Clinics in Dermatology (2006) **24**, 276–280

Clinics in Dermatology

Addison's disease

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Abstract Addison's disease, or primary adrenal insufficiency, results in glucocorticoid and mineralocorticoid deficiency. Orthostatic hypotension, fever, and hypoglycemia characterize acute adrenal crisis, whereas chronic primary adrenal insufficiency presents with a more insidious history of malaise, anorexia, diarrhea, weight loss, joint, and back pain.
The cutaneous manifestations include darkening of the skin especially in sun-exposed areas and hyperpigmentation of the palmar creases, frictional surfaces, vermilion border, recent scars, genital skin, and oral mucosa.
Measurement of basal plasma cortisol is an insensitive screening test. Synthetic adrenocorticotropin 1-24 at a dose of 250 μg works well as a dynamic test. Elevated plasma levels of adrenocorticotropin and renin confirm the diagnosis.
Treatment involves replacement of the deficient hormones.
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Introduction

Addison's disease, or primary adrenal insufficiency, was first described by Addison in 1855 as follows: "the characteristic features... are general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connexion with a diseased condition of the suprarenal capsules."[1] Addison's elegant monograph detailed the clinical features of this disorder at a time when the function of the adrenal glands was unknown; the discovery of the essential nature of the adrenal glands and the isolation of adrenal hormones occurred later.

We now recognize that the disorder described by Addison represents a primary inability of the adrenal cortex to synthesize and secrete glucocorticoid (primarily cortisol) and mineralocorticoid (primarily aldosterone) hormones. In response, the pituitary corticotropes increase secretion of adrenocorticotropin (ACTH) in an effort to stimulate the adrenal glands. The pathophysiology of Addison's disease thus contrasts with secondary adrenal insufficiency that occurs as a result of ACTH deficiency. In the latter setting, glucocorticoid production is insufficient, but mineralocorticoid production is essentially normal, as it is regulated primarily by salt and water metabolism rather than ACTH.

Primary and secondary adrenal insufficiency share many clinical features (see below). However, they differ in that only primary adrenal insufficiency is characterized by mineralocorticoid deficiency and by hyperpigmentation. Hyperpigmentation is related to melanocyte stimulation by ACTH and α-melanocyte-stimulating hormone. ACTH is a more potent stimulator of melanogenesis than α-melanocyte-stimulating hormone.[2] Without treatment, adrenal insufficiency can be fatal[1,3]; hence, early recognition is

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0738-081X/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.clindermatol.2006.04.006

extremely important. In this regard, cutaneous manifestations play an important role in suggesting primary adrenal disease. Secondary forms of adrenal insufficiency are caused by pituitary or hypothalamic disorders or by withdrawal from exogenous steroids and are not considered further here.[4]

Clinical presentation

The characteristic clinical presentation of acute primary adrenal insufficiency includes orthostatic hypotension, agitation, confusion, circulatory collapse, abdominal pain, and fever. These features are most likely to be caused by hemorrhage or metastasis or precipitated by acute infection and can lead to death if not treated. In contrast, the typical history and clinical findings of chronic primary adrenal insufficiency include a longer history of malaise, fatigue, anorexia, weight loss, joint and back pain, and darkening of the skin (see below). Patients may crave salt and develop unusual food preferences, such as drinking the brine surrounding pickles. Associated biochemical features for both presentations include hyponatremia, hypoglycemia, hyperkalemia, unexplained eosinophilia, and mild prerenal azotemia.[5]

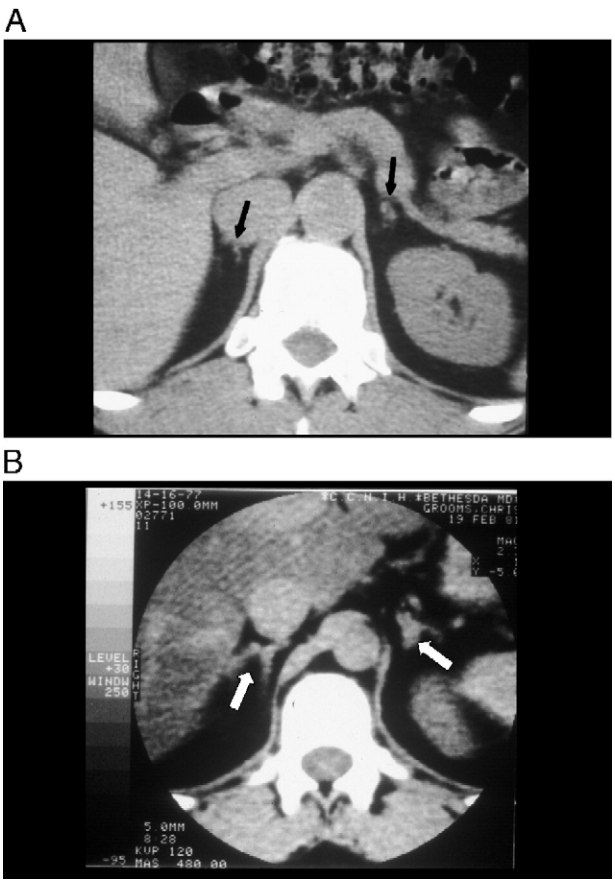

Fig. 1 A, Atrophic adrenal glands (arrows) typical of primary autoimmune adrenal failure. B, Normal size adrenal glands (arrows).

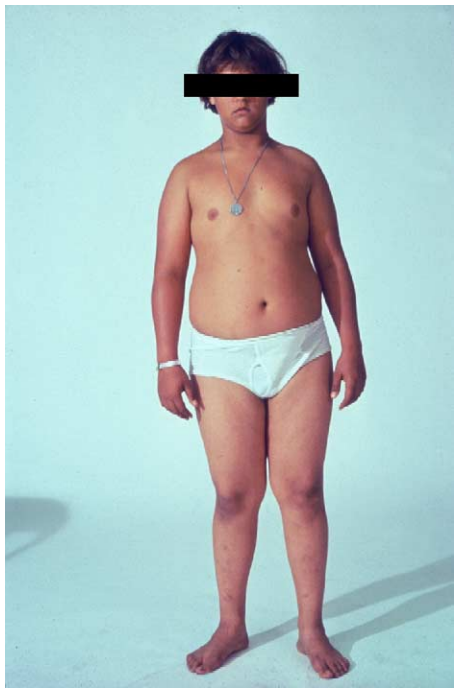

Fig. 2 Generalized bronzing of skin with hyperpigmentation of knees.

The underlying causes of primary adrenal insufficiency may contribute to the clinical presentation. Broadly speaking, the etiologies are either infiltrative disorders that invade the normal cortex or destructive disorders that specifically attack or disrupt the adrenal cells. The first category includes infectious causes, especially tuberculosis, which is the most common cause of adrenal insufficiency in the developing world, as well as other fungal infections (histoplasmosis, coccidiomycosis, blastomycosis), in which caseating granulomas invade normal adrenal tissue.[3,6] End-stage AIDS-associated opportunistic infections such as cytomegalovirus or *Mycobacterium avium-intracellulare* may reduce adrenal function.[7] The infectious disorders are often accompanied by clinical manifestations of each disease. Adrenal tissue may be replaced by bilateral metastases (most commonly primary carcinoma of the lung, breast, kidney, or gut, or primary lymphoma), although adrenal insufficiency is uncommon.[8] Intra-adrenal hemorrhage also may lead to insufficient steroidogenesis, usually in a hospitalized patient receiving long-term prophylactic anticoagulation, and may present with back pain.[9] Adrenal glands affected by these disorders tend to be large on computerized tomography scan.

Autoimmune destruction is the most common etiology of primary adrenal insufficiency in industrialized countries[10] and may occur alone or, rarely, in association with inherited autoimmune polyglandular syndromes. These latter syndromes tend to present either in childhood (type 1), in association with hypoparathyroidism and mucocutaneous candidiasis,[11] or in adulthood (type 2), in association with insulin-dependent diabetes mellitus, autoimmune thyroid

disease, alopecia areata, and vitiligo.[12] The presence of the associated conditions suggests the polyglandular syndromes. Adrenal glands affected by autoimmune destruction are small on computerized tomography scan (Fig. 1).

Adrenaleukodystrophy is a rare X-linked condition characterized by deficiency of peroxisomal membrane adrenoleukodystrophy protein, which transports activated acyl-CoA derivates into the peroxisomes where they are shortened by β oxidation. This deficiency results in accumulation of very long chain fatty acids in the blood, adrenal gland, brain, testis, and liver. Associated neurological abnormalities in childhood include cognitive and gait disturbances, whereas spinal cord and peripheral nerve demyelination characterize the adult form.[13]

Cutaneous manifestations of Addison's disease

Darkening of the skin, especially in the sun-exposed areas, is a hallmark sign of primary adrenal insufficiency (Fig. 2).[3,5] This hyperpigmentation may be homogeneous or blotchy and occurs in all racial and ethnic groups, although it may be more difficult to discern in very dark-skinned individuals.[14] In addition, isolated darker areas occur at the palmar creases, flexural areas, sites of friction, recent scars, vermilion border of the lips, and genital skin (Figs. 3-7). It is important to recognize that increased pigmentation of the palmar creases may be normal in darker skinned individuals. Hence, comparison with other family members and the presence or absence of additional abnormal pigmentation should be considered when evaluating this sign. The buccal, periodontal, and vaginal mucosa also may exhibit patchy macular areas of increased pigmentation. Addison described this well: "It may be said to present a dingy or smoky appearance, or various tints or shades of deep amber or chestnut brown…This singular discoloration usually increases with the advance of the disease."[1]

Patients with an autoimmune etiology of primary adrenal disease may also present with vitiligo (Fig. 8) or alopecia areata, presumably because of autoimmune destruction of the

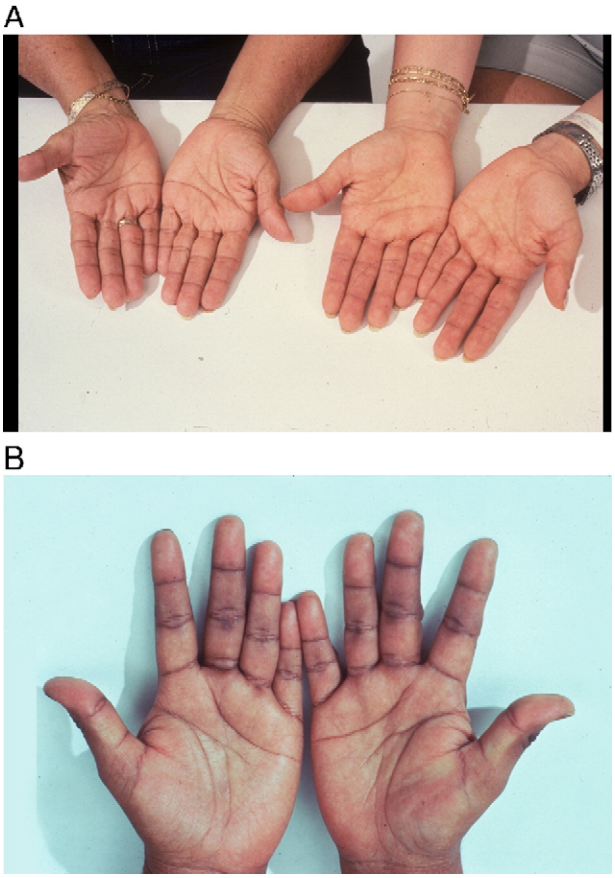

Fig. 3 A, Mild hyperpigmentation of palmar creases on left. B, Extreme hyperpigmentation of palmar creases.

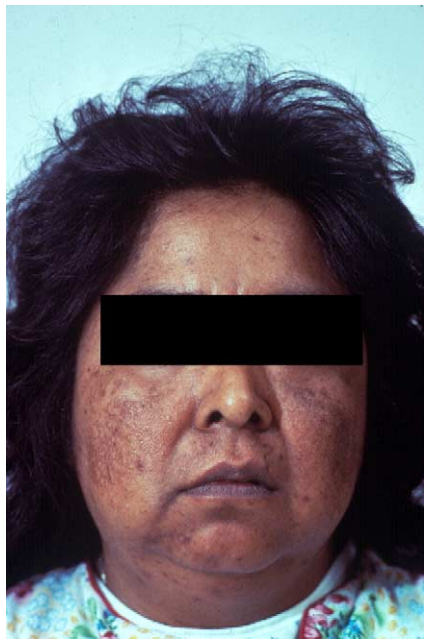

Fig. 4 Generalized hyperpigmentation of face with increased pigmentation of acne scars and lips.

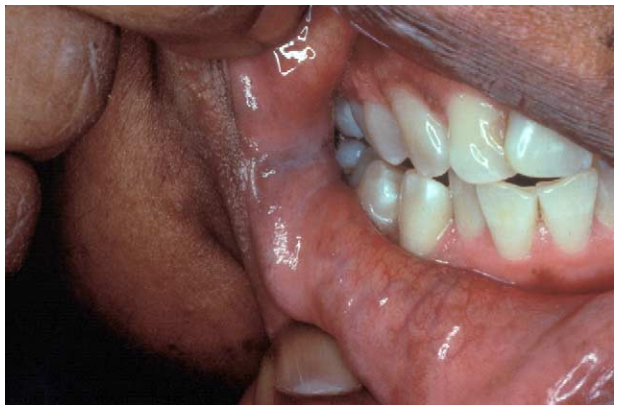

Fig. 5 Periodontal and buccal mucosal hyperpigmentation.

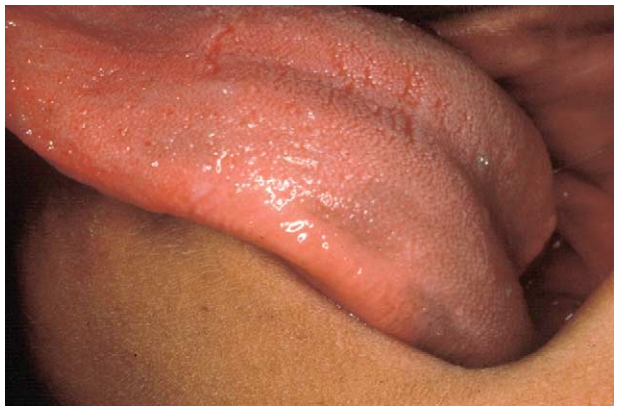

Fig. 6 Hyperpigmentation of the side of the tongue at the base.

melanocyte and hair follicle, and this may be an additional helpful cutaneous clue.[12,15] They also may present with mucocutaneous candidiasis (type 1 polyglandular disease).

Diagnosis

Biochemical testing is needed to confirm the diagnosis of adrenal insufficiency. Few data address the best way to diagnose acute adrenal insufficiency in the setting of hypotension. It is thought that plasma cortisol should be greater than 18 μg/dL (479 nmol/L) in this 'stressful' situation, and that lower values suggest adrenal insufficiency. With a more chronic presentation, a morning serum cortisol is a convenient and inexpensive but relatively insensitive screening test for adrenal insufficiency. The disorder is virtually excluded by values more than 19 μg/dL (524 nmol/L) and is likely if the value is less than 3 μg/dL (83 nmol/L).[16] However, patients in the intermediate range of 3 to 19 μg/dL require additional evaluation. Because plasma cortisol concentrations are pulsatile, both healthy individuals and patients with adrenal insufficiency may have results in this range. Measurement of urine free cortisol is not a useful diagnostic test.[16]

There is controversy about what stimulation test to use to confirm the diagnosis of chronic adrenal insufficiency.[4] The cortisol response to exogenous ACTH (1-24, cosyntropin) is a convenient test of adrenal steroidogenic ability. In the classic test, a supraphysiologic 250-μg dose of ACTH is given intravenously or intramuscularly at any time of day. This dose is a maximal stimulus to the adrenal gland; hence, the peak serum cortisol level measured 30 to 60 minutes later is greater than 18 μg/dL (479 nmol/L). Lower values indicate adrenal insufficiency. This test works well for chronic primary adrenal insufficiency. In that setting, other tests such as insulin-induced hypoglycemia and lower doses of the ACTH stimulation test are not superior and have associated risks or problems.[4]

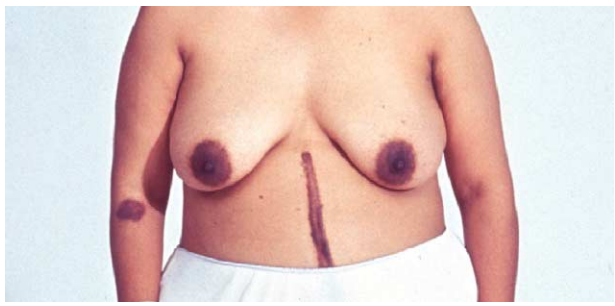

Fig. 7 Hyperpigmentation of the nipples and scar. This patient has adrenal insufficiency because of adrenalectomy.

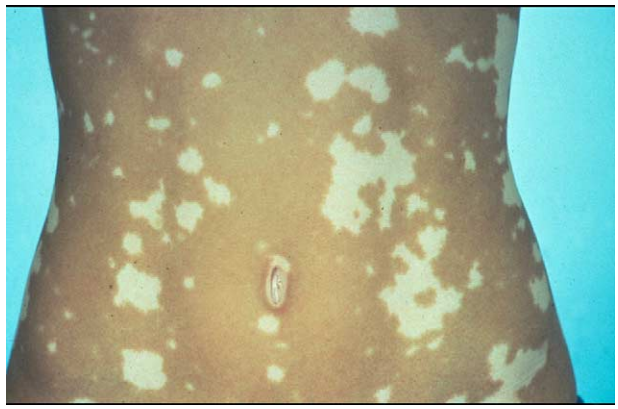

Fig. 8 Vitiligo in a patient with adrenal insufficiency.

Measurement of plasma ACTH helps to determine if the disorder is primary (values above the normal range) or secondary (low values). Hypokalemia and elevated plasma renin activity identify mineralocorticoid deficiency and thus also discriminate primary adrenal insufficiency. All patients should then be considered for further testing to determine a specific etiology by the presence of antibodies to 21-hydroxylase (CYP21A2) (autoimmune etiology)[17] or a very long chain fatty acid measurement in males (adrenoleukodystrophy).[18] Identification of large adrenal glands on imaging may help guide additional evaluation for infiltrative disorders, malignancy, or hemorrhage.

Management

Treatment of primary adrenal insufficiency involves physiologic replacement of the deficient glucocorticoid and mineralocorticoid hormones. Patients with acute adrenal insufficiency should receive fluid resuscitation and medical care as appropriate, in addition to supraphysiologic "stress" doses of hydrocortisone given intravenously (100 mg every 8 hours).

For chronic therapy, oral hydrocortisone (12 to 15 mg/M^2 daily) provides glucocorticoid replacement that can be easily titrated and given as divided doses during the day to grossly recapitulate the normal diurnal pattern of cortisol secretion. Other glucocorticoids, especially prednisone (5-7.5 mg/d), provide a longer half life and may be superior to hydrocortisone in relieving fatigue, but this has not been tested by a direct comparison trial.

Oral fludrocortisone (0.05 to 0.3 mg/d) replaces mineralocorticoids. The optimal dose will vary depending on whether the glucocorticoid administered also has mineralocorticoid activity (eg, hydrocortisone does), as well as the salt intake of the patient (which decreases mineralocorticoid requirements).

Patients with primary adrenal insufficiency also are dehydroepiandrosterone-deficient, and replacement of this hormone at a daily dose of 50 mg improved well-being and scores of fatigue, depression, and anxiety in one study. Women, but not men, evidenced improvement in sexual interest and the level of satisfaction with sex.[19] This finding has not been replicated in all studies; hence, there is no consensus on the need for dehydroepiandrosterone replacement.[20]

Although there are few data to support the practice, glucocorticoid doses are increased during physically stressful situations. If the patient cannot absorb oral agents because of vomiting or diarrhea or if the patient has collapsed, intramuscular glucocorticoid should be given before transport to a medical facility. Otherwise, the daily oral dose is doubled when fever or nausea is present, although the dose need not be increased for minimal stress such as tooth extraction. For more stressful situations, such as surgery or trauma, hydrocortisone is initially given as a 75 to 300 mg parenteral divided daily dose and tapered as the condition resolves.[21] Patients and their families require education about these recommendations during physiologic stress conditions and should receive a kit containing prefilled syringes with injectable steroid for emergency injection and carry a card or jewelry that identifies their condition.

Unfortunately, there is no simple way to assess whether the replacement dose of glucocorticoid is correct. Clinical evaluation is used to identify signs and symptoms of over- or underreplacement. Recurrence of symptoms of adrenal insufficiency suggests underreplacement. These symptoms may be vague, such as malaise, and may be difficult to ascribe to glucocorticoid deficiency. Development of cushingoid features of glucocorticoid excess such as weight gain, hyperglycemia, hypertension, or osteopenia suggests overtreatment. In primary adrenal insufficiency, plasma ACTH levels decrease but generally remain elevated at 100 to 200 pg/mL; hence, plasma ACTH levels cannot be used to adjust treatment. Because of rapid clearance, plasma cortisol levels do not reflect the adequacy of a hydrocortisone dose nor does urine free cortisol excretion. The fludrocortisone dose should be adjusted so that plasma renin activity is normal.[22] In patients with continued salt craving or hypotension, evaluation of plasma renin activity, adjustment of fludrocortisone dosage, and addition of salt should be considered before the glucocorticoid dose is increased to avoid excess glucocorticoid treatment. New hirsutism, acne, or other signs of androgen excess may suggest overreplacement with dehydroepiandrosterone.

Acknowledgment

This work was supported in part by the intramural program of NICHD and NCI, NIH.

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