Daniel F. Kelly, M.D., Director of the Neuro-Endocrine Tumor Center at the John Wayne Cancer Institute and Saint John's Health Center in Santa Monica, California.

Adenoma sub-type 2: Cushing's disease

Cushing's disease is caused by an ACTH-secreting adenoma. This serious endocrinopathy is a subset of Cushing's syndrome which refers to elevated blood cortisol levels. Cushing's syndrome may arise from tumors of the pituitary, adrenal glands or from tumors arising elsewhere in the body (ectopic ACTH producing tumors). The cause of Cushing's syndrome is a pituitary adenoma in over 70% of patients. Most ACTH-secreting adenomas are microadenomas. Cushing's disease is relatively uncommon, affecting 10 to 15 of every million people each year, and most commonly affects adults aged 20 to 50 years; women account for over 70% of cases. Given that Cushing's disease causes so many common problems affecting the general population such as obesity, hypertension and diabetes, it is possible that many patients with Cushing's disease are undiagnosed for years or perhaps never diagnosed.

Symptoms

Body changes including weight gain in the face (moon face), above the collar bone (supraclavicular) and on back of neck (buffalo hump) are commonly seen in patients with Cushing's disease. Skin changes may include easy bruising, with purplish stretch marks (stria) and red cheeks (plethora) as well as excess hair growth (hirsutism) on the face and body. The high cortisol levels also cause weakness, fatigue and muscle wasting. Women may develop menstrual disorders including amenorrhea (absence of menses) and decreased libido. Additional serious consequences may include hypertension, diabetes mellitus and depression.

Diagnosis

Patients are often diagnosed with Cushing's disease after several years of symptoms which might include progressive weight gain, new onset hypertension or diabetes and mood changes. Comparison of old and recent photographs will often demonstrate changes in appearance. Unfortunately, the diagnosis of Cushing's disease is often long delayed and can be difficult to make. An endocrinologist should always supervise the evaluation for Cushing's disease.

Hormonal diagnosis*:* The first step in diagnosing Cushing's disease is to confirm the presence of excessive cortisol secretion. This diagnosis is most easily made by performing a low-dose dexamethasone suppression test, a 24-hour urinary free cortisol collection, and/or a midnight serum cortisol level or a midnight salivary cortisol test. Once the diagnosis of Cushing's syndrome is established, the source of the excess cortisol should be determined: either from an adrenal gland tumor, an ectopic ACTH-producing tumor, or a pituitary ACTH-producing adenoma. Serum ACTH levels and a high-dose dexamethasone suppression test are typically used for this determination. Petrosal Sinus Sampling is an angiographic and edocrinological test used to distinguish between ectopic ACTH production and pituitary ACTH production (Cushing's disease). Petrosal sinus sampling should never be performed before the diagnosis of ACTH-dependent Cushing's syndrome is established.

Imaging: Once the diagnosis of Cushing's syndrome is confirmed hormonally, a pituitary MRI can detect the presence of an adenoma in approximately 70% of cases. Dynamic post-gadolinium coronal MRI is a recent technique that helps diagnose small adenomas that may not be seen on a conventional pituitary MRI. CT scans of the adrenal glands are very useful for determining the presence or absence of an adrenal tumor causing Cushing's syndrome.

Treatment

Transsphenoidal Surgery*:* The only way to achieve long term remission of Cushing's disease is by transsphenoidal removal of the adenoma. Long-term remission or "cure rates" range from 80-90% for microadenomas and from 30-70% for macroadenomas and invasive adenomas.

Medical therapy: In patients who fail to have remission of their Cushing's disease or syndrome state after surgery, there are several medications that can lower cortisol levels. These include "adrenal-directed" medications ketoconazole and aminoglutethimide which inhibit steroid (cortisol) production in the adrenal glands. They are initially effective but have some side effects, and the overall long-term control of Cushing's disease with these drugs is rather poor.

Radiosurgery (SRT) or Stereotactic Radiotherapy (SRS): For patients whose Cushing's disease is not controlled with surgery, SRT (multiple doses) and SRS (one dose), which provide precise doses of radiation directly to the tumor, are effective in controlling cortisol levels and tumor growth in 50 – 70% of patients. However, the lowering of cortisol levels generally takes significantly longer with SRT compared to SRS. Also, SRT and SRS may result in loss of normal pituitary function over 5 to 10 years. Neurologic complications such as visual loss and temporal lobe damage rarely occur with SRT and SRS.