ADRENAL GLAND DISORDERS

The two most common conditions associated with adrenal gland dysfunction: glucocorticoid insufficiency (eg, Addison disease) and glucocorticoid excess (Cushing syndrome). Other adrenal disorders are congenital adrenal hyperplasia, pheochromocytoma, hypoaldosteronism, and hyperaldosteronism.

❖ Physiology, Anatomy, and Biochemistry of The Adrenal Gland

The adrenal gland is located on the upper segment of the kidney. It consists of an outer cortex and an inner medulla. The adrenal medulla secretes the catecholamines: epinephrine (adrenaline) and norepinephrine (noradrenaline), which are involved in the regulation of the sympathetic nervous system. The adrenal cortex consists of three histologically distinct zones. Each zone is responsible for production of different hormones. The outer zona glomerulosa is responsible for the production of the mineralocorticoids: aldosterone, 18-hydroxy-corticosterone, corticosterone, and deoxycorticosterone, the zona fasciculate is the middle layer and produces the glucocorticoid hormone cortisol, and an innermost layer called the zona reticularis produces the androgens: androstenedione, dehydroepiandrosterone (DHEA), and the sulfated form of dehydroepiandrosterone (DHEA-S). Only a small amount of testosterone and estrogen is produced in the adrenal glands. Androstenedione and DHEA are converted in the periphery, largely to testosterone and estrogen.

Adrenal hormone production is controlled by the hypothalamus and pituitary. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus and stimulates secretion of adrenocorticotropic hormone (ACTH; also known as corticotropin) from the anterior pituitary. ACTH in turn stimulates the adrenal cortex to produce cortisol. When sufficient or excessive cortisol levels are reached, a negative feedback is exerted on the secretion of CRH and ACTH, thereby decreasing overall cortisol production. The control of adrenal androgen synthesis also follows a similar negative feedback mechanism.

❖ ADRENAL INSUFFICIENCY

Adrenal insufficiency refers to the inability of the adrenal glands to produce adequate amounts of cortisol for normal physiologic functioning or in times of stress. The condition is classified as primary, secondary, or tertiary, depending on the etiology.

⇨ Pathophysiology

Primary adrenal insufficiency, also known as Addison disease, occurs when the adrenal glands are unable to produce cortisol, aldosterone, and androgen. It may be caused by autoimmune disorder, infection, or infarction.

Secondary adrenal insufficiency occurs as a result of pituitary gland dysfunction, whereby decreased production and secretion of ACTH leads to a decrease in cortisol and androgen synthesis. It may be caused by exogenous steroid use (from chronic suppression), surgery, trauma, infection or infarction.

Tertiary adrenal insufficiency is a disorder of the hypothalamus that results in decreased production and release of CRH, which in turn decreases pituitary ACTH production and release. In contrast to Addison disease, aldosterone production is unaffected in the secondary and tertiary forms of the disease.

⇨ **Clinical Presentation and Diagnosis**

The common complains include **A**bdominal pain (nausea, vomiting), **D**ark skin (hyperpigmentation caused by elevated ACTH concentrations), **S**alt cravings, **O**rthostatic hypotension, weakness and fatigue, weight loss, dehydration, hyponatremia, hyperkalemia, elevated blood nitrogen.

Rapid cosyntropin (synthetic ACTH) stimulation test is the gold standard test for diagnosing primary adrenal insufficiency and blunted increase in cortisol concentrations suggest adrenal insufficiency.

⇨ **Treatment and Outcome Evaluation**

»» ***Chronic Adrenal Insufficiency***

The **general goals of treatment** are to manage symptoms and prevent development of adrenal crisis. *Lifelong glucocorticoid replacement therapy may be necessary for patients with adrenal insufficiency, and mineralocorticoid replacement therapy is usually required for those with Addison disease.*

Glucocorticoids with sufficient mineralocorticoid activity are generally required. However, the addition of a potent mineralocorticoid such as fludrocortisone, along with adequate salt intake, is sometimes needed to prevent sodium loss, hyperkalemia, and intravascular volume depletion. Mineralocorticoid supplementation typically is not indicated for the treatment of secondary or tertiary adrenal insufficiency because aldosterone production is often unaffected. Moreover, patients with secondary or tertiary adrenal insufficiency may only require replacement therapy until the HPA axis recovers.

Hydrocortisone is often prescribed because it most closely resembles endogenous cortisol with its relatively high mineralocorticoid activity and short half-life, and allows the design of regimens that simulate the normal circadian cycle. Other glucocorticoids, however, can be used.

⇨ For the treatment of primary adrenal insufficiency (Addison disease) in adults, 15–25 mg/day of oral hydrocortisone is typically administered in two divided doses, with two-thirds of the dose given in the morning upon awakening to mimic the early

morning rise in endogenous cortisol, and the remaining one-third of the dose given in the late afternoon to avoid insomnia and allow for the lowest concentration in the blood at around midnight. Hydrocortisone may also be given in three doses but this may decrease adherence.

The longer acting glucocorticoids (eg, prednisone, dexamethasone) may provide a more prolonged clinical response thereby avoiding symptom recurrence that can occur at the end of the dosing interval with short-acting agents such as hydrocortisone. Longer-acting agents also may improve adherence in some patients.

Monitor the patient's weight, blood pressure, and serum electrolytes along with symptom resolution and general well-being; adjust dosages accordingly as needed.

Doses of hydrocortisone, dexamethasone, prednisone, and other glucocorticoids may need to be increased or decreased in patients taking cytochrome P-450 (CYP450) 3A4 inducers or inhibitors, respectively.

Glucocorticoid therapy at physiologic replacement doses should not lead to development of Cushing syndrome; however, careful monitoring should still be performed, and the smallest effective dose used. Educate patients regarding the need for increased glucocorticoid dosage during excessive physiologic stress. In addition, administer oral fludrocortisone at a daily dose of approximately 0.05 to 0.2 mg in the morning. Monitor for resolution of hypotension, dizziness, dehydration, hyponatremia, and hyperkalemia; and increase the dose if needed. Conversely, consider decreasing the dose if adverse reactions from mineralocorticoid administration such as hypertension, hypokalemia, fluid retention, and other significant adverse events occur. In patients receiving hydrocortisone, it should be noted that this drug also possesses mineralocorticoid activity. All patients with Addison disease should also maintain adequate sodium intake. Lastly, although controversial, consider giving DHEA 25–50 mg/day (in the morning) to female patients who do not experience an improvement in mood and well-being even with adequate glucocorticoid and mineralocorticoid replacement.

⇨ Patients with secondary and tertiary adrenal insufficiency are treated with oral hydrocortisone or a longer-acting glucocorticoid as described for primary adrenal insufficiency. However, patients with secondary and tertiary adrenal insufficiency may require a lower dose.

❖ HYPERCORTISOLISM (CUSHING SYNDROME)

Cushing syndrome refers to the pathophysiologic changes associated with exposure to supraphysiologic cortisol concentrations (endogenous hypercortisolism) or pharmacologic doses of glucocorticoids (exogenous hypercortisolism). Cushing syndrome from endogenous causes is a rare condition.

⇨ Pathophysiology

Cushing syndrome can be classified as ACTH-dependent or ACTH-independent. ACTH-dependent Cushing syndrome results from ACTH-secreting (or rarely CRH-secreting) adenomas. The term *Cushing disease* refers specifically to Cushing syndrome from an ACTH-secreting pituitary adenoma.

ACTH-independent Cushing syndrome is due either to excessive cortisol secretion by the adrenal glands (independent of ACTH stimulation) or to exogenous glucocorticoid administration.

The plasma ACTH concentration is elevated in ACTH-dependent conditions but not in ACTH-independent conditions because elevated cortisol concentrations suppress pituitary ACTH secretion via negative feedback. ACTH and cortisol concentrations are elevated episodically in ACTH-dependent disease due to random hypersecretion of ACTH.

⇨ Clinical Presentation

Signs and Symptoms (Percent Prevalence)

General appearance:

•• Weight gain and obesity, manifesting as truncal obesity (90%)

•• Rounded and puffy face (“moon facies”) (75%)

•• Dorsocervical (“buffalo hump”) and supraclavicular fat accumulation

•• Hirsutism (75%)

Skin changes from atrophy of dermis and connective tissue:

•• Thin skin

•• Facial plethora (70%)

•• Skin striae (“stretch marks” that are usually red or purple in appearance and greater than 1 cm) (50%)—not common in patients older than 40 years of age

•• Acne (35%)

•• Easy bruising (40%)

•• Hyperpigmentation—typically with ectopic ACTH syndrome

Metabolic:

•• Hyperglycemia that can range from impaired glucose tolerance (75%) to diabetes mellitus (20%–50%)

•• Hyperlipidemia (70%)

•• Polyuria (30%)

Cardiovascular:

•• Hypertension (from mineralocorticoid effect of cortisol) (85%)

•• Peripheral edema

Genitourinary:

•• Menstrual irregularities (typically amenorrhea) (70%) and erectile dysfunction (85%)

⇨ **Diagnosis**

Presence of hypercortisolism through 24-hour urinary free cortisol concentration.

⇨ **Treatment**

The **goal of treatment** in patients with Cushing syndrome is reversal of hypercortisolism and management of the associated comorbidities, including the potential for long-term sequelae such as cardiac hypertrophy.

Surgical resection is considered the treatment of choice for Cushing syndrome from endogenous causes if the tumor can be localized and if there are no contraindications. The treatment of choice for Cushing syndrome from exogenous causes is gradual discontinuation of the offending agent.

»» ***Nonpharmacologic Therapy***

Transsphenoidal pituitary microsurgery is the treatment of choice for Cushing disease.

Pituitary irradiation or bilateral adrenalectomy is usually reserved for patients who are not surgical candidates or for those who relapse or do not achieve complete remission following pituitary surgery.

The treatment of choice in patients with adrenal adenomas is *unilateral laparoscopic adrenalectomy.*

»» ***Pharmacologic Therapy***

Pharmacotherapy is indicated when the ectopic ACTH secreting tumor cannot be localized; to control hypercortisolism to prepare for surgery; and in patients who: (1) are not surgical candidates; (2) have failed surgery or had a relapse after surgery; or (3) have Cushing disease awaiting the onset of effect of pituitary radiation.

The drugs used are classified according to their mechanism and site of action (a- Inhibitors of adrenal steroidogenesis: ketoconazole, metyrapone, etomidate; b- Adrenolytic agent: mitotane; c- Peripheral glucocorticoid antagonist: mifepristone (RU 486)). The most widely used therapeutic class is the adrenal steroidogenesis inhibitors, which can improve hypercortisolism by inhibiting enzymes involved in the biosynthesis of cortisol.

In drug-induced Cushing syndrome, discontinuation of the offending agent is the best management option. However, abrupt withdrawal of the glucocorticoid can result in adrenal insufficiency or exacerbation of the underlying disease.

Glucocorticoid doses less than 7.5 mg/day of prednisone or its equivalent for less than 3 weeks generally would not be expected to lead to suppression of the HPA axis.

PITUITARY GLAND DISORDERS

Physiology of The Pituitary Gland

The pituitary, referred to as the "master gland," is a small endocrine gland located at the base of the brain and is responsible for the regulation of many other endocrine glands and body systems.

Functionally, the gland consists of two distinct sections: the anterior pituitary lobe and the posterior pituitary lobe. The hypothalamus synthesizes two hormones, *oxytocin* and *vasopressin*. These hormones are stored and released from the posterior pituitary lobe. The anterior pituitary lobe is under the control of several releasing and inhibiting hormones secreted from the hypothalamus via a portal vein system. It synthesizes and secretes six major hormones: *ACTH (corticotropin), GH (somatotropin), TSH (thyrotropin), FSH, LH, and prolactin*.

❖ GROWTH HORMONE EXCESS

⇨ Epidemiology and Etiology

Acromegaly affects both genders equally, and the average age of presentation is 44 years. In more than 95% of cases, overproduction of GH is caused by a benign pituitary adenoma, whereas malignant adenomas are rare. Most pituitary adenomas occur spontaneously as a result of a sporadic genetic mutation acquired during life. Although these tumors can produce GH, they more commonly secrete GHRH, resulting in excessive GH and insulin-like growth factor-I (IGF-I) production.

⇨ Pathophysiology

Acromegaly is a rare disorder that manifests gradually over time and typically occurs after fusion of the epiphyses (growth plates) of the long bones. Gigantism refers to GH excess that occurs during childhood before epiphyseal closure and results in excessive linear growth.

⇨ Diagnosis

Diagnosis of acromegaly is based on both clinical and biochemical findings. GH is suppressed after administration of a 75-g oral glucose challenge because postprandial hyperglycemia inhibits secretion of GH. Therefore, measurement of serum GH secretion in response to an oral glucose tolerance test (OGTT) is the primary biochemical test for diagnosing acromegaly. Failure of an OGTT to suppress GH serum concentrations indicates that the patient is diagnosed with acromegaly. In addition to clinical presentation, an elevated IGF-I serum concentration helps to confirm the diagnosis (GH alone is unreliable, given the pulsatile pattern of release in the body).

⇨ Clinical Presentation (Symptoms and Signs)

•• Coarsening of facial features
•• Increased hand volume, ring and shoe size
•• Increased spacing between teeth
•• Increased acne or oily skin with thick, irregular, and patchy skin discoloration
•• Enlarged tongue, nose, lips, and forehead (frontal bossing)
•• Deepening of voice

⇨ Acromegaly Treatment

The goals of therapy are as follows:

•• Reduce fasting morning GH and IGF-I concentrations as close to normal as possible
•• Reduce tumor size to relieve tumor mass effect
•• Prevent tumor recurrence
•• Preserve normal pituitary function
•• Improve clinical signs and symptoms
•• Alleviate significant morbidities
•• Reduce mortality rates to those of the general population

Surgical Treatment

According to the American Association of Clinical Endocrinologists (AACE) treatment guidelines for acromegaly, *surgical resection of the pituitary tumor through transsphenoidal pituitary microsurgery is the treatment of choice for most patients with GH-producing pituitary adenomas*.

Pharmacologic Therapy

Pharmacologic therapy is often necessary for patients in whom surgery is not an option. Somatostatin analogs, GH receptor antagonists, and dopamine agonists are the primary pharmacologic therapies used for the management of acromegaly. Pharmacologic therapy avoids hypopituitarism and other surgical risks.

»» *Somatostatin Analog (GH-Inhibiting Hormone)*

Somatostatin analogs are the mainstay of pharmacotherapy for the treatment of acromegaly when surgery is not appropriate, or as an adjuvant therapy until patients achieve a sustained response to radiation therapy. These agents mimic endogenous somatostatins and bind to somatostatin receptors in the pituitary to cause potent inhibition of GH, insulin, and glucagon secretion. Long term treatment can sustain GH suppression, alleviate soft tissue manifestations, and reduce tumor size.

The long-acting preparations of octreotide and lanreotide are considered the cornerstone of therapy because of improved patient adherence and acceptability.

»» *GH-Receptor Antagonist*

Pegvisomant is the only genetically engineered GH-receptor antagonist that blocks the action of GH. Pegvisomant is indicated for treatment of acromegaly in patients who have an inadequate response to surgery or radiation therapy.

Pegvisomant is recommended in patients who have inadequate response to somatostatin analogs, or as an adjuvant for patients who have only a partial response to somatostatin analogs.

»» *Dopamine Agonists*

Dopamine is one of the neurotransmitters that can increase GH secretion in healthy adults. However, dopamine agonists administered to patients with acromegaly exert the opposite effect and suppress GH release from the tumor.

The first dopamine agonist used for acromegaly, bromocriptine, achieved normal IGF-I concentrations in fewer than 10% of patients. Cabergoline, a selective long-acting dopamine agonist with improved tolerability, can effectively reduce GH and IGF-I concentrations in approximately 40% of patients. *Cabergoline may be considered for patients with modest elevation of GH and IGF-I concentrations less than two times the upper limit of normal. It may also be used as adjunctive therapy in patients unresponsive to monotherapy with somatostatin analogs or pegvisomant*.

»» *Radiation Therapy*

Radiation therapy is an important adjunctive therapy in patients with residual GH excess after surgery or pharmacologic therapy. Treatment involves the use of radiation to destroy rapidly growing tumor cells, and often results in a reduction in tumor size. A major complication of radiation therapy is hypopituitarism, requiring lifelong hormone replacement.

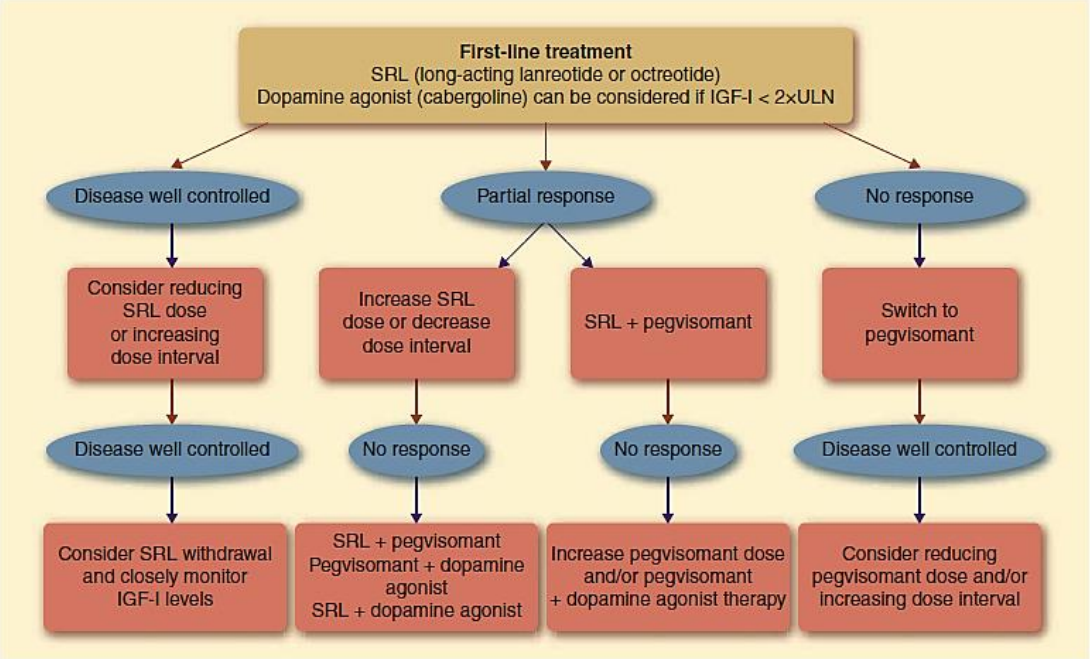

FIGURE 46–4. Medical management of patients with acromegaly.[7] A proposed algorithm for the medical management of acromegaly after surgery or as primary treatment strategy when surgery is inappropriate. Radiation therapy as rescue therapy has not been considered in this algorithm because its use is usually determined by a multidisciplinary management team. IGF-I, insulin-like growth factor I; SRL, somatostatin receptor ligan; ULN, upper limit of normal. (Reprinted by permission from Macmillan Publishers Ltd: Nature

❖ GROWTH HORMONE DEFICIENCY

⇨ Pathophysiology

GH deficiency exists when GH is absent or produced in inadequate amounts. GH deficiency may be congenital, acquired, or result from disruption of the hypothalamus–pituitary axis. GH deficiency may be an isolated condition or occasionally be accompanied by another endocrine disorder (eg, panhypopituitarism).

⇨ Clinical presentation

Delayed growth velocity or short stature, central obesity, immaturity of the face or prominence of the forehead are the most common symptoms.

⇨ Diagnosis

The gold standard for diagnosis of adults with GH deficiency is the insulin tolerance test (ITT), with glucagon as an alternative if GHRH is unavailable. Adults exhibiting a peak GH concentration of less than 5.1 ng/mL (5.1 mcg/L; 230 pmol/L) after two ITT simulation tests would warrant treatment.

⇨ Treatment

The goal of treatment for GH deficiency is to correct associated clinical symptoms. In adults, the goal is to achieve normal physiologic GH concentrations in an attempt to reverse metabolic, functional, and psychological abnormalities.

»»Pharmacologic Therapy

Recombinant GH therapy is the main pharmacologic treatment for GH deficiency in both children and adults. It promotes skeletal, visceral, and general body growth; stimulates protein anabolism; and affects bone, fat, and mineral metabolism. GH therapy requires subcutaneous or intramuscular administrations. Because two thirds of GH secretion normally occurs during sleep, it is recommended to administer GH injections in the evening.

❖ HYPERPROLACTINEMIA

⇨ Epidemiology and Etiology

Hyperprolactinemia affects women of reproductive age more than men. Any medications that antagonize dopamine or stimulate prolactin release can induce hyperprolactinemia. Therefore, it is important to exclude medication-induced hyperprolactinemia from other common causes such as pregnancy, primary hypothyroidism, benign prolactin-secreting pituitary adenoma (prolactinoma), and renal insufficiency.

⇨ Pathophysiology

High prolactin concentrations inhibit the release of gonadotropin-releasing hormone by the hypothalamus and subsequently suppress secretion of LH and FSH from the anterior pituitary. High prolactin concentrations result in reduced gonadal hormone concentrations, often leading to reproductive dysfunction and galactorrhea (inappropriate breast milk production).

⇨ Clinical presentation

Amenorrhea, anovulation, infertility, hirsutism, and acne are present in women, while erectile dysfunction, decrease libido, gynecomastia, and reduce muscle mass are seen in men. Headache, visual disturbance, and bone loss are also present.

⇨ Diagnosis

In combination with clinical symptoms, one or more serum prolactin concentrations greater than 25 ng/mL (25 mcg/L; 1087 pmol/L) will confirm the diagnosis of hyperprolactinemia in women. However, prolactin concentrations greater than 500 ng/mL (500 mcg/L; 21739 pmol/L) are almost always associated with the presence of a macroprolactinoma.

⇨ Treatment

Because hyperprolactinemia is often associated with hypogonadism, the goals for management of hyperprolactinemia are as follows:

•• Normalize prolactin concentration
•• Restore normal gonadal function and fertility
•• Prevent development of osteoporosis

If a pituitary tumor is present:

• Ablate or reduce tumor size to relieve tumor mass effect
• Preserve normal pituitary function
• Prevent progression of pituitary tumor or hypothalamic disease

»» General Approaches to Treatment

Treatment options for the management of hyperprolactinemia include: (a) clinical observation, (b) pharmacologic therapy with dopamine agonists, (c) transsphenoidal pituitary adenomectomy, and (d) radiation therapy. Clinical observation and close monitoring are justifiable in patients with asymptomatic elevation of prolactin.

Dopamine agonists are the first-line treatment of choice for all patients with symptomatic hyperprolactinemia; transsphenoidal surgery and radiation therapy are reserved for patients who are resistant to or severely intolerant of pharmacologic therapy.

»» Pharmacologic Therapy

Dopamine is the principal neurotransmitter responsible for the inhibition of prolactin secretion from the anterior pituitary. Thus, dopamine agonists are the main pharmacologic therapy used for management of hyperprolactinemia. Two dopamine agonists bromocriptine and cabergoline are used for the management of hyperprolactinemia.

Bromocriptine

Bromocriptine directly binds to the D2 dopamine receptors. Treatment with bromocriptine may also restore menses and fertility in women and improve testosterone secretion, sperm count and erectile function in men.

Cabergoline

Cabergoline has a higher affinity for D2 dopamine receptors than bromocriptine and possesses a long half-life, allowing for once- or twice-weekly administration. Cabergoline appears to be better tolerated than bromocriptine, and may be more effective in normalizing prolactin concentrations and restoring menses. It is also effective in treating hyperprolactinemia in patients who are resistant to or intolerant of bromocriptine and in men and women with microprolactinomas and macroprolactinomas.

»» Nonpharmacologic Therapy

In a small number of patients who have failed or are intolerant of dopamine agonists, transsphenoidal adenomectomy may be necessary. Surgical treatment is also considered in patients with non-prolactin-secreting tumors or macroprolactinomas that jeopardize the optic chiasm.