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Clinical manifestations of adrenal insufficiency in adults

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INTRODUCTION

The symptoms and signs of adrenal insufficiency depend upon the rate and extent of loss of adrenal function, whether mineralocorticoid production is preserved, and the degree of physical stress. The onset of adrenal insufficiency is often very gradual, and it may go undetected until an illness or other stress precipitates adrenal crisis.

The acute and chronic clinical manifestations of adrenal insufficiency in adults are reviewed here. The causes, diagnosis, and treatment of the different forms of adrenal insufficiency are reviewed separately. (See "Causes of primary adrenal insufficiency (Addison disease)" and "Causes of secondary and tertiary adrenal insufficiency in adults" and "Determining the etiology of adrenal insufficiency in adults" and "Treatment of adrenal insufficiency in adults".)

ADRENAL CRISIS

Main features — The predominant manifestation of adrenal crisis is shock, but the patients often have nonspecific symptoms such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, confusion, or coma (table 1). In one study, the incidence of adrenal crisis was similar in patients with primary (8 percent) and secondary (6 percent) causes of adrenal insufficiency [1].

Pathophysiology — As suggested by its occurrence in both causes of adrenal insufficiency, both mineralocorticoid and glucocorticoid deficiency can participate in the development of adrenal crisis. The physiologic basis for this is the ability of aldosterone or synthetic mineralocorticoid to promote sodium retention as well as to enhance vasoconstrictor responses of the vasculature [2]. Thus, adrenal crisis can occur in patients who are receiving physiologic or even pharmacologic doses of synthetic glucocorticoid if their mineralocorticoid requirements are not met [3,4]. Glucocorticoid deficiency can contribute to hypotension by causing decreased vascular responsiveness to angiotensin II and norepinephrine, decreased synthesis of renin substrate, and increased prostacyclin production [5-7].

Precipitating factors — The syndrome of adrenal crisis (acute adrenal insufficiency) in adults typically occur in the following situations, most of which involve a recent abrupt change in glucocorticoid exposure:

- In chronic primary adrenal insufficiency, when patients experience serious infection or other acute major stress. Adrenal crisis may be the initial presentation in a previously undiagnosed patient, in whom the stressor appears to tip the balance to frank hypotension [1,8].

- It may also occur in patients with known primary or secondary adrenal insufficiency who are under-replaced, either because of: (1) insufficient daily doses of glucocorticoid and/or mineralocorticoid; (2) failure to take more glucocorticoid during an infection or other major illness; or (3) persistent vomiting or diarrhea caused by viral gastroenteritis or other gastrointestinal disorders, leading to decreased absorption. (See "Treatment of adrenal insufficiency in adults".)

- An acute cause of adrenal gland destruction, such as bilateral infarction or hemorrhage, may precipitate adrenal crisis. (See "Causes of primary adrenal insufficiency (Addison disease)", section on 'Hemorrhagic infarction'.)

- Development of an acute cause of secondary or tertiary adrenal insufficiency, such as pituitary infarction. (See 'Secondary/tertiary adrenal insufficiency' below.)

- Unmasking of secondary adrenal insufficiency in patients who are abruptly withdrawn from supraphysiologic doses of glucocorticoid. Importantly, in addition to oral medications, this includes any formulation having systemic absorption (eg, inhaled glucocorticoids) [9]. (See "Glucocorticoid withdrawal".)

Clinical presentation

Autoimmune primary adrenal insufficiency — Adrenal crisis due to chronic destructive or autoimmune processes most commonly presents as hypotension with cardiovascular collapse [10] (see "Definition, classification, etiology, and pathophysiology of shock in adults"). In addition to shock, other features may include:

- Abdominal tenderness, which may be elicited on deep palpation and is usually generalized. The cause is unknown; in adrenal insufficiency associated with polyglandular autoimmune failure, it may be a manifestation of the serositis associated with this disorder [11].

- Patients with longstanding primary adrenal insufficiency who present in crisis may be hyperpigmented (due to chronic corticotropin [ACTH] hypersecretion) and have weight loss, serum electrolyte abnormalities, and other manifestations of chronic adrenal insufficiency (table 2) [12].

- Fever, which is usually caused by infection and may be exaggerated by hypocortisolemia. It should be assumed that **fever indicates infection** that must be identified and treated. The combination of abdominal pain and fever may lead to the incorrect diagnosis of an acute surgical abdomen, with potentially catastrophic surgical exploration.

- Adrenal insufficiency is sometimes part of the polyglandular autoimmune syndrome type 2, which typically presents in childhood or early adulthood and includes type 1 diabetes, Hashimoto's thyroiditis, celiac disease, pernicious anemia, and thrombocytopenic purpura [13].

In addition, septic shock itself may occasionally cause transient, relative adrenal insufficiency. This topic is reviewed separately. (See "Diagnosis of adrenal insufficiency in adults", section on 'Critical illness' and "Glucocorticoid therapy in septic shock in adults".)

Secondary/tertiary adrenal insufficiency — These patients may have symptoms and signs of chronic adrenal insufficiency or of deficient secretion of other anterior pituitary hormones. Hypoglycemia is a rare presenting manifestation of acute adrenal insufficiency; it is more common in secondary adrenal insufficiency caused by isolated ACTH deficiency [9,12,14]. (See "Clinical manifestations of hypopituitarism".)

However, adrenal crisis can occur when the loss of pituitary function is sudden and severe, as in pituitary apoplexy (pituitary infarction); the symptoms in these patients are due mainly to **acute cortisol deficiency**. (See "Causes of hypopituitarism", section on 'Pituitary apoplexy'.)

Patients with pituitary apoplexy resulting from infarction of a large tumor usually complain of severe headache; they may also have acute visual loss or reduction in visual fields. However, because glucocorticoids have a role in maintaining peripheral vascular adrenergic tone, sudden loss of ACTH secretion, particularly in conjunction with other serious illness, can lead to hypotension and shock [15]. (See "Causes of hypopituitarism", section on 'Pituitary apoplexy'.)

Patients with secondary adrenal insufficiency do not have dehydration, and hypotension is less prominent [16]. The mechanisms for hypotension in this setting also worsen the hypotension present in primary adrenal insufficiency. Glucocorticoids are necessary for adrenal medullary epinephrine synthesis, and patients with adrenal insufficiency have decreased serum epinephrine and compensatory increases in serum norepinephrine concentrations [17]. This may cause slightly lower basal systolic blood pressure and an exaggerated increase in pulse rate in response to upright posture. Additionally, glucocorticoids have a permissive effect to potentiate the vasoconstrictive effects of catecholamines on the vasculature [18].

In some patients, there may be clinical manifestations of a pituitary or hypothalamic tumor, such as symptoms and signs of deficiency of other anterior pituitary hormones, headache, or visual field defects.

Patients with rare genetic syndromes of panhypopituitarism (for example, PIT-1 or PROP-1 mutations) may have additional extrapituitary manifestations. These are reviewed separately. (See "Causes of hypopituitarism", section on 'Genetic diseases'.)

Bilateral adrenal injury, hemorrhage, and infarction — Adrenal insufficiency is a potential complication of blunt trauma, bilateral adrenal necrosis caused by hemorrhage, emboli, sepsis, or, very rarely, adrenal vein thrombosis after a back injury [19-21]. These patients do not have evidence of preexisting adrenal insufficiency. This topic is reviewed in more detail separately. (See "Causes of primary adrenal insufficiency (Addison disease)", section on 'Hemorrhagic infarction' and "Causes of primary adrenal insufficiency (Addison disease)", section on 'Bilateral adrenal injury'.)

CHRONIC ADRENAL INSUFFICIENCY

Patients with chronic primary adrenal insufficiency may have symptoms and signs of glucocorticoid, mineralocorticoid, and, in women, androgen deficiency (table 2). In contrast, patients with secondary or tertiary adrenal insufficiency usually have normal mineralocorticoid function.

The diagnosis is usually obvious in patients with the full-blown syndrome of adrenal insufficiency. However, its onset is often insidious, with the gradual development of symptoms, most of which are nonspecific. In its early stage, therefore, diagnosis may be difficult. The clinical presentation of primary adrenal insufficiency in children is discussed separately. (See "Causes of primary adrenal insufficiency in children".)

Features of both primary and secondary adrenal insufficiency — The presenting signs and symptoms of adrenal insufficiency are often nonspecific, resulting in long delays in diagnosis. Nonspecific features include [22-24]:

Fatigue — Fatigue is extremely common in both primary (84 to 95 percent of patients) and secondary adrenal insufficiency [22]. Fatigue and gastrointestinal complaints often lead to an incorrect diagnosis. In one study of 216 patients, 20 percent had symptoms for more than five years before diagnosis [25].

Weight loss — Weight loss is primarily due to anorexia, but dehydration may contribute. The amount of weight lost can vary from 2 to 15 kg and may not become evident until adrenal failure is advanced [26]. In one study of 219 patients with adrenal insufficiency, 66 percent of those with primary and 30 percent of those with secondary causes had lost weight [25].

Gastrointestinal complaints — Gastrointestinal symptoms, usually nausea, occasionally vomiting, abdominal pain, or diarrhea that may alternate with constipation, are common and correlate with the severity of adrenal insufficiency. Vomiting and abdominal pain often herald adrenal crisis, and the fluid loss due to vomiting or diarrhea may precipitate the crisis.

The cause of gastrointestinal symptoms in adrenal insufficiency is not known. Esophagogastroduodenoscopy and gastrointestinal radiography are usually normal [27], but gastric emptying may be delayed [28]. Peptic ulcer disease is rare [29]. Steatorrhea responsive to glucocorticoid replacement has occasionally been reported [29,30].

Gastrointestinal symptoms are less common in secondary adrenal insufficiency [12,25], suggesting that electrolyte disturbances may be involved in their etiology.

Reproductive (women) — Amenorrhea develops in approximately 25 percent of women. It may be due to the effects of chronic illness or weight loss. Women with autoimmune-mediated adrenal insufficiency may develop autoimmune-mediated primary ovarian insufficiency [31]. Women with pituitary disease may develop hypogonadal hypogonadism. (See "Pathogenesis and causes of spontaneous primary ovarian insufficiency (premature ovarian failure)" and "Clinical manifestations of hypopituitarism".)

Musculoskeletal — Diffuse myalgia and arthralgia are frequent symptoms in patients with adrenal insufficiency. Occasional patients have predominantly musculoskeletal symptoms, and a few have flexion contractures of legs [32,33]. Serum concentrations of muscle enzymes, muscle biopsy, and electromyography are usually normal. The myalgia and arthralgia disappear rapidly with hormone replacement, but reversal of the contractures may take months and require orthopedic measures.

Psychiatric — Many patients with severe or longstanding, untreated adrenal insufficiency have psychiatric symptoms, including [34]:

- Mild to moderate organic brain syndrome in 5 to 20 percent.
- Impairment of memory that can progress to confusion, delirium, and stupor.
- Depression in 20 to 40 percent, manifested by apathy, poverty of thought, and lack of initiative.
- Psychosis in 20 to 40 percent, manifested by social withdrawal, irritability, negativism, poor judgment, agitation, hallucinations (40 percent), paranoid delusions, and bizarre or catatonic posturing (8 percent).
- Mania (12 percent), anxiety (24 percent), disorientation (20 percent), and hallucinations (40 percent) were described in another series of 25 patients with primary adrenal insufficiency [35].

These psychiatric symptoms occur early in the disease and may predate other symptoms, making the diagnosis of their cause difficult. Most of these symptoms disappear within a few days after glucocorticoid therapy is begun, but the psychosis may persist for several months. Improvement does not correlate with correction of electrolyte imbalance except, on occasion, in patients with severe hyponatremia.

Auricular-cartilage calcification — Calcification of the auricular cartilages may occur in longstanding primary or secondary adrenal insufficiency [27,36,37]. This finding occurs exclusively in men; it is thought to result from chronic cortisol deficiency and does not improve with glucocorticoid replacement [36].

Features of primary adrenal insufficiency — In addition to the signs and symptoms above, which occur regardless of the cause of adrenal insufficiency, there are signs and symptoms that are more specific for primary adrenal insufficiency. These include [22]:

Postural hypotension — Cardiovascular symptoms include postural dizziness or syncope. In most patients, the blood pressure is low, but some have only postural hypotension. These symptoms are most common in primary adrenal insufficiency due to volume depletion resulting from aldosterone deficiency. Serum concentrations of endothelin 1 (a vasoconstrictive peptide) and of adrenomedullin (a vasodilator peptide) are reported to be increased [38,39]. However, the contribution of these and other vasoactive agents to the hypotension of primary adrenal insufficiency, if any, is unknown. (See "Pathophysiology of heart failure: Neurohumoral adaptations", section on 'Neurohumoral adaptations'.)

Salt craving — Salt craving, sometimes with massive salt ingestion (eg, pickle juice), is a distinctive feature in some patients. To make it more palatable, salt may be "chased" with lemon juice. Increased thirst for iced liquids is often reported.

Hyperpigmentation — Hyperpigmentation, which is evident in nearly all patients with chronic primary adrenal insufficiency, is the most characteristic physical finding [40]. It is a consequence of cortisol deficiency and is due to increased production of proopiomelanocortin, a prohormone that is cleaved into the biologically active hormones corticotropin (ACTH), melanocyte-stimulating hormone (MSH), and others. The elevated MSH results in increased melanin synthesis, causing hyperpigmentation. In humans, melanin is synthesized in epidermal melanocytes lying just below the basal cells of the epithelium.

The resulting brown hyperpigmentation is generalized but is most conspicuous in areas exposed to light (such as the face, neck, and backs of hands) and areas exposed to chronic friction or pressure (such as the elbows, knees, spine, knuckles, waist [belt], midriff [girdle], and shoulders [brassiere straps]) (picture 1). Pigmentation is also prominent in the palmar creases, where it escapes being worn away by friction, and in areas that are normally pigmented, such as the areolae, axillae, perineum, and umbilicus [26,31]. However, since pigmentation of the palmar creases may be normal in darker-skinned individuals, comparison with other family members and the presence or absence of additional abnormal pigmentation should be considered when evaluating this palmar hyperpigmentation.

Other patterns of hyperpigmentation include:

- The vermilion (outer) border of the lips may darken.
- Patchy pigmentation on the inner surface of lips and the buccal mucosa along the line of dental occlusion (picture 2). It may also occur under the tongue, along the gingival border in patients with chronic periodontal disease, and on the hard palate.

- Generalized buccal, vaginal, and anal mucosal membrane hyperpigmentation is usually seen only in patients whose skin is normally pigmented, such as Black and Native American individuals. Hyperpigmentation in general is less noticeable in Black individuals, but generalized darkening may be evident.
- Existing freckles become darker, and numerous new brown or black freckles may appear.
- Scars acquired when primary adrenal insufficiency is present and untreated are permanently pigmented, those acquired earlier remain unpigmented, and those acquired during treatment do not become pigmented.
- The hair and nails may become darker, the nails showing longitudinal bands of darkening (picture 3).

The hyperpigmentation begins to fade within several days and largely disappears after a few months of adequate glucocorticoid therapy. Recovery is due to keratinization and then sloughing of the pigmented basal layer of the epidermis. Fading of hair and nails takes longer because the pigmented part of the hair shaft or nail grows out slowly, and scars never fade because the melanin is trapped in fibrous connective tissue.

Vitiligo — Patchy, often bilaterally symmetrical areas of depigmented skin (vitiligo), the result of autoimmune destruction of dermal melanocytes, occur on the trunk or extremities in 10 to 20 percent of patients with autoimmune but not those with other causes of adrenal insufficiency [31,41]. (See "Causes of primary adrenal insufficiency (Addison disease)".)

Laboratory findings

Electrolyte abnormalities — Hyponatremia is found in 70 to 80 percent of patients, reflecting both sodium loss and volume depletion caused by mineralocorticoid deficiency and increased vasopressin secretion caused by cortisol deficiency [22]. In secondary adrenal insufficiency, hyponatremia can occur early in the disease and may be the initial manifestation [42].

Hypercalcemia is a rare occurrence that may be associated with acute renal insufficiency [43]. (See "Etiology of hypercalcemia".)

Hypoglycemia — Hypoglycemia may occur after prolonged fasting or, rarely, several hours after a high-carbohydrate meal [26,31]. Hypoglycemia is most common in patients with secondary adrenal insufficiency caused by isolated ACTH deficiency [12,14] and patients with type 1 diabetes mellitus who develop adrenal insufficiency. In primary adrenal insufficiency, it is most often present in infants and children and is rare in adults in the absence of infection, fever, or alcohol ingestion.

The increased prevalence in secondary adrenal insufficiency is not simply due to concomitant loss of growth hormone secretion, because it is the presenting feature in over one-third of the patients with isolated ACTH deficiency [12,14]. One possible explanation is that the absence of dehydration and hypotension permits the patients to tolerate their illness longer and present with symptoms of chronic glucocorticoid deficiency rather than mineralocorticoid deficiency.

In those with both type 1 diabetes and primary adrenal insufficiency, sensitivity to their exogenous insulin is increased because of loss of the gluconeogenic effect of cortisol and the hyperglycemic effects of epinephrine [17,44]. (See "Physiologic response to hypoglycemia in healthy individuals and patients with diabetes mellitus".)

Hematologic findings — Normocytic anemia is seen in up to 15 percent of patients [31], although patients with polyglandular autoimmune syndrome types 1 and 2 may have coexisting pernicious anemia. Relative eosinophilia was reported to be a marker of adrenal insufficiency by George Thorn in 1948 [45]. Small subsequent series suggest that the eosinophil count is greater than 500/mm^3 in less than 20 percent of patients [46]. Thus, while the presence of eosinophilia may suggest adrenal insufficiency, it does not have a high sensitivity, and when found incidentally, other causes such as allergy or infection should be investigated [47]. (See "Pathogenesis of autoimmune adrenal insufficiency", section on 'Other antibodies'.)

Hyperkalemia — Hyperkalemia, often associated with a mild hyperchloremic acidosis, occurs in up to 40 percent of patients with primary adrenal insufficiency, due to mineralocorticoid deficiency.

Other — One study found that the combination of a history of glucocorticoid withdrawal, nausea, hyperkalemia, and eosinophilia was a useful predictor of adrenal insufficiency in an inpatient population [48].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Adrenal insufficiency".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5^{th} to 6^{th} grade reading level, and they answer the four or five key questions a patient might have about a given

condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Addison disease (The Basics)" and "Patient education: Adrenal crisis (The Basics)")
- Beyond the Basics topics (see "Patient education: Adrenal insufficiency (Beyond the Basics)")

SUMMARY

- **General principles** – The symptoms and signs of adrenal insufficiency depend upon the rate and extent of loss of adrenal function, whether mineralocorticoid production is preserved, and the degree of stress. Although many of the symptoms are similar in patients with primary or secondary/tertiary adrenal insufficiency, there are some important differences.
- **Acute adrenal insufficiency** – The syndrome of adrenal crisis (acute adrenal insufficiency) in adults may occur in the following situations (see 'Adrenal crisis' above):
  - In a previously undiagnosed patient with primary adrenal insufficiency who has been subjected to serious infection or other acute major stress.
  - In a patient with known primary adrenal insufficiency who does not take more glucocorticoid during an acute infection (can occur during acute viral infections such as influenza) or other major illness or has persistent vomiting caused by viral gastroenteritis or other gastrointestinal disorders. (See 'Autoimmune primary adrenal insufficiency' above.)
  - After bilateral adrenal infarction or bilateral adrenal hemorrhage. (See 'Bilateral adrenal injury, hemorrhage, and infarction' above.)

- Rarely in patients with secondary or tertiary adrenal insufficiency but is sometimes seen with acute cortisol deficiency due to pituitary apoplexy or in patients withdrawn abruptly from suppressive doses of corticosteroids. (See 'Secondary/tertiary adrenal insufficiency' above.)

- The predominant manifestation of adrenal crisis is shock, but the patients often have nonspecific symptoms such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, confusion, or coma (table 1). (See 'Main features' above.)

- **Chronic adrenal insufficiency**

  - **Primary** – The most common clinical features of chronic primary adrenal insufficiency are listed above. Most patients present with chronic malaise, lassitude, fatigue (worsened by exertion and improved with bed rest), weakness, anorexia, and weight loss. Hypoglycemia is not common. (See 'Features of primary adrenal insufficiency' above.)

  - **Secondary or tertiary** – Many of the symptoms of secondary or tertiary adrenal insufficiency are the same as those for primary adrenal insufficiency and are presumably due to glucocorticoid rather than mineralocorticoid deficiency. These include weakness, fatigue, myalgias, and arthralgias. (See 'Features of both primary and secondary adrenal insufficiency' above.)

    The major differences from primary adrenal insufficiency are that in secondary or tertiary adrenal insufficiency:

    - Hyperpigmentation is not present, because corticotropin (ACTH) secretion is not increased.

    - Dehydration is not present, and hypotension is less prominent.

    - Hyponatremia and volume expansion may be present (reflecting increased vasopressin secretion) but hyperkalemia is not (reflecting the presence of aldosterone).

    - Gastrointestinal symptoms are less common, suggesting that electrolyte disturbances may be involved in their etiology.

    - Hypoglycemia is more common in secondary adrenal insufficiency.

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REFERENCES

1. Hahner S, Loeffler M, Bleicken B, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. Eur J Endocrinol 2010; 162:597.
2. Feldman RD, Gros R. Vascular effects of aldosterone: sorting out the receptors and the ligands. Clin Exp Pharmacol Physiol 2013; 40:916.
3. Jacobs TP, Whitlock RT, Edsall J, Holub DA. Addisonian crisis while taking high-dose glucocorticoids. An unusual presentation of primary adrenal failure in two patients with underlying inflammatory diseases. JAMA 1988; 260:2082.
4. Cronin CC, Callaghan N, Kearney PJ, et al. Addison disease in patients treated with glucocorticoid therapy. Arch Intern Med 1997; 157:456.
5. Saruta T, Suzuki H, Handa M, et al. Multiple factors contribute to the pathogenesis of hypertension in Cushing's syndrome. J Clin Endocrinol Metab 1986; 62:275.
6. Ohtani R, Yayama K, Takano M, et al. Stimulation of angiotensinogen production in primary cultures of rat hepatocytes by glucocorticoid, cyclic adenosine 3',5'-monophosphate, and interleukin-6. Endocrinology 1992; 130:1331.
7. Jeremy JY, Dandona P. Inhibition by hydrocortisone of prostacyclin synthesis by rat aorta and its reversal with RU486. Endocrinology 1986; 119:661.
8. Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab 2015; 100:407.
9. Piédrola G, Casado JL, López E, et al. Clinical features of adrenal insufficiency in patients with acquired immunodeficiency syndrome. Clin Endocrinol (Oxf) 1996; 45:97.
10. Bouachour G, Tirot P, Varache N, et al. Hemodynamic changes in acute adrenal insufficiency. Intensive Care Med 1994; 20:138.
11. Tucker WS Jr, Niblack GD, McLean RH, et al. Serositis with autoimmune endocrinopathy: clinical and immunogenetic features. Medicine (Baltimore) 1987; 66:138.

12. Burke CW. Adrenocortical insufficiency. Clin Endocrinol Metab 1985; 14:947.
13. Kahaly GJ. Polyglandular autoimmune syndromes. Eur J Endocrinol 2009; 161:11.
14. Stacpoole PW, Interlandi JW, Nicholson WE, Rabin D. Isolated ACTH deficiency: a heterogeneous disorder. Critical review and report of four new cases. Medicine (Baltimore) 1982; 61:13.
15. Randeva HS, Schoebel J, Byrne J, et al. Classical pituitary apoplexy: clinical features, management and outcome. Clin Endocrinol (Oxf) 1999; 51:181.
16. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet 2014; 383:2152.
17. Zuckerman-Levin N, Tiosano D, Eisenhofer G, et al. The importance of adrenocortical glucocorticoids for adrenomedullary and physiological response to stress: a study in isolated glucocorticoid deficiency. J Clin Endocrinol Metab 2001; 86:5920.
18. Yang S, Zhang L. Glucocorticoids and vascular reactivity. Curr Vasc Pharmacol 2004; 2:1.
19. Rao RH, Vagnucci AH, Amico JA. Bilateral massive adrenal hemorrhage: early recognition and treatment. Ann Intern Med 1989; 110:227.
20. Xarli VP, Steele AA, Davis PJ, et al. Adrenal hemorrhage in the adult. Medicine (Baltimore) 1978; 57:211.
21. Warkentin TE, Safyan EL, Linkins LA. Heparin-induced thrombocytopenia presenting as bilateral adrenal hemorrhages. N Engl J Med 2015; 372:492.
22. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol 2015; 3:216.
23. Erichsen MM, Løvås K, Skinningsrud B, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. J Clin Endocrinol Metab 2009; 94:4882.
24. Mitchell AL, Pearce SH. Autoimmune Addison disease: pathophysiology and genetic complexity. Nat Rev Endocrinol 2012; 8:306.
25. Bleicken B, Hahner S, Ventz M, Quinkler M. Delayed diagnosis of adrenal insufficiency is common: a cross-sectional study in 216 patients. Am J Med Sci 2010; 339:525.
26. DUNLOP D. EIGHTY-SIX CASES OF ADDISON'S DISEASE. Br Med J 1963; 2:887.
27. JARVIS JL, JENKINS D, SOSMAN MC, THORN GW. Roentgenologic observations in Addison's disease; a review of 120 cases. Radiology 1954; 62:16.
28. Valenzuela GA, Smalley WE, Schain DC, et al. Reversibility of gastric dysmotility in cortisol deficiency. Am J Gastroenterol 1987; 82:1066.

29. Tobin MV, Aldridge SA, Morris AI, et al. Gastrointestinal manifestations of Addison's disease. Am J Gastroenterol 1989; 84:1302.
30. McBrien DJ, Jones RV, Creamer B. Steatorrhoea in Addison's disease. Lancet 1963; 1:25.
31. Irvine WJ, Barnes EW. Adrenocortical insufficiency. Clin Endocrinol Metab 1972; 1:549.
32. Ebinger G, Six R, Bruyland M, Somers G. Flexion contractures: a forgotten symptom in Addison's disease and hypopituitarism. Lancet 1986; 2:858.
33. Shapiro MS, Trebich C, Shilo L, Shenkman L. Myalgias and muscle contractures as the presenting signs of Addison's disease. Postgrad Med J 1988; 64:222.
34. Leigh H, Kramer SI. The psychiatric manifestations of endocrine disease. Adv Intern Med 1984; 29:413.
35. Anglin RE, Rosebush PI, Mazurek MF. The neuropsychiatric profile of Addison's disease: revisiting a forgotten phenomenon. J Neuropsychiatry Clin Neurosci 2006; 18:450.
36. Barkan A, Glantz I. Calcification of auricular cartilages in patients with hypopituitarism. J Clin Endocrinol Metab 1982; 55:354.
37. Calvo Catalá J, Hortelano Martínez E, González-Cruz Cervellera MI, et al. [Calcification of auricular cartilages in a patient with adrenal insufficiency: presentation of a case and review of the literature]. An Med Interna 1994; 11:496.
38. Letizia C, Centanni M, Scuro L, et al. High plasma levels of endothelin-1 in untreated Addison's disease. Eur J Endocrinol 1996; 135:696.
39. Letizia C, Cerci S, Centanni M, et al. Circulating levels of adrenomedullin in patients with Addison's disease before and after corticosteroid treatment. Clin Endocrinol (Oxf) 1998; 48:145.
40. Barnett AH, Espiner EA, Donald RA. Patients presenting with Addison's disease need not be pigmented. Postgrad Med J 1982; 58:690.
41. Zelissen PM, Bast EJ, Croughs RJ. Associated autoimmunity in Addison's disease. J Autoimmun 1995; 8:121.
42. Cuesta M, Garrahy A, Slattery D, et al. The contribution of undiagnosed adrenal insufficiency to euvolaemic hyponatraemia: results of a large prospective single-centre study. Clin Endocrinol (Oxf) 2016; 85:836.
43. Ahn SW, Kim TY, Lee S, et al. Adrenal insufficiency presenting as hypercalcemia and acute kidney injury. Int Med Case Rep J 2016; 9:223.
44. Armstrong L, Bell PM. Addison's disease presenting as reduced insulin requirement in insulin dependent diabetes. BMJ 1996; 312:1601.

45. THORN GW, FORSHAM PH. A test for adrenal cortical insufficiency; the response to pituitary andrenocorticotropic hormone. J Am Med Assoc 1948; 137:1005.
46. Spry C. Eosinophilia in Addison's disease. Yale J Biol Med 1976; 49:411.
47. Skiest DJ, Keiser P. Clinical significance of eosinophilia in HIV-infected individuals. Am J Med 1997; 102:449.
48. Oboni JB, Marques-Vidal P, Pralong F, Waeber G. Predictive factors of adrenal insufficiency in patients admitted to acute medical wards: a case control study. BMC Endocr Disord 2013; 13:3.

Topic 159 Version 21.0

GRAPHICS

Clinical and laboratory findings suggesting adrenal crisis

Dehydration, hypotension, or shock out of proportion to severity of current illness
Nausea and vomiting with a history of weight loss and anorexia
Abdominal pain, so-called "acute abdomen"
Unexplained hypoglycemia
Unexplained fever
Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia
Hyperpigmentation or vitiligo
Other autoimmune endocrine deficiencies, such as hypothyroidism or gonadal failure

Adapted from: Burke CW. Adrenocortical insufficiency. Clin Endocrinol Metab 1985; 14:947.

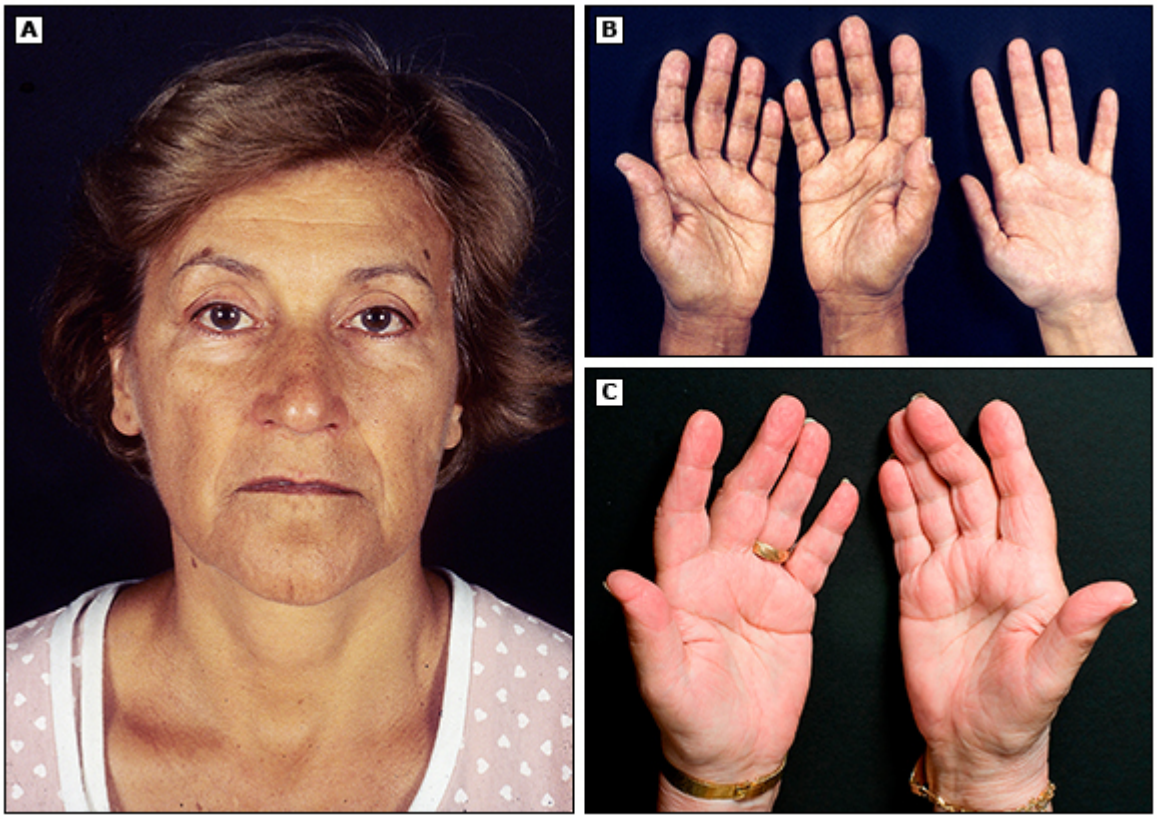
Graphic 78490 Version 3.0

Clinical manifestations of chronic adrenal insufficiency

Symptom	Frequency (%)
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	6 to 13
Sign	
Weight loss	100
Hyperpigmentation	94
Hypotension (systolic BP <110 mmHg)	88 to 94
Vitiligo	10 to 20
Auricular calcification	5
Laboratory abnormality	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

BP: blood pressure.

Hyperpigmentation in Addison disease



(A) A 57-year-old female presented with symptoms of primary adrenal insufficiency secondary to autoimmune Addison disease. Diffuse skin hyperpigmentation had developed during the last year, as illustrated by her facial appearance.

(B) The hands demonstrate increased pigmentation of the palmar creases and wrists compared to a healthy female control (far right).

(C) With long-term glucocorticoid and mineralocorticoid therapy, her hyperpigmentation resolved, as shown by the normal palmar skin pigmentation in the patient at age 83.

Of note, she wears a medical bracelet indicating her requirement for glucocorticoids in case of severe illness.

Courtesy of André Lacroix, MD.

Graphic 74922 Version 4.0

Buccal hyperpigmentation due to ACTH excess

Lips and gums of a 32-year-old male demonstrating hyperpigmentation of the buccal mucosa along the line of dental occlusion (an area of repeated trauma) and of the gums (in the area of chronic inflammatory periodontal disease). The high plasma ACTH concentrations responsible for the hyperpigmentation were due, in this case, to primary adrenal insufficiency; similar changes can be seen in patients with ACTH-dependent Cushing syndrome or Nelson syndrome.

ACTH: corticotropin.

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Graphic 56401 Version 6.0

Hyperpigmentation of nails in primary adrenal insufficiency

Fingers of a patient with Addison's disease beneath fingers of an individual with similar baseline skin pigmentation without Addison's disease. In the patient with Addison's disease, there is hyperpigmentation of the skin and increased pigmentation of the distal portion of the nails. The proximal portion of the nails are not hyperpigmented, reflecting the reduction in corticotropin (ACTH) secretion following the initiation of glucocorticoid therapy.

Courtesy of David N Orth, MD.

Graphic 57205 Version 4.0