considered to be consistent with Cushing's syndrome. Because of the difficulty of obtaining nighttime plasma cortisol levels, measurement of late-night salivary cortisol has been developed to assess hypercortisolism. This test appears to have a high degree of sensitivity and specificity for diagnosis of Cushing's syndrome. Multiple measurements of UFC or salivary cortisol may be needed either diagnose or exclude Cushing's syndrome, especially in subjects with suggestive signs and symptoms of hypercortisolism.

Differential Diagnosis

Once the diagnosis of Cushing's syndrome is established, the cause of the hypercortisolism needs to be ascertained by biochemical studies that evaluate the feedback regulation of the HPA axis; this can be accomplished by venous sampling and imaging procedures. The initial approach is to measure basal ACTH levels, which are normal or elevated in Cushing's disease and the ectopic ACTH syndrome but are suppressed in primary adrenal Cushing's syndrome. Patients with a suppressed ACTH level can proceed to adrenal imaging studies. To distinguish between Cushing's disease and the ectopic ACTH syndrome, the high-dose or 8-mg overnight dexamethasone suppression test, the ovine CRH (oCRH) test, and bilateral simultaneous inferior petrosal sinus sampling (IPSS) are used.

In the dexamethasone suppression test (Liddle test), 0.5 mg of dexamethasone is given orally every 6 hours for 2 days (low dose), followed by 2 mg of dexamethasone every 6 hours for another 2 days (high dose). On the second day of high-dose dexamethasone, the UFC level will be suppressed to less than 10% of the baseline collection value in patients with pituitary adenomas but not in patients with the ectopic ACTH syndrome or adrenal cortisol-secreting tumors. The Liddle test has some methodologic drawbacks, and results should be interpreted cautiously; other confirmatory tests should be performed before surgery is recommended.

An overnight high-dose dexamethasone suppression test is helpful in establishing the cause of Cushing's syndrome. In this test, a baseline cortisol level is measured at 8:00 AM, 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 occurs in patients with pituitary Cushing's disease, is defined as a decrease in plasma cortisol to less than 50% of the baseline level.

The oCRH test can also be used to establish the cause of Cushing's syndrome, but this test was not available in the United States in 2014.

Bilateral IPSS 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 oCRH. Significant gradients at baseline and after oCRH stimulation between petrosal sinus and peripheral samples suggest pituitary Cushing's disease. 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 the ectopic ACTH syndrome or adrenal adenomas have no ACTH gradient between their petrosal and peripheral samples. After oCRH administration, a central-to-peripheral gradient of more than 3.2 is consistent with pituitary Cushing's disease. The use of oCRH has enabled complete distinction of pituitary from nonpituitary Cushing's syndrome. An ACTH gradient ipsilateral to the side of the tumor is found in 70% to 80% of pituitary Cushing's disease patients sampled. Although this procedure requires an radiologist who is experienced in IPSS, it is available at many tertiary care facilities.

Magnetic resonance imaging (MRI) with gadolinium is the preferred procedure for localizing a pituitary adenoma. In many centers, a *dynamic* MRI is performed; the pituitary is visualized as the gadolinium enters and leaves the gland. Because about 10% of normal individuals are found to have a nonfunctioning pituitary adenoma on pituitary MRI, pituitary imaging should 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 or, in some cases, radiation therapy (see Chapter 62). 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.

In patients with the ectopic ACTH syndrome, the goal is to localize the tumor by appropriate scans so it can be removed surgically. A unilateral adrenalectomy is the treatment of choice in patients with a cortisol-secreting adrenal adenoma. Cortisol-secreting adrenal carcinomas initially should also be managed surgically; however, the prognosis is poor, with only 20% of patients surviving more than 1 year after diagnosis.

Medical treatment for hypercortisolism may be needed to prepare patients who are undergoing or have undergone pituitary irradiation and are awaiting its effects before surgery as well as those who are not surgical candidates or elect not to have surgery. Ketoconazole, *o,p′*-DDD (mitotane), metyrapone, aminoglutethimide, mifepristone, and trilostane are the most commonly used agents for adrenal blockade and can be used alone or in combination. The somatostatin analogue, pasireotide, which decreases ACTH and may decrease tumor size, is a recently FDA-approved drug for treating Cushing's disease.

Primary Mineralocorticoid Excess

Pathophysiology

The causes of primary aldosteronism (see Table 64-3) are aldosterone-producing adenoma (75%), bilateral adrenal hyperplasia (25%), adrenal carcinoma (1%), and glucocorticoid-remediable hyperaldosteronism (<1%). Adrenal enzyme defects (11β-HSD type II, 11β-hydroxylase, and 17α-hydroxylase deficiencies) and apparent mineralocorticoid excess (from ingestion of licorice or carbenoxolone, which inhibit 11β-HSD type II, or from a congenital defect in this enzyme) are also states of functional mineralocorticoid overactivity. Secondary aldosteronism (see Table 64-3) results from an overactive renin-angiotensin system.