Current Concepts

ADRENAL INSUFFICIENCY

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THE hypothalamic–pituitary–adrenal axis has an important role in the body’s ability to cope with stresses such as infections, hypotension, and surgery. The hypothalamus is subject to regulatory influences from other parts of the brain, especially the limbic system. The hypothalamic hormones corticotropin-releasing hormone and arginine vasopressin are important stimulants of corticotropin secretion by the anterior pituitary. In this gland, the action of the hypothalamic hormones is amplified so that a much larger number of corticotropin molecules is secreted. Similarly, in the adrenal cortex the action of corticotropin is amplified; a plasma corticotropin concentration of approximately 25 pg per milliliter (5.5 pmol per liter) results in a plasma cortisol concentration of approximately 20 μg per deciliter (550 nmol per liter). Only 5 to 10 percent of the plasma cortisol, however, is free; the majority is bound to cortisol-binding globulin. Cortisol is of vital importance for the metabolism of carbohydrates and protein and for the control of the immune system, and it controls the secretion of corticotropin, corticotropin-releasing hormone, and vasopressin by negative feedback inhibition mediated by glucocorticoid receptors. Corticotropin also stimulates the secretion of adrenal androgen and, under short-lived conditions, aldosterone.

Destruction of the adrenal cortex itself is the cause of primary adrenal insufficiency. If autoimmune adrenalitis is the underlying disorder, the medulla is usually spared. However, the synthesis of epinephrine in the adrenal medulla depends on the presence of high local cortisol concentrations. For this reason, adrenomedullary dysfunction or destruction (e.g., in tuberculous adrenalitis) may aggravate hypoglycemia in patients with primary adrenal insufficiency.

Secondary adrenal insufficiency may occur as a result of pituitary or hypothalamic disease. Because aldosterone secretion is more dependent on angiotensin II than on corticotropin, aldosterone deficiency is not a problem in hypopituitarism. Selective aldosterone deficiency can occur as a result of depressed renin secretion and angiotensin II formation.

CAUSES

Primary Adrenal Insufficiency

Primary and secondary adrenal insufficiency are hormone deficiency syndromes with many possible causes (Table 1). The prevalence of chronic primary adrenal insufficiency (Addison’s disease) has been reported to be 39 to 60 per million population. The mean age at diagnosis in adult patients is 40 years (range, 17 to 72). The most common cause was formerly tuberculous adrenalitis, but now it is autoimmune adrenalitis (slow destruction of the adrenal cortex by cytotoxic lymphocytes), sometimes accompanied by autoimmune thyroid disease and other autoimmune endocrine deficiencies (autoimmune polyclaglandular syndromes). Most patients with the adult form (type II) of the polyclaglandular syndrome (Table 1) have antibodies against the steroidogenic enzyme 21-hydroxylase, but their role in the pathogenesis of autoimmune adrenalitis is uncertain. Adrenomyeloneuropathy is an increasingly recognized cause of adrenal insufficiency in young men. It is an X-linked recessive disorder of the metabolism of long-chain fatty acids characterized by spastic paralysis as well as adrenal insufficiency; the latter may occur either before or after the neurologic disease.

Recently discovered causes of primary adrenal insufficiency are the acquired immunodeficiency syndrome (AIDS), in which the adrenal gland may be destroyed by a variety of opportunistic infectious agents in up to 5 percent of patients in late stages of the disease, and the so-called antiphospholipid syndrome, which is characterized by multiple arterial and venous thromboses, accompanied and perhaps caused by circulating antiphospholipid antibodies. Other causes are listed in Table 1. All causes of primary adrenal insufficiency involve the adrenal cortex as a whole, resulting in a deficiency of cortisol and aldosterone (plus adrenal androgen), although the severity of the deficiencies may vary. An exception in this regard is the syndrome of isolated glucocorticoid deficiency. It is due to adrenal unresponsiveness to corticotropin; responsiveness to angiotensin II is normal.

Secondary Adrenal Insufficiency

The causes of secondary adrenal insufficiency are also listed in Table 1. Among patients with pituitary
or hypothalamic disorders, especially space-occupying lesions, few have only adrenal insufficiency. Other hormonal axes are usually involved, and neurologic or ophthalmologic symptoms may accompany, precede, or follow adrenal insufficiency. Rare patients, however, have isolated corticotropin deficiency with adrenal failure, such as those with isolated deficiency of corticotropin-releasing hormone or women with lymphocytic hypophysitis. A much more frequent type of isolated secondary adrenal insufficiency is that induced by glucocorticoid therapy, which is mainly due to prolonged suppression of the production of corticotropin-releasing hormone.

**CLINICAL MANIFESTATIONS**

**Chronic Adrenal Insufficiency**

Many of the symptoms and signs of primary and secondary adrenal insufficiency are similar (Table 2), but there are some characteristic symptoms and signs of one or the other that should focus suspicion on either the adrenal cortex or the pituitary and hypothalamus. Most of the symptoms of cortisol deficiency—fatigue, weakness, listlessness, orthostatic dizziness, weight loss, and anorexia—are nonspecific and usually occur insidiously. Some patients initially present with gastrointestinal symptoms such as abdominal cramps, nausea, vomiting, and diarrhea. In other patients the disease may be misdiagnosed as depression or anorexia nervosa. Decreased libido and potency as well as amenorrhea may occur in primary as well as secondary adrenal insufficiency. Although orthostatic hypotension is more marked in primary than secondary adrenal insufficiency because of aldosterone deficiency and hypovolemia, it does occur in the latter as a result of the decreased expression of vascular catecholamine receptors.

The most specific sign of primary adrenal insufficiency is hyperpigmentation of the skin and mucosal surfaces, which is due to the high plasma corticotropin concentrations that occur as a result of decreased cortisol feedback. On the other hand, pallor may occur in patients with corticotropin deficiency. Another specific symptom of primary adrenal insufficiency is a craving for salt. Thinning of axillary and pubic hair is common in patients with hypothalamic–pituitary disease, but it is not usually found in patients with isolated corticotropin deficiency. Postmenopausal women with Addison’s disease may also lose hair in androgen-dependent locations. In young patients suspected of having adrenal insufficiency, delayed growth and puberty would point to the presence of hypothalamic–pituitary disease, as would headaches, visual disturbances, or diabetes insipidus in patients of any age.

In a patient with fatigue or other nonspecific symptoms, screening laboratory tests are often per-
formed. The following abnormalities, encountered in a varying percentage of patients with adrenal insufficiency, can lead to the diagnosis: hyponatremia (frequent), hyperkalemia, acidosis, slightly elevated plasma creatinine concentrations (the latter three in primary adrenal insufficiency), hypoglycemia, hypercalcemia (rare), mild normocytic anemia (due to cortisol and androgen deficiency), lymphocytosis, and mild eosinophilia. Although hyponatremia occurs in both primary and secondary adrenal insufficiency, its pathophysiology in the two disorders differs. In primary adrenal insufficiency it is mainly due to aldosterone deficiency and sodium wasting, whereas in secondary adrenal insufficiency it is due to cortisol deficiency, increased vasopressin secretion, and water retention.

**Acute Adrenal Insufficiency**

Considering the possibility of adrenal insufficiency is of crucial importance in critically ill patients. If the diagnosis is missed, the patient will probably die. Adrenal insufficiency should be suspected in the presence of unexplained catecholamine-resistant hypotension, especially if the patient has hyperpigmentation, vitiligo, pallor, scanty axillary and pubic hair, hyponatremia, or hyperkalemia. In addition, the possibility of spontaneous adrenal insufficiency due to adrenal hemorrhage and adrenal-vein thrombosis (Table 1) must be considered in a patient with upper abdominal or loin pain, abdominal rigidity, vomiting, confusion, and arterial hypotension. In such patients, a blood sample for the measurement of plasma cortisol and corticotropin should be obtained, a short corticotropin test (see below) should be performed, and immediate high-dose cortisol therapy should be considered or instituted. A plasma cortisol value in the normal range does not rule out adrenal insufficiency and obviates the need for other tests, whereas concentrations of less than 10 years' duration.

**Laboratory Evaluation of Adrenal Function**

**Basal Hormone Measurements**

In patients in whom adrenal insufficiency is merely to be ruled out, plasma cortisol can be measured between 8 and 9 a.m. (Table 3). In interpreting the results, it is important to remember that estrogen therapy raises plasma concentrations of corticosteroid-binding globulin and, therefore, cortisol concentrations. According to the normal reference range shown in Table 3, morning plasma cortisol concentrations of \( < 3 \) μg per deciliter (83 nmol per liter) are indicative of adrenal insufficiency and obviate the need for other tests, whereas concentrations of \( < 19 \) μg per deciliter (525 nmol per liter) rule out the disorder. All other patients need dynamic testing.

If the patient is thought to have primary adrenal insufficiency, basal plasma corticotropin and cortisol can be measured. In patients with primary adrenal insufficiency, plasma corticotropin concentrations invariably exceed 100 pg per milliliter (22 pmol per liter), even if the plasma cortisol concentration is in the normal range. Normal plasma corticotropin values rule out primary, but not mild secondary, adrenal insufficiency (Fig. 1). Measurement of basal plasma corticotropin can be used to differentiate between primary and secondary adrenal insufficiency (Fig. 1). Basal plasma aldosterone concentrations are low or at the lower end of normal values in primary adrenal insufficiency, whereas the plasma renin activity or concentration is increased because of the sodium wasting.

**Adrenal Autoantibody Tests**

The standard test for detecting antibodies against the adrenal cortex is the indirect immunofluorescence technique used on sections of bovine or human adrenal cortex cut in a cryostat. The sensitivity of this test in patients with autoimmune adrenalitis is about 70 percent, and the specificity is very high. Recently, a simple binding assay that uses radiolabeled recombinant human 21-hydroxylase was described. Its sensitivity and specificity were higher than those of the older assay in patients with autoimmune adrenalitis, especially in those with disease of less than 10 years' duration. With a similar technique, antibodies against the adrenal side-chain–cleavage enzyme and 17-hydroxylase were detected less often in autoimmune adrenalitis than were antibodies against 21-hydroxylase.

**Corticotropin Stimulation Tests**

The short corticotropin stimulation test, which uses 250 μg of cosyntropin \( (\alpha1-24\text{-corticotropin}) \), is the most commonly used test for the diagnosis of primary adrenal insufficiency. The corticotropin can be given intravenously or intramuscularly before 10 a.m., and plasma cortisol is measured before and 30 or, preferably, 60 minutes after the injection. Adrenal function is considered to be normal if the basal or the post-corticotropin plasma cortisol concentration is at least 18 μg per deciliter (500 nmol per liter), even if the plasma cortisol concentration is in the normal range.
Table 3. Hormonal-Function Tests for Adrenal Insufficiency.*

<table>
<thead>
<tr>
<th>Reason for Test</th>
<th>Hormone Test</th>
<th>Normal Range</th>
<th>Interpretation Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rule out adrenal insufficiency</td>
<td>Measurement of basal plasma cortisol between 8 and 9 a.m.</td>
<td>Plasma cortisol, 6–24 µg/dl</td>
<td>If plasma cortisol ≤3 µg/dl, adrenal insufficiency confirmed; if &gt;19 µg/dl, adrenal insufficiency ruled out</td>
<td>Grinspoon and Biller23</td>
</tr>
<tr>
<td></td>
<td>Conventional corticotropin test</td>
<td>Basal or post-corticotropin plasma cortisol, ≥20 µg/dl</td>
<td>Insufficient increase in plasma cortisol in most cases of adrenal insufficiency</td>
<td>May et al.,28 Oelkers et al.,29 Grinspoon and Biller23</td>
</tr>
<tr>
<td></td>
<td>Low-dose corticotropin test</td>
<td>Basal or post-corticotropin plasma cortisol, ≥18 µg/dl</td>
<td>Probably insufficient increase in plasma cortisol in all cases of adrenal insufficiency</td>
<td>Tordjman et al.,24 Broide et al.25</td>
</tr>
<tr>
<td>Primary adrenal insufficiency suspected</td>
<td>Conventional corticotropin test</td>
<td>Basal or post-corticotropin plasma cortisol, ≥20 µg/dl</td>
<td>No increase in plasma cortisol or adrenal insufficiency</td>
<td>May et al.,28 Grinspoon and Biller23</td>
</tr>
<tr>
<td></td>
<td>Measurement of basal plasma cortisol and corticotropin</td>
<td>Plasma cortisol, 6–24 µg/dl; plasma corticotropin, 5–45 pg/ml</td>
<td>Plasma cortisol low or in the low-normal range, but plasma corticotropin always &gt;100 pg/ml in primary adrenal insufficiency</td>
<td>Blevins et al.,28 Oelkers et al.26</td>
</tr>
<tr>
<td>Secondary adrenal insufficiency suspected</td>
<td>Insulin-induced hypo-glycemia</td>
<td>Plasma glucose, &lt;40 mg/dl; plasma cortisol, ≥20 µg/dl</td>
<td>Little or no increase in plasma cortisol in secondary adrenal insufficiency</td>
<td>Grinspoon and Biller,21 Pavor et al.27</td>
</tr>
<tr>
<td></td>
<td>Short metyrapone test</td>
<td>Plasma 11-deoxycortisol at 8 hr, ≥7 µg/dl; plasma corticotropin, ≥150 pg/ml</td>
<td>Insufficient increase in plasma corticotropin (very sensitive) and 11-deoxycortisol in secondary adrenal insufficiency</td>
<td>Fiad et al.,29 Oelkers,30 Steiner et al.30</td>
</tr>
<tr>
<td></td>
<td>Corticotropin-releasing hormone test</td>
<td>Depends on dose, time of administration, and species of origin (human, ovine) of corticotropin releasing hormone</td>
<td>Insufficient increase in plasma corticotropin and cortisol in secondary adrenal insufficiency</td>
<td>Grinspoon and Biller,21 Schlaeghe et al.,21 Trainer et al.22</td>
</tr>
<tr>
<td></td>
<td>Low-dose corticotropin test</td>
<td>Basal or corticotropin-stimulated plasma cortisol, ≥18 µg/dl</td>
<td>Probably insufficient stimulation in all cases of secondary adrenal insufficiency</td>
<td>Tordjman et al.,24 Broide et al.25</td>
</tr>
<tr>
<td>Secondary adrenal insufficiency due to hypothalamic disease suspected</td>
<td>Insulin-induced hypo-glycemia</td>
<td>Plasma glucose, &lt;40 mg/dl; plasma cortisol, ≥20 µg/dl</td>
<td>Little or no increase in plasma cortisol in secondary adrenal insufficiency due to hypothalamic disease</td>
<td>Grinspoon and Biller,21 Pavor et al.27</td>
</tr>
<tr>
<td></td>
<td>Corticotropin-releasing hormone test on different day</td>
<td>Transient increase in plasma corticotropin and cortisol</td>
<td>Prolonged, exaggerated plasma corticotropin response; weak plasma cortisol response in hypothalamic disease</td>
<td>Grinspoon and Biller,21 Orth33</td>
</tr>
</tbody>
</table>

*To convert values for cortisol to nanomoles per liter, multiply by 27.6; to convert values for corticotropin to picomoles per liter, multiply by 0.22; to convert values for 11-deoxycortisol to nanomoles per liter, multiply by 28.9; and to convert values for glucose to millimoles per liter, multiply by 0.055.

per liter)23 or, preferably, at least 20 µg per deciliter (550 nmol per liter).3 Most physicians use the highest plasma cortisol value (before or after the injection of corticotropin) as the criterion of normality and not the absolute increase in plasma cortisol after the injection of corticotropin. In patients with primary adrenal insufficiency, exogenous corticotropin does not stimulate cortisol secretion, because the adrenal cortex is maximally stimulated by endogenous corticotropin. In patients with secondary adrenal insufficiency, plasma cortisol increases little or not at all after the administration of corticotropin, because of adrenocortical atrophy. In patients with secondary adrenal insufficiency that is mild or of recent onset, however, the test may be normal even though the results of the insulin or metyrapone tests (see below) are abnormal.28,35,36 The results may be normal because of the large dose of corticotropin that is given (250 µg); in normal subjects, as little as 5 µg of cosyntropin or 10 µg of human corticotropin stimulates the adrenal cortex almost maximally.24,25 On the basis of these observations, the recently described low-dose short corticotropin stimulation test (0.5 µg per square meter of body-surface area or 1 µg intravenously)24,25 should be suitable for detecting mild secondary adrenal insufficiency, such as may occur in patients with asthma who are taking an inhaled glucocorticoid.25,26 The normal response in those tests is a plasma cortisol concentration of at least 18 µg per deciliter at baseline or 20 to 60 minutes after the corticotropin injection.24,25 If the test result is slightly abnormal — e.g., a maximal post-corticotropin plasma cortisol value of 17 µg per deciliter (470 nmol per liter) or a basal plasma cortisol value of 16 µg per deciliter (442 nmol per liter) with no increase after corticotropin injection — an insulin or a metyrapone test should be performed, because experience with the low-dose corticotropin test is still limited. The plasma hormone values used to define normal and ab-
normal findings in this test and in those described in the next section are not absolute, and clinical judgment must be used in interpreting them.

**Tests Involving Insulin-Induced Hypoglycemia, Metyrapone, and Corticotropin-Releasing Hormone**

Three tests are used to evaluate patients with suspected secondary adrenal insufficiency (Table 3).4,23 Hypoglycemia (plasma glucose concentration, <40 mg per deciliter [2.2 mmol per liter]) induced by the intravenous injection of 0.1 to 0.15 U of regular insulin per kilogram of body weight stimulates the entire hypothalamic–pituitary–adrenal axis. The test should be performed in the morning. Plasma glucose and cortisol (in some centers also corticotropin) are measured before and 15, 30, 45, 60, 75, and 90 minutes after the injection of insulin. Signs of activation of the sympathetic nervous system (tachycardia, sweating, and tremor) should occur. In normal subjects, the plasma cortisol concentration increases to at least 20 μg per deciliter27 or 18 μg per deciliter.23 As for the high-dose short corticotropin test, use of the higher cutoff point (≥20 μg per deciliter) is preferable because it minimizes underdiagnosis of adrenal insufficiency. With some exceptions,38 all degrees of adrenal insufficiency are detected by this test. However, the test is expensive, contraindicated in patients with coronary heart disease or seizures, and unnecessary in patients known to have low basal plasma cortisol concentrations. Concomitant measurements of plasma corticotropin increase the sensitivity of the test.29

The short metyrapone test is based on measuring the plasma concentration of the cortisol precursor 11-deoxycortisol and cortisol at 8 a.m. after the oral administration of the adrenal 11-hydroxylase inhibitor metyrapone (30 mg per kilogram, given with a snack) at midnight. In normal subjects, the plasma 11-deoxycortisol concentration increases to at least 7 μg per deciliter (200 nmol per liter).23,28,30 In patients with adrenal insufficiency, the increase is smaller and is related to the severity of the corticotropin deficiency. However, an insufficient increase in plasma 11-deoxycortisol is indicative of adrenal insufficiency only if the simultaneously measured plasma cortisol concentration is less than 8 μg per deciliter (230 nmol per liter). Otherwise, the inhibition of 11-hydroxylase by metyrapone is insufficient. The metyrapone test is more sensitive for detecting mild secondary adrenal insufficiency if both plasma corticotropin and 11-deoxycortisol are measured.29,30

Corticotropin-releasing hormone (1 μg per kilogram or 100 μg intravenously) stimulates corticotropin secretion less strongly than does insulin-induced hypoglycemia or metyrapone.31-33 After corticotropin-releasing hormone is injected, plasma corticotropin and cortisol should be measured every 15 minutes for 60 to 90 minutes; the plasma corticotropin value usually peaks at 15 or 30 minutes, and the cortisol value usually peaks 30 or 45 minutes after the injection of corticotropin-releasing hormone.32 This test is less well standardized than are the insulin and metyrapone tests, but its results correlate well with those of the insulin test in patients with glucocorticoid-induced corticotropin deficiency.31 A special aspect of this test is that it can distinguish between corticotropin deficiency and deficiency of corticotropin-releasing hormone.33

**Radiologic Evaluation**

Radiologic procedures should be ordered only after an endocrinologic diagnosis established by hormone tests. An exception to this rule is a case in which a patient is suspected of having a pituitary or hypothalamic tumor (on the basis of headache or visual disturbance); such patients should undergo magnetic resonance imaging. The results of magnetic resonance imaging of the hypothalamic–pituitary region are superior to those of computed tomography (CT) in most situations connected with secondary adrenal insufficiency. Analysis of sagittal and coronal sections provides the most information.12,39 A CT or lateral skull radiograph also should be obtained if bone invasion by a pituitary tumor is suspected or if calcifications in a craniopharyngioma are to be demonstrated.
In patients with primary adrenal insufficiency caused by autoimmune adrenalitis or adrenomyeloneuropathy, imaging of the adrenal glands is not necessary. In all other cases, a CT scan of the adrenal glands should be performed for the differential diagnosis. Marked enlargement of the adrenal glands with or without calcifications in patients with tuberculous adrenal insufficiency is usually a sign of active infection and an indication for treatment with antituberculous drugs.40,41 The adrenal glands are also enlarged in patients with adrenal insufficiency caused by fungal infections, metastatic cancer, lymphoma, and AIDS.3,4 A CT-guided fine-needle biopsy of adrenal masses can be helpful in the differential diagnosis.

TREATMENT

Replacement Therapy

Patients with symptomatic adrenal insufficiency, but not those with minimal abnormalities on hormone tests, should be treated with hydrocortisone or cortisone in the early morning and afternoon. The usual initial dose is 25 mg of hydrocortisone (divided into doses of 15 and 10 mg) or 37.5 mg of cortisone (divided into doses of 25 and 12.5 mg), but the daily dose may be decreased to 20 or 15 mg of hydrocortisone as long as the patient’s well-being and physical strength are not reduced. The goal should be to use the smallest dose that relieves the patient’s symptoms, in order to prevent weight gain and osteoporosis.2,4,21,42 Measurements of urinary cortisol may help determine the appropriate dose of hydrocortisone.

Patients with primary adrenal insufficiency should also receive fludrocortisone, in a single daily dose of 50 to 200 µg, as a substitute for aldosterone. The dose can be guided by measurements of blood pressure, serum potassium, and plasma renin activity, which should be in the upper-normal range.19,26 All patients with adrenal insufficiency should carry a card containing information on current therapy and recommendations for treatment in emergency situations, and they should also wear some type of warning bracelet or necklace, such as those issued by Medic Alert.21 Patients must be advised to double or triple the dose of hydrocortisone temporarily whenever they have any febrile illness or injury, and should be given ampules of glucocorticoid for self-injection or glucocorticoid suppositories to be used in the case of vomiting.43

Emergency Therapy

Patients with acute adrenal insufficiency need immediate treatment with a high dose of intravenous hydrocortisone (100 mg as a bolus dose followed by an infusion of 100 to 200 mg given over a period of 24 hours). Patients with hypovolemia and hyponatremia should be given isotonic saline intravenously. The volume needed may be large and should be supplemented with glucose. In most patients, oral therapy can be resumed in one or two days.3,4,21

CONCLUSIONS

Primary adrenal insufficiency can become a life-threatening disorder in any stressful situation, since cortisol secretion cannot be increased at all. The symptoms of secondary adrenal insufficiency as part of hypothalamic or pituitary disease can range from severe to absent. Mild secondary adrenal insufficiency can be detected with sensitive hormone tests and does not usually require regular treatment with hydrocortisone. However, patients should temporarily be treated with hydrocortisone in stressful situations, such as during major surgery. Acute adrenal insufficiency in a patient with a previously unknown adrenal disorder is a demanding diagnostic challenge. The patient will die if the diagnosis is not made in time. On the other hand, treatment of an adrenal crisis with full recovery of a dangerously ill patient within a few days is one of the greatest achievements of modern medicine.


