

Cushing's Syndrome

HORMONAL HAVOC

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Nicholas A. Tritos, MD, ScD

Most weight gain is no mystery—the result of too much food and too little exercise. But that was hardly the case with 69-year-old Fedela Vincent, who put on about 80 pounds in just a few years, despite eating a healthy, low-calorie diet and working out regularly at the gym.

The 5-foot-tall, attractive blonde found her body changing to the point that she barely recognized herself. Her face grew puffy, a hump developed on her back, and her bustline became so large that she could no longer fold her arms over her chest. An itchy rash spread over her body, and her hair began to fall out.

Her doctor accused her of nighttime snacking and prescribed more exercise. But she progressively weakened until she could barely walk.

Insomnia, mood swings and anxiety attacks plagued her. When Bob, her husband of 48 years, brought her coffee in the morning, he never knew if she would be “sweet or a tyrant.” Nevertheless, he was a devoted caregiver.

After visits to half a dozen doctors and nutritionists, Vincent was finally referred to Lahey Clinic’s Nicholas Tritos, MD, ScD, an endocrinologist with expertise in pituitary problems. After a battery of tests, he determined Vincent had Cushing’s syndrome, a relatively rare hormonal disorder. “When he told me, I was just so relieved,” Vincent says. “I had started to think I was going crazy.”

Cushing’s syndrome can result from either the body’s overproduction of the hormone cortisol or prolonged use of high-dose corticosteroid medications, which mimic cortisol’s effect. (Corticosteroids, such as prednisone, are used to treat inflammatory diseases like rheumatoid arthritis and asthma, prevent organ transplant rejection, and relieve bursitis and back pain. They should not be confused with anabolic steroids, the muscle-building drugs.)

Cortisol is made by the adrenal glands, located on top of each kidney. It acts as a chemical signal to other parts of the body. “Cortisol is a hormone essential to life,” says Tritos. “It helps the body respond to both physical and emotional stress as well as regulate the conversion of food into energy and control blood pressure.”

Overproduction of cortisol can arouse a constant “fight or flight” response. And it can damage blood vessels and eventually lead to a heart attack.

Cushing’s syndrome, named after pioneering neurosurgeon Harvey Cushing (a distant cousin of Gary Cushing, MD, chair of Lahey’s Department of Endocrinology), affects an estimated 10 to 15 people out of a million in the United States. While it occurs most frequently in women aged 40 to 50, Cushing’s can affect either sex at any age, including infancy.

A Difficult Diagnosis

When Cushing's syndrome is caused by overproduction of cortisol in the body (referred to as endogenous), it is much less obvious than when it is related to corticosteroid medications. The condition often goes unnoticed because weight gain—typically the primary symptom—is so common, and not all care providers are sensitized to Cushing's syndrome.

Classic symptoms of Cushing's are a moon face, weight gain in the torso but not the arms or legs, and purplish stretch marks on the stomach. "But presentation can vary tremendously," says Tritos. "Some patients can be thin and have Cushing's. Symptoms may also include unexplained osteoporosis and bone fractures, especially in a young person, and women may have a lack of menstrual periods or excessive hair growth on the face. Some studies suggest 2 to 3 percent of people with poorly controlled type 2 diabetes may actually have Cushing's syndrome."

Even when Cushing's is suspected, ferreting out the source of excessive cortisol can be difficult. Making cortisol is a multistep process, and any faulty parts in the production line can affect the end product.

Normally, the hypothalamus, the body's command center located in the brain, sends corticotropin-releasing hormone (CRH) to the nearby pituitary gland. CRH then triggers the pea-sized pituitary to secrete the hormone adrenocorticotropin (ACTH), which travels through the bloodstream to the adrenal glands. ACTH, in turn, prompts the adrenals to release cortisol. And, in what's called a feedback loop, cortisol goes back to the brain and inhibits the further release of CRH and ACTH.

Cortisol overproduction can result from the following conditions:

Pituitary tumors—In this form of the syndrome, known as Cushing's disease, a pituitary tumor (almost always benign, or noncancerous) makes too much ACTH, which stimulates the adrenals to make too much cortisol. Pituitary tumors account for about 70 percent of cases of endogenous Cushing's.

Ectopic ACTH production—Benign or malignant (cancerous) tumors located elsewhere in the body, most commonly the lungs, may produce ACTH on their own, without the control of the pituitary. About 15 percent of Cushing's syndrome is attributable to ectopic tumors.

Adrenal tumors—Benign growths called adrenal adenomas can also secrete excess cortisol. Rapid development of Cushing's symptoms may be due to rare adrenal cancers.

A Battery of Tests

In addition to symptoms and medical history, laboratory testing provides important information for a diagnosis of Cushing's syndrome. An easy and inexpensive way to test for elevated cortisol levels is with a saliva sample, which the patient collects at home late at night. "Normally, cortisol is made mostly in the early morning hours to prepare our bodies for the day ahead," explains Tritos. "The level gradually declines throughout the day, so that it's lowest at night. But people with Cushing's syndrome always have more or less the same level."

Other ways to assess cortisol levels include 24-hour urine collection and a dexamethasone suppression test, which measures cortisol after the patient takes a synthetic steroid that normally suppresses cortisol production.

The next step is to determine the origin of the excessive cortisol by checking ACTH in the blood. Low ACTH levels mean the surplus cortisol results from an



Fedela Vincent and her husband, Bob.
Photo by Rich Beauchesne/Portsmouth Herald.



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adrenal tumor, while higher levels indicate either a pituitary or ectopic tumor.

CT or MRI scans may follow to examine the tumor directly. "Imaging can be counterproductive if done first," says Tritos. "It can confuse the diagnosis, because healthy people without Cushing's can have benign pituitary or adrenal tumors that are inactive [do not secrete hormones]." And he points out, "Only about 50 percent of pituitary tumors, which can be as small as 1 or 2 millimeters, can be seen on MRI. That leaves us with the dilemma: Is the tumor really in the pituitary but too small to see, or somewhere else in the body like the chest or abdomen?"

To pinpoint the location of the tumor, a neuroradiologist can perform an inferior petrosal sinus sampling, an outpatient procedure that compares blood samples taken from the pituitary gland and from the arm. A pituitary tumor will produce more than two to three times the amount of ACTH normally found in the blood taken from an arm vein.

Curing Cushing's

Treatment depends on the cause of the excess cortisol and may include surgery, radiation therapy, or cortisol-inhibiting medications. If corticosteroid medications are to blame for Cushing's, gradually decreasing drug dosage may minimize adverse effects, while still controlling the condition being treated.

For tumors that are not widespread, surgery is the treatment of choice. "Surgery has the fastest and most reliable results," says Tritos. "If a tumor can be found and removed safely, it can lead to a cure."

Lahey surgeons remove pituitary tumors through the nose, using an endoscope or fiber-optic tube equipped with a miniature camera and tiny surgical tools. The endoscopic approach relies on the natural passageway from the back of the nose into the sinus just below the bony cavity where the pituitary sits. Unlike traditional craniotomies, this method avoids drilling into the skull, making it safer and eliminating scarring. Throughout the operation, the neurosurgeon uses a monitor for guidance around the optic nerve and other delicate brain structures.

"Surgery takes about an hour," says neurosurgeon Carlos A. David, MD. "The patient experiences very little pain and is usually ready to go home in two or three days."

Surgical removal of pituitary tumors is successful in about 85 percent of patients with Cushing's disease. To treat the rest, doctors may use radiation therapy, cortisol-inhibiting medications, or, least commonly, remove both adrenal glands. Novel medications hold promise for the future but are still under development.

The Ordeal's End

Tests proved that Fedela Vincent did indeed have Cushing's syndrome and that her condition stemmed from too much ACTH. But its origin was unclear, since MRI images of the pituitary failed to show a tumor. However, petrosal sinus sampling later indicated the gland was the source.

On Mother's Day 2006, during a record-breaking rainstorm, Vincent finally underwent surgery and had 50 percent of one side of the pituitary and 25 percent of the other removed. Although total recovery can take months, she began to feel better immediately after the operation. And fortunately, what's left of her pituitary started to function normally again after several weeks, allowing her to lose about 30 of the pounds she gained.

Vincent is grateful for support from her friends and family, and all the care she's received at Lahey. "From the first time I walked into Lahey Clinic and every time since, everyone has been so wonderful," says Vincent. "The doctors and nurses treat me like a person, not just a patient."

As a result of her experience, she now acts as an advocate for others struggling with Cushing's syndrome and encourages them to contact the Cushing's Support & Research Foundation (www.csrfs.net) or Pituitary Network Association (www.pituitary.org) for help and information.

To make an appointment with an endocrinologist at Lahey, call 781-744-3250.

