disease has many symptoms including changes in appearance, mood and thinking, and more.

Changes in appearance:

- Wide, purple stretch marks on the skin (chest, armpits, abdomen, flanks)
- Rapid and unexplained weight gain with a rounder face and abdomen
- Increased fat in the neck and above the collarbone and upper back
- Skin changes (bruising without injury, acne, hair growth) and red cheeks

Mood and thinking:

- Memory loss or not being able to think clearly
- Depression
- Mood and behavior disorders

Other symptoms:

- Fatigue
- Muscle weakness
- Menstrual cycle disorders
- Osteoporosis
- High blood glucose (diabetes)
- High blood pressure
- Blood clots in leg veins
- Heart attack
- Stroke
- Fracture

▸ **Treatment and Therapies**

Cushing Syndrome

The treatment for Cushing's syndrome depends on the cause.

Exogenous Cushing's Syndrome: This goes away after a patient stops taking the cortisol-like medications they were using to treat another condition. Your doctor will determine when it is appropriate for you to slowly decrease and eventually stop using the steroid medication. These medications need to be stopped gradually.

Endogenous Cushing's Syndrome: The initial approach is almost always surgery to remove the tumor that is causing high cortisol levels. Although surgery is usually successful, some people may also need medications that lower cortisol or radiation therapy to destroy remaining tumor cells. Some people must have both adrenal glands removed to control Cushing syndrome.

Cushing Disease

The first choice of therapy for Cushing disease is surgical removal of the tumor. Cure rates with an experienced pituitary surgeon are about 90% in people with small tumors. A patient will typically have transsphenoidal microsurgery through the nasal sinuses.

People who are not cured with one surgery, may need to have repeat surgery. When surgery does not work, radiation therapy may treat any remaining tumor cells. The radiation takes some time to have its full effect. Several medications to block the adrenal glands from producing cortisol

(such as ketoconazole, metyrapone or mitotane and more recently approved osilodrostat) can be used while waiting for radiation to have an effect.

In some cases, a type of drug called a dopamine agonist, such as cabergoline, can reduce ACTH levels and cortisol production. Pasireotide (given by injection under the skin) can also reduce ACTH levels and cortisol production. Mifepristone, a glucocorticoid agonist, is another medication that stops cortisol from working on the body. Rarely, the adrenal glands are removed surgically to stop cortisol overproduction.

▸ Questions for Your Healthcare Provider

- What underlying conditions could be affecting my cortisol levels?
- How can I manage cortisol levels to regain my health?
- What testing is needed to determine the cause of my symptoms?
- Which type of Cushing syndrome do I have?
- What should I do if my Cushing syndrome is caused by my medication?
- Will I need medicines to treat any of my symptoms?
- After treatment, how long will it take for my symptoms to go away?
- Should I see any additional specialists for my care?

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