Australian Addison's Disease Association

What is Addison's?

Addison's disease is a rare endocrine, or hormonal disorder that affects about 1 in 100,000 people. It occurs in all age groups and afflicts men and women equally. The disease is characterized by weight loss, muscle weakness, fatigue, low blood pressure, and sometimes darkening of the skin in both exposed and nonexposed parts of the body.

Addison's disease occurs when the adrenal glands do not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. For this reason, the disease is sometimes called **chronic adrenal insufficiency**, or hypocortisolism.

Cortisol is normally produced by the adrenal glands, located just above the kidneys. It belongs to a class of hormones called glucocorticoids, which affect almost every organ and tissue in the body. Scientists think that cortisol has possibly hundreds of effects in the body. Cortisol's most important job is to help the body respond to stress. Among its other vital tasks, cortisol:

- helps maintain blood pressure and cardiovascular function;
- helps slow the immune system's inflammatory response;
- helps balance the effects of insulin in breaking down sugar for energy; and
- helps regulate the metabolism of proteins, carbohydrates, and fats

Because cortisol is so vital to health, the amount of cortisol produced by the adrenals is precisely balanced. Like many other hormones, cortisol is regulated by the brain's hypothalamus and the pituitary gland, a bean-sized organ at the base of the brain. First, the hypothalamus sends "releasing hormones" to the pituitary gland. The pituitary responds by secreting other hormones that regulate growth, thyroid and adrenal function, and sex hormones such as estrogen and testosterone. One of the pituitary's main functions is to secrete ACTH (adrenocorticotropin), a hormone that stimulates the adrenal glands. When the adrenals receive the pituitary's signal in the form of ACTH, they respond by producing cortisol. Completing the cycle, cortisol then signals the pituitary to lower secretion of ACTH.

Aldosterone belongs to a class of hormones called mineralocorticoids, also produced by the adrenal glands. It helps maintain blood pressure and water and salt balance in the body by helping the kidney retain sodium and excrete potassium. When aldosterone production falls too low, the kidneys are not able to regulate salt and water balance, causing blood volume and blood pressure to drop.

Causes

Failure to produce adequate levels of cortisol, or adrenal insufficiency, can occur for different reasons. The problem may be due to a disorder of the adrenal glands themselves (primary adrenal insufficiency) or to inadequate secretion of ACTH by the pituitary gland (secondary adrenal insufficiency).

Primary Adrenal Insufficiency

Most cases of Addison's disease are caused by the gradual destruction of the adrenal cortex, the outer layer of the adrenal glands, by the body's own immune system. About 70 percent of reported cases of Addison's disease are due to autoimmune disorders, in which the immune system makes antibodies that attack the body's own tissues or organs and slowly destroy them. Adrenal insufficiency occurs when at least 90 percent of the adrenal cortex has been destroyed. As a result, often both glucocorticoid and mineralocorticoid hormones are lacking. Sometimes only the adrenal gland is affected, as in idiopathic adrenal insufficiency; sometimes other glands also are affected, as in the polyendocrine deficiency syndrome.

The polyendocrine deficiency syndrome is classified into two separate forms, referred to as type I and type II. Type I occurs in children, and adrenal insufficiency may be accompanied by underactive parathyroid glands, slow sexual development, pernicious anemia, chronic candida infections, chronic active hepatitis, and, in very rare cases, hair loss. Type II, often called Schmidt's syndrome, usually afflicts young adults. Features of type II may include an underactive thyroid gland, slow sexual development, and diabetes mellitus. About 10 percent of patients with type II have vitiligo, or loss of pigment, on areas of the skin. Scientists think that the polyendocrine deficiency syndrome is inherited because frequently more than one family member tends to have one or more endocrine deficiencies.

Tuberculosis (TB) accounts for about 20 percent of cases of primary adrenal insufficiency in developed countries. When adrenal insufficiency was first identified by Dr. Thomas Addison in 1849, TB was found at autopsy in 70 to 90 percent of cases. As the treatment for TB improved, however, the incidence of adrenal insufficiency due to TB of the adrenal glands has greatly decreased.

Less common causes of primary adrenal insufficiency are chronic infections, mainly fungal infections; cancer cells spreading from other parts of the body to the adrenal glands; amyloidosis; and surgical removal of the adrenal glands. Each of these causes is discussed in more detail below.

Secondary Adrenal Insufficiency

This form of Addison's disease can be traced to a lack of ACTH, which causes a drop in the adrenal glands' production of cortisol but not aldosterone. A temporary form of secondary adrenal insufficiency may occur when a person who has been receiving a glucocorticoid hormone such as prednisone for a long time abruptly stops or interrupts taking the medication. Glucocorticoid hormones, which are often used to treat inflammatory illnesses like rheumatoid arthritis, asthma, or ulcerative colitis, block the release of both corticotropin-releasing hormone (CRH) and ACTH. Normally, CRH instructs the pituitary gland to release ACTH. If CRH levels drop, the pituitary is not stimulated to release ACTH, and the adrenals then fail to secrete sufficient levels of cortisol.

Another cause of secondary adrenal insufficiency is the surgical removal of benign, or noncancerous, ACTH-producing tumors of the pituitary gland (Cushing's disease). In this case, the source of ACTH is suddenly removed, and replacement hormone must be taken until normal ACTH and cortisol production resumes. Less commonly, adrenal insufficiency occurs when the pituitary gland either decreases in size or stops producing ACTH. This can result from tumors or infections of the area, loss of blood flow to the pituitary, radiation for the treatment of pituitary tumors, or surgical removal of parts of the hypothalamus or the pituitary gland during neurosurgery of these areas.

Symptoms

The symptoms of adrenal insufficiency usually begin gradually. Chronic, worsening fatigue and muscle weakness, loss of appetite, and weight loss are characteristic of the disease. Nausea, vomiting, and diarrhea occur in about 50 percent of cases. Blood pressure is low and falls further when standing, causing dizziness or fainting. Skin changes also are common

in Addison's disease, with areas of hyperpigmentation, or dark tanning, covering exposed and nonexposed parts of the body. This darkening of the skin is most visible on scars; skin folds; pressure points such as the elbows, knees, knuckles, and toes; lips; and mucous membranes.

Addison's disease can cause irritability and depression. Because of salt loss, craving of salty foods also is common. Hypoglycemia, or low blood sugar, is more severe in children than in adults. In women, menstrual periods may become irregular or stop.

Because the symptoms progress slowly, they are usually ignored until a stressful event like an illness or an accident causes them to become worse. This is called an addisonian crisis, or acute adrenal insufficiency. In most patients, symptoms are severe enough to seek medical treatment before a crisis occurs. However, in about 25 percent of patients, symptoms first appear during an addisonian crisis.

Symptoms of an addisonian crisis include sudden penetrating pain in the lower back, abdomen, or legs; severe vomiting and diarrhea, followed by dehydration; low blood pressure; and loss of consciousness. Left untreated, an addisonian crisis can be fatal.

Diagnosis

In its early stages, adrenal insufficiency can be difficult to diagnose. A review of a patient's medical history based on the symptoms, especially the dark tanning of the skin, will lead a doctor to suspect Addison's disease.

A diagnosis of Addison's disease is made by biochemical laboratory tests. The aim of these tests is first to determine whether there are insufficient levels of cortisol and then to establish the cause. X-ray exams of the adrenal and pituitary glands also are useful in helping to establish the cause.

ACTH Stimulation Test

This is the most specific test for diagnosing Addison's disease. In this test, blood and/or urine cortisol levels are measured before and after a synthetic form of ACTH is given by injection. In the so called short, or rapid, ACTH test, cortisol measurement in blood is repeated 30 to 60 minutes after an intravenous ACTH injection. The normal response after an injection of ACTH is a rise in blood and urine cortisol levels. Patients with either form of adrenal insufficiency respond poorly or do not respond at all.

When the response to the short ACTH test is abnormal, a "long" ACTH stimulation test is required to determine the cause of adrenal insufficiency. In this test, synthetic ACTH is injected either intravenously or intramuscularly over a 48- to 72-hour period, and blood and/or urine cortisol are measured the day before and during the 2 to 3 days of the injection. Patients with primary adrenal insufficiency do not produce cortisol during the 48- to 72-hour period; however, patients with secondary adrenal insufficiency have adequate responses to the test on the second or third day.

In patients suspected of having an addisonian crisis, the doctor must begin treatment with injections of salt, fluids, and glucocorticoid hormones immediately. Although a reliable diagnosis is not possible while the patient is being treated, measurement of blood ACTH and cortisol during the crisis and before glucocorticoids are given is sufficient to make the diagnosis. Once the crisis is controlled and medication has been stopped, the doctor will delay further testing for up to 1 month to obtain an accurate diagnosis.

Insulin-Induced Hypoglycemia Test

A reliable test to determine how the hypothalamus and pituitary and adrenal glands respond to stress is the insulin-induced hypoglycemia test. In this test, blood is drawn to measure the blood glucose and cortisol levels, followed by an injection of fast-acting insulin. Blood glucose and cortisol levels are measured again at 30, 45, and 90 minutes after the insulin injection. The normal response is for blood glucose levels to fall and cortisol levels to rise.

Other Tests

Once a diagnosis of primary adrenal insufficiency has been made, x-ray exams of the abdomen may be taken to see if the adrenals have any signs of calcium deposits. Calcium deposits may indicate TB. A tuberculin skin test also may be used.

If secondary adrenal insufficiency is the cause, doctors may use different imaging tools to reveal the size and shape of the pituitary gland. The most common is the CT scan, which produces a series of x-ray pictures giving a cross-sectional image of a body part. The function of the pituitary and its ability to produce other hormones also are tested.

Treatment

Treatment of Addison's disease involves replacing, or substituting, the hormones that the adrenal glands are not making. Cortisol is replaced orally with hydrocortisone tablets, a synthetic glucocorticoid, taken once or twice a day. If aldosterone is also deficient, it is replaced with oral doses of a mineralocorticoid, called fludrocortisone acetate (Florinef)), which is taken once a day. Patients receiving aldosterone replacement therapy are usually advised by a doctor to increase their salt intake. Because patients with secondary adrenal insufficiency normally maintain aldosterone production, they do not require aldosterone replacement therapy. The doses of each of these medications are adjusted to meet the needs of individual patients.

During an addisonian crisis, low blood pressure, low blood sugar, and high levels of potassium can be life threatening. Standard therapy involves intravenous injections of hydrocortisone, saline (salt water), and dextrose (sugar). This treatment usually brings rapid improvement. When the patient can take fluids and medications by mouth, the amount of hydrocortisone is decreased until a maintenance dose is achieved. If aldosterone is deficient, maintenance therapy also includes oral doses of fludrocortisone acetate.

Special Problems

Surgery

Patients with chronic adrenal insufficiency who need surgery with general anesthesia are treated with injections of hydrocortisone and saline. Injections begin on the evening before surgery and continue until the patient is fully awake and able to take medication by mouth. The dosage is adjusted until the maintenance dosage given before surgery is reached.

Pregnancy

Women with primary adrenal insufficiency who become pregnant are treated with standard replacement therapy. If nausea and vomiting in early pregnancy interfere with oral medication, injections of the hormone may be necessary. During delivery, treatment is similar to that of patients needing surgery; following delivery, the dose is gradually tapered and the usual maintenance doses of hydrocortisone and fludrocortisone acetate by mouth are not reached until about 10 days after childbirth.

Patient Education

A person who has adrenal insufficiency should always carry identification stating his or her condition in case of an emergency. The card should alert emergency personnel about the need to inject 100 mg of cortisol if its bearer is found severely injured or unable to answer questions. The card should also include the doctor's name and telephone number and the name and telephone number of the nearest relative to be notified. When traveling, it is important to have a needle, syringe, and an injectable form of cortisol for emergencies. A person with Addison's disease also should know how to increase medication during periods of stress or mild upper respiratory infections. Immediate medical attention is needed when severe infections or vomiting or diarrhea occur. These conditions can precipitate an addisonian crisis. A patient who is vomiting may require injections of hydrocortisone.

It is very helpful for persons with medical problems to wear a descriptive warning bracelet or neck chain to alert emergency personnel.