Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) refers to autosomal recessive disorders of adrenal steroid biosynthesis that result in glucocorticoid and mineralocorticoid deficiencies and compensatory increase in ACTH secretion (see Fig. 64-2). Five major types of CAH exist, and the clinical manifestations of each type depend on which steroids are in excess and which are deficient. 21α-Hydroxylase (CYP21) deficiency is the most common of these disorders and accounts for about 95% of patients with CAH. In this condition, there is a failure of 21-hydroxylation of 17-hydroxyprogesterone and progesterone to 11-deoxycortisol and 11-deoxycorticosterone, respectively, with deficient cortisol and aldosterone production. Cortisol deficiency leads to increased ACTH release, resulting in adrenal hyperplasia and overproduction of 17-hydroxyprogesterone and progesterone. Increased ACTH production also leads to increased biosynthesis of androstenedione and DHEA, which can be converted to testosterone. Patients with 21-hydroxylase deficiencies can be divided into two clinical phenotypes: classic 21-hydroxylase deficiency, which usually is diagnosed at birth or during childhood, and late-onset 21-hydroxylase deficiency, which develops during or after puberty. Two thirds of patients with classic 21-hydroxylase deficiency have various degrees of mineralocorticoid deficiency (salt-losing form); the remaining one third have the non–salt-losing type (simple virilizing form). Both decreased aldosterone production and increased concentrations of precursors that are mineralocorticoid antagonists (progesterone and 17-hydroxyprogesterone) contribute to salt loss.

Late-onset 21-hydroxylase deficiency represents an allelic variant of classic 21-hydroxylase deficiency and is characterized by a mild enzymatic defect. This deficiency is the most common autosomal recessive disorder in humans and is present at high frequency in Ashkenazi Jews. The syndrome usually develops at the time of puberty with signs of virilization (hirsutism and acne) and amenorrhea or oligomenorrhea. This diagnosis should be considered in women who have unexplained hirsutism and menstrual abnormalities or infertility.

The most useful initial measurement for the diagnosis of classic 21-hydroxylase deficiency is that of plasma 17-hydroxyprogesterone. A value greater than 200 ng/dL is consistent with the diagnosis. The diagnosis of late-onset 21-hydroxylase deficiency is based on the finding of an elevated level of plasma 17-hydroxyprogesterone (>1500 ng/dL) 30 minutes after administration of 0.25 mg of synthetic ACTH (1-24).

The aim of treatment for classic 21-hydroxylase deficiency is to replace glucocorticoids and mineralocorticoids, suppress ACTH and androgen overproduction, and allow for normal growth and sexual maturation in children. A proposed approach to treating classic 21-hydroxylase deficiency recommends physiologic replacement with hydrocortisone and fludrocortisone in all affected patients. Virilizing effects can be prevented by the use of an antiandrogen (flutamide) and an aromatase inhibitor (testolactone). Although the traditional treatment for late-onset 21-hydroxylase deficiency is dexamethasone (0.5 mg/day), the use of an antiandrogen such as spironolactone (100 to 200 mg/day) or flutamide (125 mg/day) is probably equally effective and has fewer side effects. Mineralocorticoid replacement is not needed in late-onset 21-hydroxylase deficiency.

11β-Hydroxylase (CYP11B1) deficiency accounts for about 5% of patients with CAH. In this syndrome, the conversions of 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone (the precursor to aldosterone) are blocked. Affected patients usually have hypertension and hypokalemia because of increased amounts of precursors with mineralocorticoid activity. Virilization occurs, as with 21-hydroxylase deficiency, and a late-onset form manifesting as androgen excess also occurs. The diagnosis is made from the finding of elevated plasma 11-deoxycortisol levels, either basally or after ACTH stimulation.

Rare forms of CAH are 3β-HSD type II deficiency, 17α-hydroxylase (CYP17) deficiency, and steroidogenic acute regulatory protein (StAR) deficiency.

SYNDROMES OF ADRENOCORTICAL HYPERFUNCTION

Hypersecretion of the glucocorticoid hormone cortisol results in Cushing's syndrome, a metabolic disorder that affects carbohydrate, protein, and lipid metabolism. Hypersecretion of mineralocorticoids such as aldosterone results in a syndrome of hypertension and electrolyte disturbances.

Cushing's Syndrome

Pathophysiology

Increased production of cortisol is seen in both physiologic and pathologic states (Table 64-3). Physiologic hypercortisolism occurs with stress, during the last trimester of pregnancy, and in persons who regularly perform strenuous exercise. Pathologic conditions of elevated cortisol levels include exogenous or endogenous Cushing's syndrome and several psychiatric states, such as depression, alcoholism, anorexia nervosa, panic disorder, and alcohol or narcotic withdrawal.

Cushing's syndrome may be caused by exogenous administration of ACTH or glucocorticoid or by endogenous overproduction of these hormones. Endogenous Cushing's syndrome is either ACTH dependent or ACTH independent. ACTH dependency accounts for 85% of patients and includes pituitary sources of ACTH (Cushing's disease) and ectopic sources of ACTH. Pituitary Cushing's disease accounts for 90% of patients with ACTH-dependent Cushing's syndrome. Ectopic secretion of ACTH occurs most commonly in patients with small cell lung carcinoma. These patients are older, usually have a history of smoking, and primarily exhibit signs and symptoms of lung cancer rather than those of Cushing's syndrome. Patients with the clinically apparent ectopic ACTH syndrome, in contrast, have mostly intrathoracic (lung and thymic) carcinoids. ACTH-independent causes account for 15% of patients with Cushing's syndrome and include adrenal adenomas, adrenal carcinomas, micronodular adrenal disease, and autonomous macronodular adrenal disease. The female-to-male ratio for noncancerous forms of Cushing's syndrome is 4 : 1.

Clinical Presentation

The clinical signs, symptoms, and common laboratory findings of hypercortisolism observed in patients with Cushing's syndrome are listed in Table 64-4 (see also Fig. 64-2). Patients with