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In Brief

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Author Disclosure

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Thomas Addison initially described a syndrome of weakness and hyperpigmentation associated with adrenal gland destruction in 1855. Much progress in understanding the causes of this condition has been made since then, especially in the last few decades. Although effective diagnostic and therapeutic interventions are available, the nonspecific symptoms and rarity of the disorder (estimated prevalence of 90 to 140 cases per 1 million in the Western population) often result in delayed diagnosis, which leads to unnecessary morbidity and mortality.

Also known as primary adrenal insufficiency, Addison disease is caused by any of three categories of adrenal gland defects that result in the inability to produce adequate amounts of glucocorticoid, mineralocorticoid, and adrenal androgens, despite an increased concentration of adrenocorticotropic hormone (ACTH). The first category is adrenal dysgenesis, which refers to congenital adrenal structural developmental defects. Multiple genes are essential for normal development and subsequent function of the adrenal cortex. Mutations in any of these genes can lead to adrenal dysgenesis. These genetic disorders are rare, and each has unique features. For example, mutations in the dosage-sensitive sex reversal adrenal hypoplasia gene 1 (*DAX-1*) can cause an X-linked form of congenital adrenal hypoplasia (CAH), which typically presents in males with life-threatening adrenal crisis in the newborn period and hypogonadotropic hypogonadism later in adolescence.

The clinical manifestation of adrenal crisis is similar to that of salt-wasting CAH from 21-hydroxylase deficiency. However, adrenal androgen secretion is not increased, and the response of cortisol and its precursors to ACTH stimulation is blunted or absent. Mutations of the ACTH receptor gene and related gene (*AAAS*) result in familial glucocorticoid deficiency (FGD), an autosomal recessive disorder of ACTH resistance in which cortisol and androgen secretion is deficient, while aldosterone production typically is normal. FGD usually presents in childhood with hyperpigmentation, weakness, hypoglycemia, and seizures and when associated with achalasia and alacrima, is called Allgrove or triple A syndrome.

The second category of adrenal gland defect is impaired steroidogenesis, which refers to disorders of cholesterol or steroid biosynthesis. Cholesterol biosynthesis disorders include Smith-Lemli-Opitz syndrome and abetalipoproteinemia, which interrupt the delivery of cholesterol. Steroid biosynthesis disorders include CAH (deficiency of 21-hydroxylase, 17-alpha-hydroxylase, 11-beta-hydroxylase, or 3-beta-hydroxylase dehydrogenase), lipoid CAH from deficiency of steroidogenic acute regulatory (StAR) protein, and mitochondrial DNA mutations. Among these, CAH from 21-hydroxylase is the most common cause of adrenal insufficiency in early infancy. The most common subtype results from complete enzyme deficiency, with defective production of both glucocorticoids and mineralocorticoids, and presents with severe salt wasting and adrenal crisis in the first 2 to 3 weeks after birth. Consequently, accumulated steroid precursors proximal to the enzymatic block are shunted into the androgen synthesis pathway, leading to overproduction of adrenal androgens. The excess androgens cause virilization in the female fetus, the most common cause of ambiguous genitalia in female infants.

The last category, adrenal destruction, refers to pathologic processes that damage the adrenal gland. Autoimmune destruction of the adrenal cortex is the

most common cause of Addison disease beyond infancy, but infections, metabolic and infiltrative or metastatic diseases, and the effects of drugs are other causes. Autoimmune damage to the adrenal gland may be isolated or can occur in the context of autoimmune polyendocrine syndrome (APS type 1 or 2). APS-1 has an early childhood onset and consists of a triad of hypoparathyroidism, chronic mucocutaneous candidiasis, and Addison disease. APS-2, on the other hand, has an adult onset, typically in the fourth decade of life, and is defined by Addison disease, thyroiditis, and diabetes mellitus.

Adrenal destruction also is a feature of an X-linked recessive disorder of the metabolism of long-chain fatty acids characterized by progressive neurologic dysfunction and primary adrenal insufficiency. Its two phenotypes, adrenoleukodystrophy and adrenomyeloneuropathy, affect 1 in 20,000 males and account for as many as 10% of all cases of adrenal insufficiency in children and young men. Defective beta-oxidation in peroxisomes leads to accumulation of very long-chain fatty acids in the adrenal cortex, among other sites. Adrenal insufficiency commonly presents in infancy with acute adrenal crisis, often preceding the neurologic symptoms. Other manifestations of adrenoleukodystrophy begin in infancy or childhood with weakness and spasticity, and the disorder progresses rapidly to dementia, blindness, and quadriparesis. Adrenomyeloneuropathy begins in adolescence or early adulthood with weakness, spasticity, and distal polyneuropathy but is milder and progresses more slowly.

Infection remains an important cause of adrenal failure. Historically, tuberculosis (TB) was the leading cause of Addison disease. As treatment for TB improved, the incidence of adrenal insufficiency related to the disease greatly decreased, now accounting for only about 20% of cases in developed countries. However, TB still is the leading cause of Addison disease in developing countries. Meningococcal infection can lead to bilateral adrenal hemorrhage, known as Friedrichson-Waterhouse syndrome. Chronic infections with fungi, cytomegalovirus, and human immunodeficiency virus can lead to adrenal infiltration and subsequent failure. In addition, a variety of medications used in the treatment of these infections interferes with adrenal function, potentially resulting in adrenal insufficiency.

Most children who have Addison disease experience ill-defined fatigue, generalized muscular weakness, loss of appetite, and poor weight gain. Some patients crave salt. Teenagers may notice loss of pubic and axillary hair. Signs and symptoms generally are nonspecific and can mimic a gastrointestinal disorder, with nausea, vomiting, and abdominal pain, or a psychiatric disorder, especially depression. "Muddy" hyperpigmentation is an important physical sign. Addison disease can progress to a potentially fatal Addisonian crisis that involves sudden sharp leg pain, lower back or abdominal pain, nausea, vomiting, hyponatremic dehydration, hyperkalemia, metabolic acidosis, hypotension, hypoglycemia, shock, or sudden death. The crisis occurs with physiologic stress or when corticosteroid therapy is withdrawn without tapering the dose.

Diagnosing Addison disease requires a high degree of suspicion. Measurement of electrolytes, along with basal early morning cortisol, ACTH, and plasma renin, can screen for adrenal insufficiency. Glucocorticoid deficiency is confirmed by an elevated plasma ACTH concentration (frequently $>$100 pg/mL [22 pmol/L]) and a low serum cortisol concentration (generally $<$10 mcg/dL [275.9 nmol/L]). When the diagnosis is in doubt, a stimulation test with synthetic ACTH should be performed. A normal response is a rise in serum cortisol concentration after 60 minutes to a peak of 18 mcg/dL (496.6 nmol/L) or more. A subnormal response confirms the diagnosis of adrenal insufficiency. If an enzymatic defect in steroidogenesis is suspected, an ACTH stimulation test with complete adrenal biochemical profile (cortisol, aldosterone, androgens, and all their precursor hormones) can highlight the underlying enzyme defect. Mineralocorticoid deficiency is confirmed with a relatively low aldosterone value in the face of hyperreninemia.

If autoimmune Addison disease is suspected, the possibility of other endocrine gland dysfunctions should be evaluated by measuring serum calcium, phosphorus, glucose, and thyrotropin. Serum parathyroid hormone should be measured if the patient has hypocalcemia. Similarly, the possibility of hypogonadism should be investigated in postmenarchal female adolescents presenting with oligomenorrhea or amenorrhea by measuring serum follicle-stimulating hormone and luteinizing hormone and possible hypogonadism in males by measuring serum testosterone and luteinizing hormone.

Acute adrenal insufficiency is a medical emergency. Management involves initial fluid resuscitation with a 20-mL/kg bolus of normal saline. Repeated boluses may be needed. Replacement of fluid losses should be continued with isotonic crystalloid solutions containing dextrose (typically 5% dextrose with normal saline) at a rate of 1.5 to 2 times the maintenance requirement. Stress doses of hydrocortisone (100 mg/m^2 per day) are vital and should be administered as early as possible, concomitant with intravenous fluid treatment. Central venous access and vasopressors, along with higher glucose concentrations, may be required in profoundly ill patients. Life-threatening hyperkalemia may require additional therapy with sodium polystyrene, intravenous calcium, insulin, and bicarbonate.

Long-term treatment of Addison disease requires glucocorticoid and mineralocorticoid replacement, with careful attention to coexisting hormonal deficiencies, particularly hypothyroidism. Treating hypothyroidism without correcting adrenal insufficiency may precipitate a severe adrenal crisis. For children, the preferred cortisol replacement is oral hydrocortisone (10 to 20 mg/m^2 per day divided into three doses) because of its short half-life and minimal suppression of growth. Other preparations that have longer half-lives (prednisone or dexamethasone) can be used, if needed, to facilitate adherence. Normal growth rate, sense of well-being, and good energy level signal effective replacement therapy. Mineralocorticoid deficiency is treated with fludrocortisone at a dose of 0.1 to 0.2 mg/day. In newborns and infants, sodium chloride supplementation also may be required; in older children and adults, dietary intake is typically adequate without the need for further supplementation.

Androgen deficiency, although not life-threatening, may affect well-being. Adrenal androgen replacement is being studied in adults, but no data are available for children and adolescents.

Every patient should wear a medical alert bracelet or necklace that has an emergency medical information card attached. In times of stress, an increased dose of glucocorticoid is required to mirror normal physiologic response. Doubling or tripling the daily maintenance dose of oral hydrocortisone for mild stresses generally is adequate. In most instances, stress doses are administered for only 24 to 48 hours, unless the underlying illness is prolonged. Emergency injectable hydrocortisone must be available in case of vomiting or inability to tolerate oral intake. The hormone should be injected intramuscularly at home at a dose of 50 mg/m^2, which provides coverage for approximately 6 to 8 hours. Consultation with a clinician is recommended. If the patient's condition does not improve or worsens, emergency evaluation and treatment with intravenous hydrocortisone must be undertaken. In conditions of severe stress, such as major surgery, intensive trauma, and sepsis, treatment should be similar to that for adrenal crisis.

Comment: Of historic interest, Addison actually had two diseases attached to his name. In addition to the disease related to adrenal insufficiency, he also described a fatal "idiopathic anemia" for which he could find no treatment and, at autopsy, no cause. What came to be called Addison anemia later was termed pernicious anemia by German physician Anton Biermer. Although the groups of patients Addison described as having these two diseases were separate, in a twist of fate, it turns out that children who have APS-1 can have both adrenal insufficiency and pernicious anemia—they can be stricken with both Addison diseases. The unifying mechanism, autoimmune destruction of the adrenal cortex and of the gastric parietal cells that produce intrinsic factor, appears to result from a mutation in the autoimmune regulator gene, *21q22.3*.

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Editor, In Brief

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