ADRENAL INSUFFICIENCY

Acquired and Autoimmune Adrenal Failure

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This article describes the causes, symptoms, signs and changes seen in adrenal insufficiency as well as the tests and procedures used for its diagnosis.

The Adrenal Glands and Their Function

The adrenal glands are situated directly above the kidneys. Different hormones are produced in the gland's different layers. In primary disorders, damage to the adrenal cortex, the outer layer of the adrenal glands, is responsible for inadequate hormone production of both cortisol and aldosterone. Cortisol helps regulate the immune response, helps the body use sugar and protein for energy and helps the body recover from infection and stress. Aldosterone helps regulate the body's fluid balance, ensuring that we have adequate amounts of water, salt, and potassium in the body.

Normally, the production and release of cortisol and aldosterone are regulated by the hypothalamus in the brain via the pituitary gland. When the hypothalamus, which is the master gland, recognizes that the cortisol level is low, it secretes a hormone known as corticotropin-releasing-hormone or CRH. CRH, in turn, prompts the pituitary gland to secrete a hormone called adrenocorticotropin or ACTH. ACTH, in turn, stimulates the adrenal glands to produce and release cortisol. Normally, when cortisol levels fall, the pituitary secretes more ACTH to help correct the problem, and ACTH levels are elevated.

When the Adrenal Glands Fail

Adrenal insufficiency is a condition that occurs when the adrenal glands produce inadequate amounts of the adrenal hormones cortisol, and sometimes, aldosterone. This condition can occur as a primary or secondary disorder, and it can have congenital or acquired origins. Primary conditions occur in less than 1 per 100,000 persons. Secondary conditions are more common.

Adrenal insufficiency, which affects slightly more women than men, varies in severity, ranging from a subclinical or mild condition to an extreme, sometimes fatal, form, which is known as an Addisonian crisis. Most primary adrenal insufficiency is autoimmune in nature and caused by Addison's disease, which is described in a separate article, or as the result of infection.

In Polyglandular Syndromes
Primary conditions may also occur in patients with autoimmune polyglandular syndromes (APS). In these syndromes one or more other autoimmune conditions, including diabetes, hypoparathyroidism, autoimmune thyroid disease, and other endocrine and non-endocrine disorders, are also present. These syndromes, which are classified as types 1-4 APS, are also described in a separate article.

Causes

Autoimmune disease accounts for about 80 percent of all cases of primary adrenal insufficiency. Most other cases result from infection (with tuberculosis, cytomegalovirus, the HIV virus, fungi, and other infectious agents), or as a complication of various metabolic and genetic disorders such as adrenal hyperplasia and adrenoleukodystrophy, or as a sequelae to certain metastatic cancers.

Also, in some bleeding disorders, such as antiphospholipid syndrome or in trauma, adrenal insufficiency may result from thrombosis or hemorrhage. Secondary conditions are related to both long and short-term use of corticosteroids (prednisone, prednisolone and others) or megesterol acetate. Other causes include high doses of medications used to lower cortisol levels in Cushing's syndrome or as a consequence of surgery for pituitary tumors. Patients who have been on long-term glucocorticoid therapy in the past may develop adrenal insufficiency later if they are subjected to acute stress, trauma, or infection. Secondary autoimmune conditions in APS Syndrome occur in about 50 percent of patients with primary or autoimmune adrenal insufficiency. In only about five percent of patients with other autoimmune conditions, particularly diabetes, does Addison's disease later occur.

Secondary or Central Adrenal Insufficiency

In secondary or central adrenal insufficiency, the hypothalamus fails to respond to low cortisol and doesn't release CRH, or the pituitary gland fails to recognize the hypothalamic signal or is otherwise unable to produce ACTH. Without these signals from the hypothalamus and pituitary glands, the adrenal cortex does not get the message or order to produce more cortisol. Consequently, cortisol levels fall. Steroids, which elevate blood cortisol levels, decrease ACTH levels. Seeing adequate cortisol in the blood, the hypothalamus stops secreting CRH, causing ACTH levels to fall. This disruption of the pituitary-hypothalamic-adrenal axis continues to be disrupted even when steroids are stopped. In some cases, this can occur after only two weeks of steroid use. Without adequate ACTH, cortisol production is limited.

Signs and Symptoms

Adrenal insufficiency causes few symptoms until marked destruction of the adrenal gland occurs or cortisol levels fall to negligible levels. In most cases, adrenal insufficiency is first suspected when other laboratory test abnormalities are discovered on routine
physical examinations or patients mention symptoms of weight loss, muscle weakness, and fatigue. The abnormal laboratory tests that typically occur in primary adrenal insufficiency include low sodium levels (hyponatremia), elevated potassium levels (hyperkalemia), high ketone levels, low blood sugar, and high calcium levels (hypercalcemia). Symptoms include low blood pressure, dizziness, weight loss, loss of appetite, and increased skin pigmentation or bronzing and salt cravings. Areas of skin discoloration or vitiligo may also appear.

**Acute and Chronic Adrenal Insufficiency**

Acute conditions usually result from infection, traumatic deliveries in infancy, or systemic coagulation disorders (disseminated intravascular coagulopathies). Patients with acute conditions of adrenal insufficiency often present with symptoms of dehydration, low blood pressure, low blood sugar, depression or altered mental status.

Chronic disorders, which develop over time and are often autoimmune, are more likely to cause weight loss and increased skin pigmentation, particularly around the nipples, genitals, along the creases of the palms, and over scar tissue. Orthostatic hypotension, a condition of decreased blood pressure on standing, may also occur. Some female patients may have decreased underarm and genital hair because of low androgen levels. In males, androgens are produced in the genitals rather than the adrenal glands.

**Diagnosis**

When adrenal insufficiency is suspected, blood for an AM cortisol level along with an ACTH level and an aldosterone level is drawn. With a normal range of 9-25, mcg/dl, blood cortisol levels higher than 19 generally rule out the possibility of adrenal insufficiency. Levels lower than 3 suggest adrenal insufficiency, and levels between 3-19 are indeterminate. In primary adrenal insufficiency, the blood ACTH level is high. A low cortisol with a high ACTH is sufficient to diagnose primary adrenal insufficiency; a low ACTH with a low cortisol level is seen in secondary adrenal insufficiency. Further tests can be used to differentiate pituitary from hypothalamic causes in secondary conditions.

Regardless of the cortisol level, if adrenal insufficiency is highly suspect, an ACTH stimulation test is performed. In this test the patient is given an injection containing cosyntropin, a synthetic form of ACTH. Cortisol levels are tested prior to administering the drug and at 30 and 60 minutes after the ACTH is given. In adrenal insufficiency the rise in blood cortisol levels is negligible. A longer version of the test can be used to determine if abnormal results are due to pituitary or adrenal disease.

Patients with adrenal insufficiency are also tested for adrenocorticol antibodies (ACA) and antibodies to the hormone 17-hydroxylase. In autoimmune adrenal insufficiency, these antibodies are present with highest levels seen early in the disease course. Imaging studies are used to help evaluate damaged adrenal glands. In autoimmune adrenal insufficiency, the glands are reduced in size.
Note: Blood levels of cortisol are decreased in hypothyroidism and increased in hyperthyroidism--levels improve when thyroid hormone levels are corrected. Cortisol may also be increased in pregnancy, in emotional stress, various illnesses, and by oral contraceptives, hydrocortisone, and spironolactone. A normal salt diet should be followed for 2-3 days before having blood drawn. Salivary cortisol tests are more accurate when levels are elevated than in conditions in which cortisol is low.

ACTH levels are decreased by dexamethasone, prednisone, hydrocortisone, prednisolone, methylprednisolone and megestrol acetate. ACTH levels rise with the use of amphetamines, insulin, levodopa, metoclopramide, and RU 486.

In shift workers the AM and PM cortisol and ACTH levels will be reversed.

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