Chapter 66

The Adrenal Gland

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Physiology

The adrenal glands lie at the superior pole of each kidney and are composed of two distinct regions: the cortex and the medulla. The adrenal cortex consists of three anatomic zones: the outer *zona glomerulosa*, which secretes the mineralocorticoid aldosterone; the intermediate *zona fasciculata*, which secretes cortisol; and the inner *zona reticularis*, which secretes adrenal androgens. The adrenal medulla, lying in the center of the adrenal gland, is functionally related to the sympathetic nervous system and secretes the catecholamines epinephrine and norepinephrine in response to stress.

The synthesis of all steroid hormones begins with cholesterol and is catalyzed by a series of regulated, enzyme-mediated reactions (Fig. 66–1). Glucocorticoids affect metabolism, cardiovascular function, behavior, and the inflammatory/immune response (Table 66–1). Cortisol, the natural human glucocorticoid, is secreted by the adrenal glands in response to ultradian, circadian, and stress-induced hormonal stimulation by adrenocorticotropic hormone (ACTH). Plasma cortisol has marked circadian rhythm; levels are highest in the morning. ACTH, a 39–amino acid neuropeptide, is part of the pro-opiomelanocortin (POMC) precursor molecule, which also contains β-endorphin, β-lipotropin, corticotropin-like intermediate-lobe peptide (CLIP), and various melanocyte-stimulating hormones (MSH). The secretion of ACTH by the pituitary gland is regulated primarily by two hypothalamic polypeptides: the 41–amino acid corticotropin-releasing hormone (CRH) and the decapeptide vasopressin. Glucocorticoids exert negative feedback upon CRH and ACTH secretion. The brain-hypothalamic-pituitary-adrenal (HPA) axis (Fig. 66–2) interacts with and influences the function of the reproductive, growth, and thyroid axes at multiple levels, with major participation of glucocorticoids at all levels.

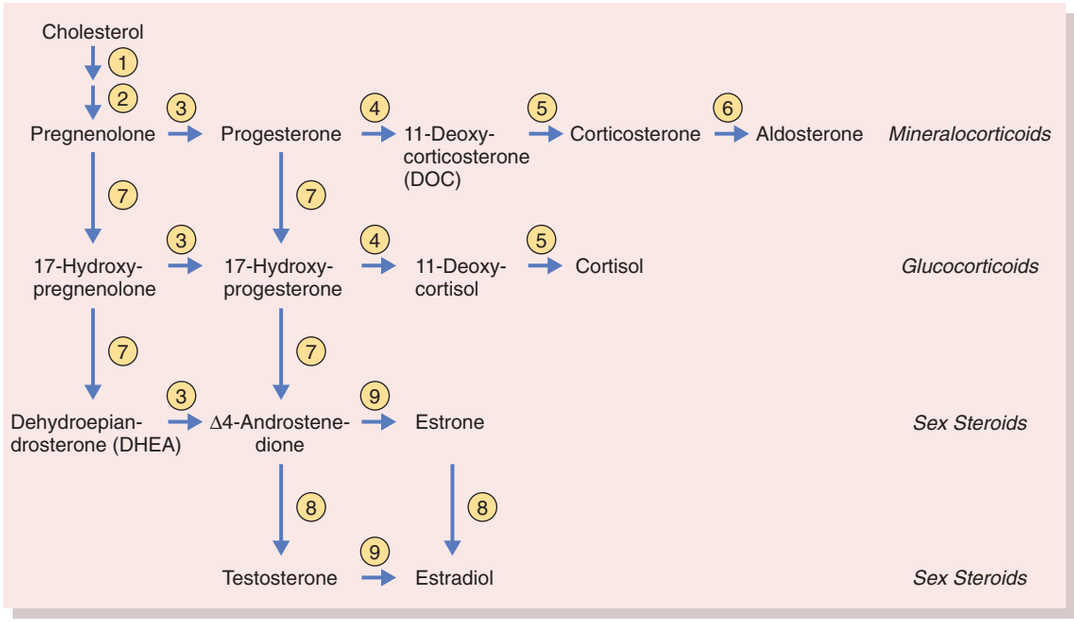
The renin-angiotensin-aldosterone system (Fig. 66–3) is the major regulator of aldosterone secretion. Renal juxtaglomerular cells secrete renin in response to a decrease in circulating volume and/or a reduction in renal perfusion pressure. Renin is the rate-limiting enzyme that cleaves the 60-kD angiotensinogen, synthesized by the liver, to the bioinactive decapeptide angiotensin I. Angiotensin I is rapidly converted to the octapeptide angiotensin II by angiotensin-converting enzyme in the lungs and other tissues. Angiotensin II is a potent vasopressor and stimulates aldosterone production but does not stimulate cortisol production. Angiotensin II is the predominant regulator of aldosterone secretion, but plasma potassium concentration, plasma volume, and ACTH levels also influence aldosterone secretion. ACTH also mediates the circadian rhythm of aldosterone; as a result, the plasma concentration of aldosterone is highest in the morning. Aldosterone binds to the type I mineralocorticoid receptor. In contrast, cortisol binds to both the type I mineralocorticoid and type II glucocorticoid receptors, although the functional binding to the former receptor is limited by the intracellular enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type II, which catabolizes cortisol to inactive cortisone. The availability of cortisol to bind to the glucocorticoid receptor is modulated by 11β-HSD type I, which interconverts cortisol and cortisone. Binding of aldosterone to the cytosol mineralocorticoid receptor leads to Na^+ absorption and K^+ and H^+ secretion by the renal tubules. The resultant increase in plasma Na^+ and decrease in plasma K^+ provide a feedback mechanism for suppressing renin and, subsequently, aldosterone secretion.

Approximately 5% of cortisol and 40% of aldosterone circulate in the free form; the remainder is bound to corticosteroid-binding globulin and albumin.

Adrenal androgen precursors include dehydroepiandrosterone (DHEA) and its sulfate and androstenedione. They are synthesized in the zona reticularis under the influence of ACTH and other adrenal androgen-stimulating factors. Although they have minimal intrinsic androgenic activity, they contribute to androgenicity by their peripheral conversion to testosterone and dihydrotestosterone. In men, excessive adrenal androgens have no clinical consequences; however in women, peripheral conversion of excess adrenal androgen precursor secretion results in acne, hirsutism, and virilization. Because of gonadal production of androgens and estrogens and secretion of norepinephrine by sympathetic ganglia, deficiencies of adrenal androgens and catecholamines are not clinically recognized.

Adrenal Insufficiency

Glucocorticoid insufficiency can be either primary, resulting from the destruction or dysfunction of the adrenal cortex, or secondary, resulting from ACTH hyposecretion (Table 66–2). Autoimmune destruction of the adrenal glands (Addison's disease) is the most common cause of primary adrenal insufficiency in the industrialized world, accounting for about 65% of



Enzyme Number	*Enzyme (Current and Trivial Name)*
1	StAR; Steroidogenic acute regulatory protein
2	CYP11A1; Cholesterol side chain cleavage enzyme/desmolase
3	3β-HSD II; 3β-Hydroxylase dehydrogenase
4	CYP21A2; 21α-Hydroxylase
5	CYP11B1; 11β-Hydroxylase
6	CYP11B2; Corticosterone Methyloxidase
7	CYP17; 17α-Hydroxylase/17, 20 lyase
8	17β-HSD; 17β-Hydroxysteroid dehydrogenase
9	CYP19; Aromatase

FIGURE 66–1 Pathways of steroid biosynthesis.

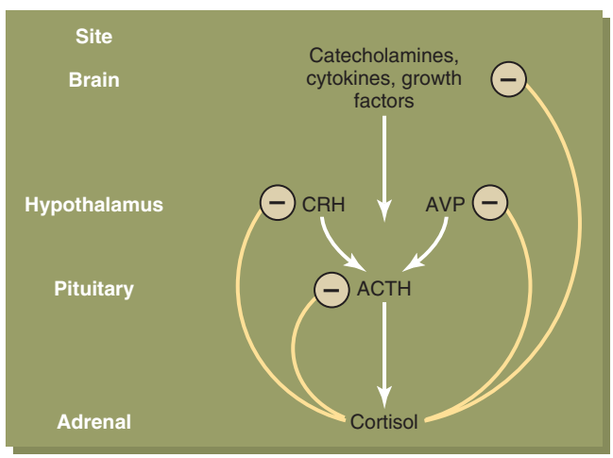


FIGURE 66–2 The brain-hypothalamic-pituitary-adrenal axis. ACTH = adrenocorticotropic hormone; AVP = arginine vasopressin; CRH = corticotropin-releasing hormone.

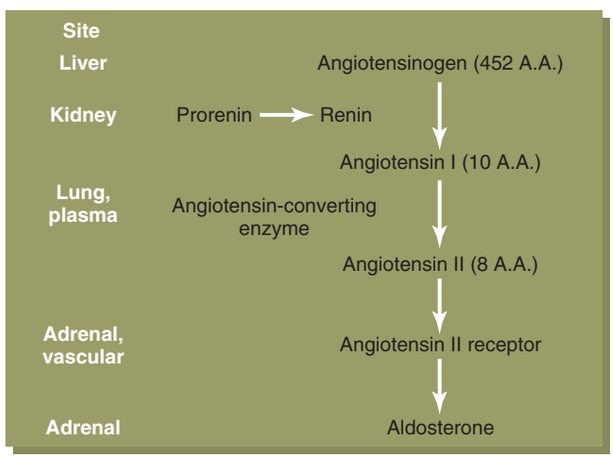


FIGURE 66–3 The renin-angiotensin-aldosterone axis. A.A. = amino acids.

TABLE 66–1 Actions of Glucocorticoids

Maintain Metabolic Homeostasis

Regulate blood glucose level, permissive effects on gluconeogenesis, increase glycogen synthesis
Raise insulin levels, permissive effects on lipolytic hormones
Increase catabolism, decrease anabolism (except fat), inhibit growth hormone axis
Inhibit reproductive axis
Mineralocorticoid activity of cortisol

Affect Connective Tissues

Cause loss of collagen and connective tissue

Affect Calcium Homeostasis

Stimulate osteoclasts, inhibit osteoblasts
Reduce intestinal calcium absorption, stimulate parathyroid hormone release, increase urinary calcium excretion, decrease reabsorption of phosphate

Maintain Cardiovascular Function

Increase cardiac output
Increase vascular tone
Permissive effects on pressor hormones, increase sodium retention

Affect Behavior and Cognitive Function

Affect Immune System

Increase intravascular leukocyte concentration
Decrease migration of inflammatory cells to sites of injury
Suppress immune system (thymolysis; suppression of cytokines, prostanoids, kinins, serotonin, histamine, collagenase, and plasminogen activator)

TABLE 66–2 Syndromes of Adrenocortical Hypofunction

Primary Adrenal Disorders

Combined Glucocorticoid and Mineralocorticoid Deficiency

Autoimmune

- Isolated autoimmune disease (Addison's disease)
- Polyglandular autoimmune syndrome, type I
- Polyglandular autoimmune syndrome, type II

Infectious
- Tuberculosis
- Fungal
- Cytomegalovirus
- Human immunodeficiency virus

Vascular
- Bilateral adrenal hemorrhage
- Sepsis
- Coagulopathy
- Thrombosis/embolism
- Adrenal infarction

Infiltration
- Metastatic carcinoma/lymphoma
- Sarcoidosis
- Amyloidosis
- Hemochromatosis

Congenital
- Congenital adrenal hyperplasia
  - 21-hydroxylase deficiency
  - 3β-ol dehydrogenase deficiency
  - 20,22-desmolase deficiency
- Adrenal unresponsiveness to ACTH
- Congenital adrenal hypoplasia
- Adrenoleukodystrophy
- Adrenomyeloneuropathy

Iatrogenic
- Bilateral adrenalectomy
- Drugs: metyrapone, aminoglutethimide, trilostane, ketoconazole, o,p′-DDD, RU-486

Mineralocorticoid Deficiency without Glucocorticoid Deficiency

Corticosterone methyloxidase deficiency
Isolated zona glomerulosa defect
Heparin therapy
Critical illness
Converting enzyme inhibitors

Secondary Adrenal Disorders

Secondary Adrenal Insufficiency

Hypothalamic/pituitary dysfunction
Exogenous glucocorticoids
After removal of an ACTH-secreting tumor

Hyporeninemic Hypoaldosteronism

Diabetic nephropathy
Tubulointerstitial diseases
Obstructive uropathy
Autonomic neuropathy
Nonsteroidal anti-inflammatory drugs
β-Adrenergic drugs

ACTH = adrenocorticotropic hormone.

cases. Usually both glucocorticoid and mineralocorticoid secretion are diminished in this condition and, if untreated, it may be fatal. Isolated glucocorticoid or mineralocorticoid deficiency may also occur, and it is becoming apparent that mild adrenal insufficiency (similar to subclinical hypothyroidism, discussed in Chapter 65) should also be diagnosed and treated. Adrenal medulla function is usually spared. Approximately 70% of the patients with Addison's disease have anti-adrenal antibodies.

Tuberculosis used to be the most common cause of adrenal insufficiency. However, its incidence in the industrialized world has decreased since the 1960s, and it now accounts for only 15 to 20% of cases of adrenal insufficiency; calcified adrenal glands can be seen in 50% of these cases. Fungal and cytomegalovirus infections, metastatic infiltration of the adrenal glands, sarcoidosis, amyloidosis, hemochromatosis, traumatic injury to both adrenal glands, bilateral adrenal hemorrhage, and sepsis (usually meningococcemia) are rare causes of adrenal insufficiency. Many patients with human immunodeficiency virus infection have decreased adrenal reserve without overt adrenal insufficiency. Congenital causes of adrenal dysfunction include congenital adrenal hyperplasia (to be discussed), adrenal unresponsiveness to ACTH, congenital adrenal

hypoplasia, and two demyelinating lipid metabolism disorders: adrenoleukodystrophy and adrenomyeloneuropathy. Iatrogenic causes of adrenal insufficiency include bilateral adrenalectomy, agents that inhibit cortisol biosynthesis (metyrapone, aminoglutethimide, trilostane, and ketoconazole), adrenolytic drugs (mitotane [o,p′-DDD]), and the glucocorticoid antagonist mifepristone (RU-486).

Addison's disease may be part of two distinct autoimmune polyglandular syndromes. Type I polyglandular autoimmune syndrome, also termed autoimmune polyendocrine-candidiasis–ectodermal dystrophy or autoimmune polyglandular failure syndrome, is characterized by the triad of hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis. Other, less common manifestations include hypothyroidism, gonadal failure, gastrointestinal malabsorption, insulin-dependent diabetes mellitus, alopecia areata and totalis, pernicious anemia, vitiligo, chronic active hepatitis, keratopathy, hypoplasia of dental enamel and nails, hypophysitis, asplenism, and cholelithiasis. This syndrome manifests in childhood. Type II polyglandular autoimmune syndrome, also called Schmidt's syndrome, is characterized by Addison's disease, autoimmune thyroid disease (Graves' disease or Hashimoto's thyroiditis), and insulin-dependent diabetes mellitus. Other associated diseases include pernicious anemia, vitiligo, gonadal failure, hypophysitis, celiac disease, myasthenia gravis, primary biliary cirrhosis, Sjögren's syndrome, lupus erythematosus, and Parkinson's disease. This syndrome usually manifests in adults.

Adrenal insufficiency commonly manifests as weight loss, increasing fatigue, vomiting, diarrhea or anorexia, and salt craving. Muscle and joint pain, abdominal pain, and postural dizziness may also occur. Signs of increased pigmentation (initially most marked on the extensor surfaces, palmar creases, and buccal mucosa) often occur secondarily to the increased production of ACTH and other POMC-related peptides by the pituitary gland. Laboratory abnormalities may include hyponatremia, hyperkalemia, mild metabolic acidosis, azotemia, hypercalcemia, anemia, lymphocytosis, and eosinophilia. Hypoglycemia may also occur, especially in children.

Acute adrenal insufficiency is a medical emergency, and treatment should not be delayed pending laboratory results. In a critically ill patient with hypovolemia, a plasma sample for cortisol, ACTH, aldosterone, and renin should be obtained, and then treatment with an intravenous bolus of 100 mg of hydrocortisone and parenteral saline administration should be initiated. A plasma cortisol concentration of more than 34 μg/dL rules out the diagnosis of adrenal crisis, whereas a value of less than 20 μg/dL in the setting of shock is consistent with adrenal insufficiency. A plasma cortisol value between 20 μg/dL and 34 μg/dL in the setting of a severely ill patient may indicate partial adrenal insufficiency.

In a patient with chronic symptoms, a 1-hour cosyntropin test should be performed. In this test, 0.25 mg ACTH (1–24) (cosyntropin) is given intravenously, and plasma cortisol is measured 0, 30, and 60 minutes later. A normal response is a plasma cortisol concentration higher than 20 μg/dL at any time during the test. A patient with a basal morning plasma cortisol concentration of less than 5 μg/dL and a stimulated cortisol concentration below 18 μg/dL probably has frank adrenal insufficiency and should receive treatment. A basal morning plasma cortisol concentration between 10 and 18 μg/dL in association with a stimulated cortisol concentration lower than 18 μg/dL probably indicates impaired adrenal reserve and a requirement for receiving cortisol replacement under stress conditions (as described later). Recently a 1-μg cosyntropin test to assess partial adrenal insufficiency has been described. This test may identify more patients who need cortisol replacement under stress conditions, but should not be used to determine which patients need daily cortisol replacement.

Once the diagnosis of adrenal insufficiency is made, the distinction between primary and secondary adrenal insufficiency needs to be made. Secondary adrenal insufficiency results from inadequate stimulation of the adrenal cortex by ACTH. This can result from lesions anywhere along the HPA axis or as a sequela of prolonged suppression of the HPA axis by exogenous glucocorticoids. Secondary adrenal insufficiency manifests similarly to primary adrenal insufficiency with a few important differences: Because ACTH and other POMC-related peptides are reduced in secondary adrenal insufficiency, hyperpigmentation does not occur. In addition, because mineralocorticoid levels are normal in secondary adrenal insufficiency, symptoms of salt craving, as well as the laboratory abnormalities of hyperkalemia and metabolic acidosis, are not present. However, hyponatremia is often seen as a result of increased antidiuretic hormone (ADH) secretion (resulting from volume depletion and ADH co-secretion with CRH), which accompanies glucocorticoid insufficiency, resulting in impaired water excretion. Because corticotropin is the most preserved of the pituitary hormones, a patient with secondary adrenal insufficiency caused by a pituitary lesion usually has symptoms and/or laboratory abnormalities consistent with hypothyroidism, hypogonadism, or growth hormone deficiency. To distinguish primary from secondary adrenal insufficiency, a basal morning plasma ACTH value and a standing (upright for at least 2 hours) serum aldosterone level and plasma renin activity should be measured. A plasma ACTH value of more than 20 pg/mL (normal 5 to 30 pg/mL) is consistent with primary adrenal insufficiency, whereas a value less than 20 pg/mL probably represents secondary adrenal insufficiency. An upright plasma renin activity of more than 3 ng/mL/hr in the setting of a suppressed aldosterone level is consistent with primary adrenal insufficiency, whereas a value less than 3 ng/mL/hr probably represents secondary adrenal insufficiency. The 1-hour cosyntropin test is suppressed in both secondary and primary adrenal insufficiency.

Secondary adrenal insufficiency occurs commonly after discontinuation of glucocorticoids. Alternate-day glucocorticoid treatment, if feasible, results in less suppression of the HPA axis than does daily glucocorticoid

therapy. The natural history of recovery from adrenal suppression is first a gradual increase in ACTH levels, followed by the normalization of plasma cortisol levels and then normalization of the cortisol response to ACTH. Complete recovery of the HPA axis can take up to 1 year, and the rate-limiting step appears to be recovery of the CRH neurons.

TREATMENT

After stabilization of acute adrenal insufficiency, patients with Addison's disease require lifelong replacement therapy with both glucocorticoids and mineralocorticoids. Unfortunately, most physicians overtreat patients with glucocorticoids and undertreat them with mineralocorticoids. Because overtreatment with glucocorticoids results in insidious weight gain and osteoporosis, the minimal cortisol dose tolerated without symptoms of glucocorticoid insufficiency (usually joint pain) is recommended. An initial regimen of 15 to 20 mg of hydrocortisone first thing in the morning and 5 mg of hydrocortisone at around 4:00 PM mimics the physiologic dose and is recommended. Whereas glucocorticoid replacement is fairly uniform in most patients, mineralocorticoid replacement varies greatly. The initial dose of the synthetic mineralocorticoid fludrocortisone should be 100 µg/day, and dosage should be adjusted to keep the standing plasma renin activity between 1 and 3 ng/mL/hour. A standing plasma renin activity higher than 3 ng/mL/hour, while the patient is taking the correct glucocorticoid dosage, is suggestive of undertreatment with fludrocortisone.

Under the stress of a minor illness (nausea, vomiting, or fever greater than 100.5°F), the hydrocortisone dose should be doubled for as short a period of time as possible. The inability to ingest hydrocortisone pills may necessitate parenteral hydrocortisone administration. Patients undergoing a major stressful event (i.e., surgery necessitating general anesthesia, or major trauma) should receive 150 to 300 mg of parenteral hydrocortisone daily (in three divided doses) with a rapid taper to normal replacement during recovery. All patients should wear a medical information bracelet and should be instructed in the use of intramuscular emergency hydrocortisone injections.

Hyporeninemic Hypoaldosteronism

Mineralocorticoid deficiency can result from decreased renin secretion by the kidneys. Resultant hypoangiotensinemia leads to hypoaldosteronism with hyperkalemia and hyperchloremic metabolic acidosis. Plasma sodium concentration is usually normal, but total plasma volume is often deficient. Plasma renin and aldosterone levels are low and unresponsive to stimuli. Diabetes mellitus and chronic tubulointerstitial diseases of the kidney are the most common underlying conditions leading to impairment of the juxtaglomerular apparatus. A subset of hyporeninemic hypoaldosteronism is caused by autonomic insufficiency and is a frequent cause of orthostatic hypotension. Stimuli such as upright posture or volume depletion, mediated by baroreceptors, do not cause a normal renin response. Administration of pharmacologic agents such as nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, and β-adrenergic antagonists can also produce conditions of hypoaldosteronism. Fludrocortisone and/or the alpha$_1$-agonist midodrine are effective in correcting the orthostatic hypotension and electrolyte abnormalities caused by hypoaldosteronism.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) refers to disorders of adrenal steroid biosynthesis that result in glucocorticoid and mineralocorticoid deficiencies. Because of deficient cortisol biosynthesis, a compensatory increase in ACTH occurs, inducing adrenal hyperplasia and overproduction of the steroids that precede blockage of enzyme production (see Fig. 66–1). There are five major types of CAH, and the clinical manifestations of each type depend on which steroids are in excess and which are deficient. All these syndromes are transmitted in an autosomal recessive pattern. 21-Hydroxylase (CYP21) deficiency is the most common of these disorders and accounts for about 95% of cases of CAH. In this condition, there is a failure of 21-hydroxylation of 17-hydroxyprogesterone and progesterone to 11-deoxycortisol and 11-deoxycortisone, respectively, with deficient cortisol and aldosterone production. Cortisol deficiency leads to increased ACTH release, causing 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 deficiency can be divided into two clinical phenotypes: classic 21-hydroxylase deficiency, usually diagnosed at birth or during childhood, and late-onset 21-hydroxylase deficiency, which manifests during or after puberty. Two thirds of patients with classic 21-hydroxylase deficiency have various degrees of mineralocorticoid deficiency (salt-losing form); the remaining third are not salt losing (simple virilizing form). Both decreased aldosterone production and increased concentrations of precursors that are mineralocorticoid antagonists (progesterone and 17-hydroxyprogesterone) contribute to salt loss in the salt-losing form, in which the enzymatic block is more severe.

The most useful 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. Late-onset 21-hydroxylase deficiency represents an allelic variant of classic 21-hydroxylase deficiency and is characterized by a mild enzymatic defect. This is the most frequent autosomal recessive disorder in humans and is present especially in Ashkenazi Jews. The syndrome usually manifests

around the time of puberty with signs of virilization (hirsutism and acne) and amenorrhea or oligomenorrhea. It should be considered in women with unexplained hirsutism and menstrual abnormalities or infertility. The diagnosis is made from the finding of an elevated plasma 17-hydroxyprogesterone level (>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, including those with the simple virilizing form. The deleterious effects of excess androgens can then be prevented by the use of an antiandrogen agent (flutamide) and an aromatase inhibitor (testolactone) that blocks the conversion of testosterone to estrogen.

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) is probably more 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 the cases of 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, 17α-hydroxylase (CYP17), and steroidogenic acute regulatory protein deficiencies.

Syndromes of Adrenocorticoid Hyperfunction

Hypersecretion of the glucocorticoid hormone cortisol results in Cushing's syndrome, a metabolic disorder affecting 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 66–3). Physiologic

TABLE 66–3 Syndromes of Adrenocortical Hyperfunction

States of Glucocorticoid Excess

Physiologic States

Stress
Strenuous exercise
Last trimester of pregnancy

Pathologic States

Psychiatric conditions (pseudo-Cushing's disorders)
- Depression
- Alcoholism
- Anorexia nervosa
- Panic disorders
- Alcohol/drug withdrawal

ACTH-dependent states
- Pituitary adenoma (Cushing's disease)
- Ectopic ACTH syndrome
  - Bronchial carcinoid
  - Thymic carcinoid
  - Islet cell tumor
  - Small cell lung carcinoma
- Ectopic CRH secretion

ACTH-independent states
- Adrenal adenoma
- Adrenal carcinoma
- Micronodular adrenal disease

Exogenous Sources

Glucocorticoid intake
ACTH intake

States of Mineralocorticoid Excess

Primary Aldosteronism

Aldosterone-secreting adenoma
Bilateral adrenal hyperplasia
Aldosterone-secreting carcinoma
Glucocorticoid-suppressible hyperaldosteronism

Adrenal Enzyme Deficiencies

11β-hydroxylase deficiency
17α-hydroxylase deficiency
11β-hydroxysteroid dehydrogenase, type II

Exogenous Mineralocorticoids

Licorice
Carbenoxolone
Fludrocortisone

Secondary Hyperaldosteronism

Associated with hypertension
- Accelerated hypertension
- Renovascular hypertension
- Estrogen administration
- Renin-secreting tumors

Without hypertension
- Bartter's syndrome
- Sodium-wasting nephropathy
- Renal tubular acidosis
- Diuretic/laxative abuse
- Edematous states (cirrhosis, nephrosis, congestive heart failure)

ACTH = adrenocorticotropin hormone; CRH = corticotropin-releasing hormone.

hypercortisolism occurs in 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, including depression, alcoholism, anorexia nervosa, panic disorder, and alcohol or narcotic withdrawal.

Cushing's syndrome may be caused by exogenous ACTH or glucocorticoid administration or by endogenous overproduction of these hormones. Endogenous Cushing's syndrome is either ACTH dependent or ACTH independent. ACTH dependency accounts for 85% of cases and includes pituitary sources of ACTH (Cushing's disease), ectopic sources of ACTH, and, in rare instances, ectopic sources of CRH. Pituitary Cushing's disease accounts for 80% of cases of 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 present primarily with signs and symptoms of lung cancer rather than of Cushing's syndrome. Patients with the clinically apparent ectopic ACTH syndrome, in contrast, have mostly intrathoracic (lung and thymic) carcinoids. The remaining patients have pancreatic, adrenal, or thyroid tumors that secrete ACTH. ACTH-independent causes account for 15% of cases of 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.

TABLE 66–4 Signs, Symptoms, and Laboratory Abnormalities of Hypercortisolism

Fat redistribution (dorsocervical and supraclavicular fat pads, temporal wasting, centripetal obesity, weight gain) (95%)
Menstrual irregularities (80% of affected women)
Thin skin/plethora (80%)
Moon facies (75%)
Increased appetite (75%)
Sleep disturbances (75%)
Hypertension (75%)
Hypercholesterolemia/hypertrigliceridemia (70%)
Altered mentation (poor concentration, decreased memory, euphoria) (70%)
Diabetes mellitus/glucose intolerance (65%)
Striae (65%)
Hirsutism (65%)
Proximal muscle weakness (60%)
Psychological disturbances (emotional lability, depression, mania, psychosis) (50%)
Decreased libido/impotence (50%)
Acne (45%)
Osteoporosis/pathologic fractures (40%)
Virilization (in women) (40%)
Easy bruisability (40%)
Poor wound healing (40%)
Edema (20%)
Increased infections (10%)
Cataracts (5%)

Clinical Manifestations

The clinical signs, symptoms, and common laboratory findings of hypercortisolism seen in patients with Cushing's syndrome are listed in Table 66–4. Typically the obesity is centripetal, with a wasting of the arms and legs; this is distinct from the generalized weight gain seen in idiopathic obesity. Rounding of the face (so-called moon facies) and a dorsocervical fat pad ("buffalo hump") may occur in obesity that is not related to Cushing's syndrome, whereas facial plethora and supraclavicular filling are more specific for Cushing's syndrome. Patients with Cushing's syndrome may have proximal muscle weakness, so the physical finding of inability to stand up from a squat can be quite revealing. Menstrual irregularities often precede other cushingoid symptoms in affected women, whereas affected men frequently complain of poor libido and impotence. Adult-onset acne or hirsutism in women should also raise the suspicion of Cushing's syndrome. The skin striae seen in cushingoid patients are violaceous (purple or dark red), with a width of at least 1 cm. Thinning of the skin on the top of the hands is a very specific sign in younger adults with Cushing's syndrome and should always be examined. Old pictures of patients are extremely helpful for evaluating the progression of the physical stigmata of Cushing's syndrome.

Associated laboratory findings in Cushing's syndrome include elevated plasma alkaline phosphatase levels, granulocytosis, thrombocytosis, hypercholesterolemia, hypertriglyceridemia, and glucose intolerance/diabetes mellitus. Hypokalemic alkalosis is an infrequent finding in patients with Cushing's syndrome and usually occurs in patients with severe hypercortisolism as a result of the ectopic ACTH syndrome.

Diagnosis (Fig. 66–4)

If the history and physical examination findings are suggestive of hypercortisolism, the diagnosis of Cushing's syndrome can usually be established by collecting urine for 24 hours and measuring urinary free cortisol (UFC). UFC excretion reflects plasma unbound cortisol that is filtered and excreted by the kidney. This test is extremely sensitive for the diagnosis of Cushing's syndrome because, in 90% of affected patients, the initial UFC level is greater than 50 µg/24 hours when measured by HPLC or mass spectroscopy cortisol assays. Patients with Cushing's disease usually have UFC levels between 100 and 500 µg/24 hours, whereas patients with the ectopic ACTH syndrome and cortisol-secreting adrenal adenomas or carcinomas frequently have UFC levels greater than 500 µg/24 hours.

Cortisol normally is secreted in a diurnal manner; the plasma concentration is highest in the early morning

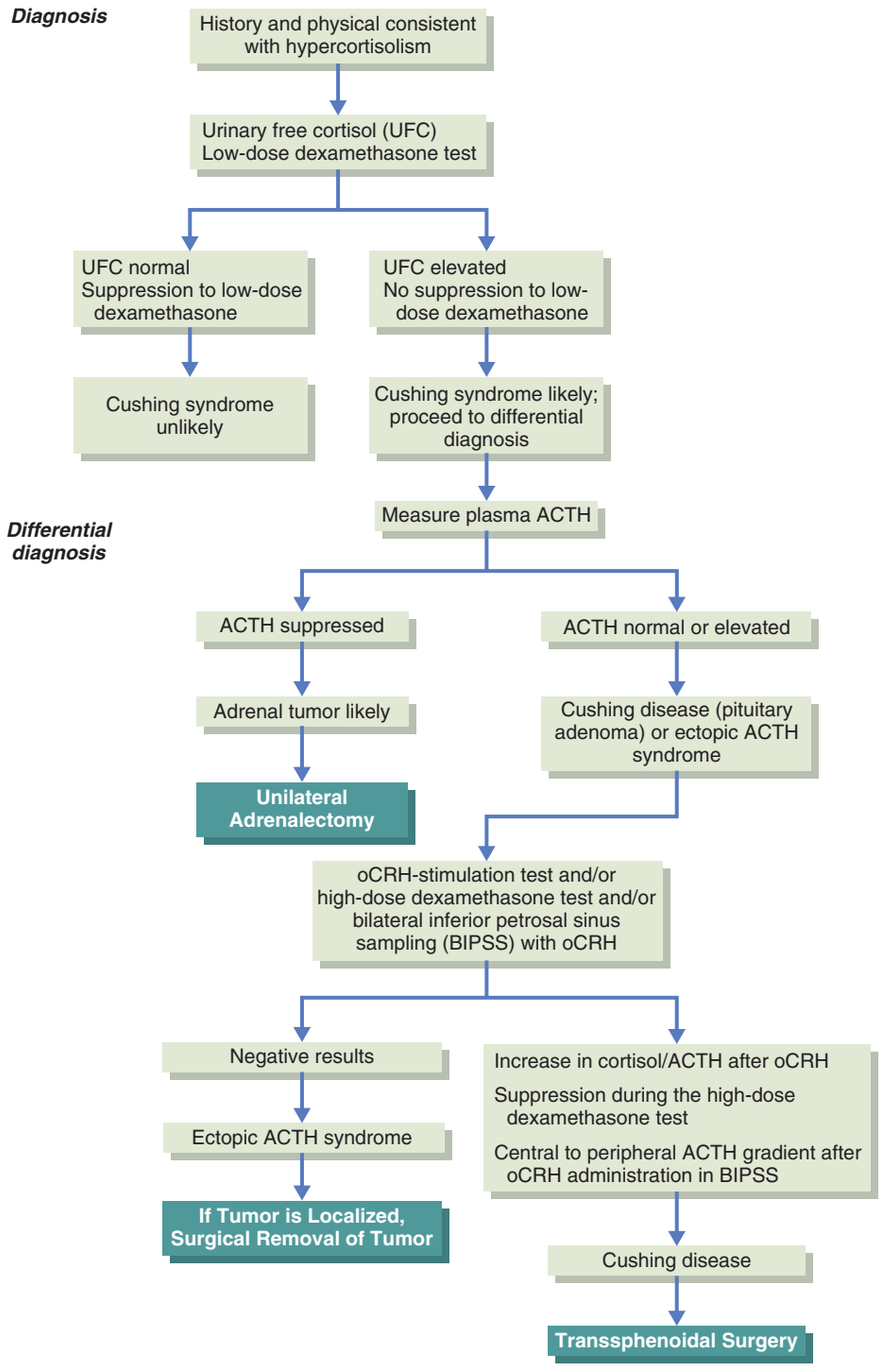


FIGURE 66–4 Flow chart for evaluating a patient with suspected Cushing's syndrome. ACTH = adrenocorticotropic hormone; oCRH = ovine corticotropin–releasing hormone.

(between 6:00 and 8:00 AM) and lowest around midnight. The normal 8:00 AM plasma cortisol level ranges between 8 and 25 µg/dL and declines throughout the day. By 11:00 PM, the values are usually less than 5 µg/dL. Most patients with Cushing's syndrome lack this diurnal variation. Thus, although their morning cortisol levels may be normal, their afternoon or evening concentrations are markedly higher. Late afternoon or night values greater than 50% of the morning values are consistent with Cushing's syndrome. Measurement of random morning cortisol levels is not particularly helpful.

The overnight dexamethasone suppression test can also be used as a screening test to evaluate patients sus-

pected of having hypercortisolism. Dexamethasone, 1 mg, is given orally at 11:00 PM, and plasma cortisol is measured the following morning at 8:00 AM. A morning plasma cortisol level greater than 3 μg/dL suggests hypercortisolism. This test is easy and can be performed in an outpatient setting. The test is fairly sensitive, although some pituitary adenomas are very sensitive to dexamethasone and can suppress cortisol production readily in this test. However, the test produces a significant number of false-positive results, especially in obese and depressed patients, the two patient populations in whom the differentiation from mild Cushing's syndrome may be difficult. For these reasons, collection of urine for measurement of 24-hour UFC excretion is a better screening test.

Differential Diagnosis

Once the diagnosis of Cushing's syndrome is established, the etiology of the hypercortisolism needs to be ascertained. This is accomplished by biochemical studies, which evaluate the feedback regulation of the HPA axis; by venous sampling techniques; and by imaging procedures. Basal ACTH levels are normal or elevated in Cushing's disease and the ectopic ACTH syndrome and are suppressed in primary adrenal Cushing's syndrome.

In the dexamethasone suppression test (Liddle test), 0.5 mg of dexamethasone is given orally every 6 hours for 2 days, followed by 2 mg of dexamethasone every 6 hours for another 2 days. On the second day of the high dosage of dexamethasone, UFC is suppressed to less than 10% of that of the baseline collection in patients with pituitary adenomas but not in patients with the ectopic ACTH syndrome or adrenal cortisol-secreted tumors. Although the Liddle test is often helpful in establishing the etiology of Cushing's syndrome, it has some disadvantages. The test requires accurate measurement of urine collections, often necessitating inpatient hospitalization. In approximately 50% of patients with bronchial carcinoids causing ectopic ACTH production, cortisol secretion is suppressible by high-dose dexamethasone, which yields a false-positive result. In addition, because patients with Cushing's syndrome are often episodic secretors of corticosteroids, considerable variation in daily UFC excretion can occur and false results can be obtained. Therefore, the Liddle test should be interpreted cautiously and other confirmatory tests should be performed before a patient is sent to surgery.

An overnight high-dose dexamethasone suppression test is helpful in establishing the etiology of Cushing's syndrome. In this test, a baseline 8:00 AM cortisol level is measured, and then 8 mg of dexamethasone is given orally at 11:00 PM. At 8:00 AM the following morning, a plasma cortisol measurement is obtained. Suppression, which would occur in patients with pituitary Cushing's disease, is defined as a decrease in plasma cortisol to less than 50% of the baseline level. Few patients with bronchial carcinoid have been examined, so the suppressibility of these tumors by high-dose overnight dexamethasone is not well established.

The ovine CRH (oCRH) test and bilateral simultaneous inferior petrosal sinus sampling are also used to establish the etiology of Cushing's syndrome. Pituitary corticotrophs of normal persons and of patients with pituitary Cushing's disease respond to oCRH by increasing the secretion of ACTH and, therefore, cortisol. Thus the oCRH test cannot be used to distinguish normal persons from patients with pituitary Cushing's disease. Patients with cortisol-secreting adrenal tumors have low or undetectable concentrations of ACTH that do not respond to oCRH. Patients with ectopic ACTH secretion have high basal ACTH levels that do not increase with oCRH. In patients with both the ectopic ACTH syndrome and primary adrenal hypercortisolism, cortisol levels do not change in response to oCRH. Discrepancies between the oCRH and dexamethasone tests necessitate further work-up for ascertainment of the diagnosis.

Bilateral inferior petrosal sinus sampling (BIPSS) is an accurate and safe procedure for distinguishing pituitary Cushing's disease from the ectopic ACTH syndrome. Venous blood from the anterior lobe of the pituitary gland empties into the cavernous sinuses and then into the superior and inferior petrosal sinuses. Venous plasma samples for ACTH determination are obtained from both inferior petrosal sinuses, along with a simultaneous peripheral sample, both before and after intravenous bolus administration of CRH. In baseline measurements, an ACTH concentration gradient of 1.6 or more between a sample from either of the petrosal sinuses and the peripheral sample is strongly suggestive of pituitary Cushing's disease, whereas patients with ectopic ACTH syndrome or adrenal adenomas have no ACTH gradient between their petrosal and peripheral samples. After CRH administration, a central-to-peripheral gradient of more than 3.2 is consistent with pituitary Cushing's disease. The use of CRH has enabled complete distinction of pituitary Cushing's disease from nonpituitary Cushing's syndrome. An ACTH gradient ipsilateral to the side of the tumor is found in 70 to 80% of patients sampled. Although BIPSS requires a radiologist experienced in petrosal sinus sampling, it is currently available at many tertiary care facilities.

Imaging of the pituitary gland by magnetic resonance imaging (MRI) with gadolinium is the preferred procedure for localizing a pituitary adenoma. This test detects approximately 50 to 60% of pituitary ACTH-secreting tumors and can detect many pituitary tumors as small as 3 mm in diameter. About 10% of normal individuals may have a nonfunctioning pituitary adenoma found on pituitary MRI. It is therefore recommended that pituitary imaging not be the sole criterion for the diagnosis of pituitary Cushing's disease.

Treatment

The preferred treatment for all forms of Cushing's syndrome is appropriate surgery. Pituitary Cushing's disease is best treated by transsphenoidal surgery. When the operation is performed by an experienced neurosurgeon, the cure rate is higher than 90%. Transsphenoidal surgery carries very low rates of morbidity and

mortality. Complications (e.g., meningitis, cerebrospinal fluid leakage, optic nerve damage, isolated thyrotropin or growth hormone deficiency) are rare. In patients with the ectopic ACTH syndrome, it is hoped that the tumor is localized by appropriate scans and then removed surgically. A unilateral adrenalectomy is the treatment of choice in patients with a cortisol-secreting adrenal adenoma. Patients with cortisol-secreting adrenal carcinomas should also be managed surgically; however, they have a poor prognosis, with only 20% surviving more than 1 year after diagnosis.

Patients who have failed initial pituitary surgery or have recurrent Cushing's disease may be treated with either pituitary irradiation or bilateral adrenalectomy. Irradiation has more long-term complications than does transsphenoidal surgery, and results in cure in about 60% of patients, but it may take up to 5 years to render a person eucortisolemic. Panhypopituitarism eventually develops in almost all these patients, and so growth hormone, thyroid, gonadal, and even steroid replacement may be needed. A more appealing option for patients with Cushing's disease who remain hypercortisolemic after pituitary surgery is bilateral adrenalectomy, followed by lifelong glucocorticoid and mineralocorticoid replacement therapy. About 10% of patients with Cushing's disease who undergo bilateral adrenalectomy develop Nelson's syndrome (hyperpigmentation and an ACTH-secreting macroadenoma that often causes visual field deficits). The incidence of Nelson's syndrome is reduced if patients have undergone pituitary irradiation. Patients who undergo bilateral adrenalectomy may, on rare occasions, develop adrenal rest tissue leading to recurrence of Cushing's syndrome.

Medical treatment for hypercortisolism may be needed to prepare patients for surgery, in patients who are undergoing or have undergone pituitary irradiation and are awaiting its effects, or in patients who are not surgical candidates or who elect not to have surgery. Ketoconazole, o,p′-DDD, metyrapone, aminoglutethimide, RU-486, and trilostane are the most commonly used agents for adrenal blockade and can be used alone or in combination.

PRIMARY MINERALOCORTICOID EXCESS

Pathophysiology

Increased mineralocorticoid activity is manifested by salt retention, hypertension, hypokalemia, and metabolic alkalosis. The causes of primary aldosteronism (see Table 66–3) are aldosterone-producing adenoma (75%), bilateral adrenal hyperplasia (25%), adrenal carcinoma (1%), and glucocorticoid-remediable hyperaldosteronism (<1%). The adrenal enzyme defects—11β-HSD type II, 11β-hydroxylase, and 17α-hydroxylase deficiencies—and apparent mineralocorticoid excess (from licorice or carbenoxolone ingestion, which inhibits 11β-HSD type II, or from a congenital defect in this enzyme) are also states of functional mineralocorticoid overactivity. Secondary aldosteronism (see Table 66–3) results from overactivation of the renin-angiotensin system.

Primary aldosteronism is usually recognized during evaluation of hypertension or hypokalemia and represents a potentially curable form of hypertension. Up to 5% of patients with hypertension have primary aldosteronism. The patients are usually between 30 and 50 years of age, and the female-to-male ratio is 2:1.

Clinical Manifestations

Hypertension, hypokalemia, and metabolic alkalosis are the main clinical manifestations of hyperaldosteronism; most of the presenting symptoms are related to hypokalemia. Symptoms in mildly hypokalemic patients are fatigue, muscle weakness, nocturia, lassitude, and headaches. If more severe hypokalemia exists, polydipsia, polyuria, paresthesias, and even intermittent paralysis and tetany can occur. Blood pressure can range from being minimally elevated to very high. Retinopathy is mild, and hemorrhages are rarely present. A positive Trousseau or Chvostek sign may occur as a result of metabolic alkalosis.

Diagnosis and Treatment

Initially, hypokalemia in the presence of hypertension must be documented (Fig. 66–5). The patient must have an adequate salt intake and discontinue diuretics before potassium measurement. If hypokalemia is found under these conditions, spironolactone should be stopped (if the patient is taking it) and a morning plasma aldosterone level and a plasma renin activity (PRA) should be measured. A serum aldosterone/PRA ratio >20 ng/dL per ng/mL/hr and a serum aldosterone level >15 ng/dL suggest the diagnosis of hyperaldosteronism.

Once the diagnosis of primary aldosteronism has been demonstrated, it is important to distinguish between an aldosterone-producing adenoma and bilateral hyperplasia, because the former is treated with surgery and the latter is treated medically. In the initial test (a postural challenge), an 8:00 AM supine blood sample is drawn for plasma aldosterone, 18-hydrocorticosterone, renin, and cortisol measurement. The patient then stands for 2 hours, and an upright sample is drawn for measurement of the same hormones. A basal plasma aldosterone level of less than 20 ng/dL is usually found in patients with bilateral hyperplasia, and a value greater than 20 ng/dL suggests the diagnosis of adrenal adenoma. In bilateral hyperplasia, plasma aldosterone often increases as a result of the increase in renin in response to the upright position, whereas, in adenoma, plasma aldosterone levels usually fall as a result of decreased stimulation by ACTH at 10:00 AM, in comparison with 8:00 AM. An 8:00 AM plasma 18-hydroxycorticosterone level of greater than 50 ng/dL that falls with upright posture occurs in most patients with an adenoma, whereas an 8:00 AM level less than 50 ng/dL that rises with upright posture occurs in most patients with bilateral hyperplasia.

A computed tomography (CT) scan of the adrenal glands should be performed to localize the tumor. If a discrete adenoma is seen in one adrenal gland, the contralateral gland is normal, and biochemical test results are consistent with an adenoma, the patient should

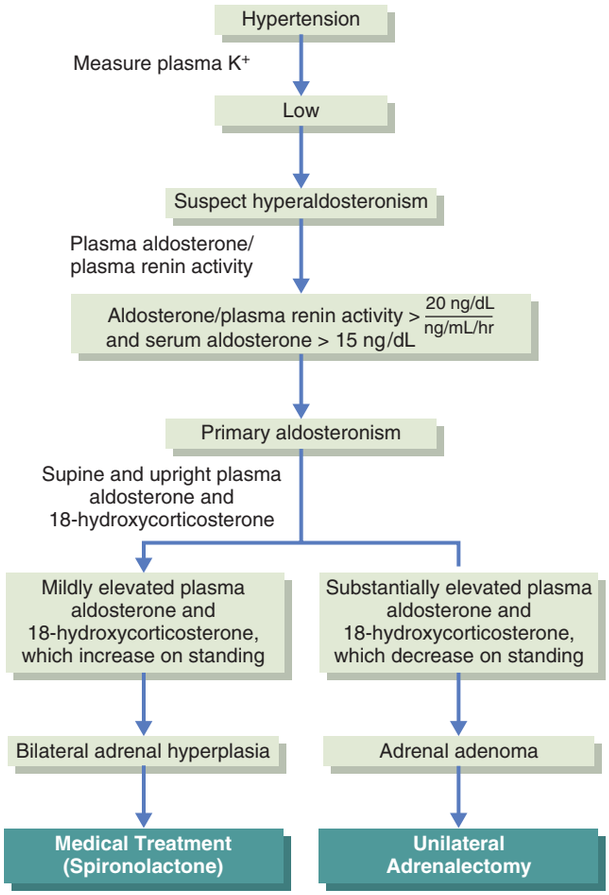


FIGURE 66–5 Flow chart for evaluating a patient with suspected primary hyperaldosteronism.

undergo unilateral adrenalectomy. Patients in whom biochemical study findings are consistent with an adenoma but CT results are consistent with bilateral disease should undergo adrenal venous sampling for aldosterone and cortisol measurement. Patients in whom biochemical and localization study findings are consistent with bilateral hyperplasia should be treated medically, usually with spironolactone. Those in whom biochemical study results are consistent with bilateral hyperplasia should also be evaluated for dexamethasone-suppressible hyperaldosteronism by receiving a trial of dexamethasone, which reverses the hyperaldosteronism in this rare autosomal dominant disorder.

Hyperaldosteronism and hypertension secondary to activation of the renin-angiotensin system can occur in patients with accelerated hypertension, those with renovascular hypertension, those receiving estrogen therapy, and, rarely, patients with renin-secreting tumors. Hyperaldosteronism without hypertension occurs in patients with Bartter's syndrome, those with sodium-wasting nephropathy, those with renal tubular acidosis, and those who abuse diuretics or laxatives.

Adrenal Medullary Hyperfunction

The adrenal medulla synthesizes the catecholamines norepinephrine, epinephrine, and dopamine from the amino acid tyrosine. Norepinephrine, the major catecholamine produced by the adrenal medulla, has predominantly α-agonist actions, causing vasoconstriction. Epinephrine acts primarily on the β-receptors, having positive inotropic and chronotropic effects on the heart, causing peripheral vasodilation, and increasing plasma glucose concentrations in response to hypoglycemia. The action of circulating dopamine is unclear. Whereas norepinephrine is synthesized in the central nervous system and sympathetic postganglionic neurons, epinephrine is synthesized almost entirely in the adrenal medulla. The adrenal medullary contribution to norepinephrine secretion is relatively small. Bilateral adrenalectomy results in only minimal changes in circulating norepinephrine levels, although epinephrine levels are dramatically reduced. Thus hypofunction of the adrenal medulla has little physiologic impact, whereas hypersecretion of catecholamines produces the clinical syndrome of pheochromocytoma.

PHEOCHROMOCYTOMA

Pathophysiology

Although pheochromocytomas can occur in any sympathetic ganglion in the body, more than 90% of pheochromocytomas arise from the adrenal medulla. The majority of extra-adrenal tumors occur in the mediastinum or abdomen. Bilateral adrenal pheochromocytomas occur in about 5% of the cases and may occur as part of familial syndromes. Pheochromocytoma occurs as part of multiple endocrine neoplasia type IIA or IIB. The former (Sipple's syndrome) is marked by medullary carcinoma of the thyroid, hyperparathyroidism, and pheochromocytoma; the latter is characterized by medullary carcinoma of the thyroid, mucosal neuromas, intestinal ganglioneuromas, marfanoid habitus, and pheochromocytoma. Pheochromocytomas are also associated with neurofibromatosis, cerebelloretinal hemangioblastosis (von Hippel-Lindau disease), and tuberous sclerosis.

Clinical Manifestations

Because the majority of pheochromocytomas secrete norepinephrine as the principal catecholamine, hypertension (often paroxysmal) is the most common finding. Other symptoms include the triad of headache, palpitations, and sweating, as well as flushing, anxiety, nausea, fatigue, weight loss, and abdominal and chest pain. These symptoms may be precipitated by emotional stress, exercise, anesthesia, abdominal pressure, or intake of tyramine-containing foods. Orthostatic hypotension can also occur. Wide fluctuations in blood pressure are characteristic, and the hypertension associated with pheochromocytoma usually does not

respond to standard antihypertensive medicines. Cardiac abnormalities, as well as idiosyncratic reactions to medications, may also occur.

Diagnosis and Treatment

Plasma free metanephrine and normetanephrine levels are the best test for confirming or excluding pheochromocytoma because the metabolism of catecholamines to free metanephrines is independent of catecholamine release and can be performed in the absence of hypertension and other symptoms. A plasma free metanephrine level greater than 0.61 nmol/L and a plasma free normetanephrine level greater than 0.31 nmol/L are consistent with the diagnosis of a pheochromocytoma. If the values are only mildly elevated, a clonidine suppression test could be performed; in this test, clonidine (0.3 mg/kg) is given orally, and plasma catecholamines (including free metanephrine and normetanephrine) are measured before and 3 hours after administration. In normal persons, catecholamine levels decrease into the normal range, whereas, in patients with a pheochromocytoma, levels are unchanged or increase. Once the diagnosis of pheochromocytoma is made, a CT scan of the adrenal glands should be performed. Most intra-adrenal pheochromocytomas are readily visible on this scan. If the CT scan is negative, extra-adrenal pheochromocytomas can often be localized by iodine-131–labeled metaiodobenzylguanidine (^{131}I-MIBG), positron emission tomography, octreotide scan, or abdominal MRI.

The treatment of pheochromocytoma is surgical if the lesion can be localized. Patients should undergo preoperative α-blockade with phenoxybenzamine 1 to 2 weeks before surgery. β-Adrenergic antagonists should be used prior to or during surgery. Approximately 5 to 10% of pheochromocytomas are malignant. ^{131}I-MIBG or chemotherapy may be useful, but the prognosis is poor. α-Methyl-*p*-tyrosine (an inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis) may be used to decrease catecholamine secretion from the tumor.

INCIDENTAL ADRENAL MASS

Clinically inapparent adrenal masses are discovered inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to suspicion of adrenal disease and, thus, are commonly known as "incidentalomas." All patients with an incidentaloma should have a 1-mg dexamethasone suppression test and measurement of urine or plasma free metanephrines. Patients with hypertension should also undergo measurement of serum potassium level and plasma aldosterone concentration/plasma renin activity ratio. Surgery should be considered in all patients with functional adrenal cortical tumors that are hormonally active or greater than 5 cm. Tumors not associated with hormonal secretion or less than 5 cm can be followed with repeat imaging and hormonal assessment.

PROSPECTUS FOR THE FUTURE

- An appreciation of the role of tissue-specific, intracellular glucocorticoid excess in common diseases such as osteoporosis, depression, cardiovascular disease, diabetes, and hypertension
- Selective adrenal adenomectomy sparing normal adrenal tissue
- An appreciation of the importance of mild (subclinical) adrenal insufficiency and excess

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