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 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's disease)" and "Causes of secondary and tertiary adrenal insufficiency in adults" and "Diagnosis of adrenal insufficiency in adults" and "Treatment of adrenal insufficiency in adults".)

ADRENAL CRISIS — The syndrome of adrenal crisis (acute adrenal insufficiency) in adults may occur in the following situations:

- 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 infection or other major illness, or has persistent vomiting caused by viral gastroenteritis or other gastrointestinal disorders.
- After bilateral adrenal infarction or bilateral adrenal hemorrhage.
- Less frequently in patients with secondary or tertiary adrenal insufficiency during acute stress, but is sometimes seen with acute cortisol deficiency due to pituitary infarction. (See 'Pituitary apoplexy' below.)
- In patients who are abruptly withdrawn from doses of glucocorticoid that cause secondary adrenal insufficiency. Importantly, this includes not only oral but inhaled medications [1].

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).

- Hypoglycemia is a rare presenting manifestation of acute adrenal insufficiency; it is more common in secondary adrenal insufficiency caused by isolated corticotropin (ACTH) deficiency [1-3].
- Patients with long-standing adrenal insufficiency who present in crisis may be hyperpigmented (due to chronic ACTH hypersecretion) and have weight loss, serum electrolyte abnormalities, and other manifestations of chronic adrenal insufficiency (table 2) [2].

The major hormonal factor precipitating adrenal crisis is mineralocorticoid, not glucocorticoid, deficiency, and the major clinical problem is hypotension. 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 [4,5].

Furthermore, patients with secondary adrenal insufficiency, in whom aldosterone secretion is usually normal, rarely present in adrenal crisis. Although it is not primarily responsible, 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 [6-8].

Primary adrenal insufficiency — Adrenal crisis most commonly presents as shock [9]. (See "Shock in adults: Types, presentation, and diagnostic approach".) 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 [10].
- 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.

In addition, septic shock itself may occasionally cause transient relative adrenal insufficiency. This topic is reviewed separately. (See "Evaluation of the response to ACTH in adrenal insufficiency", section on 'Critical illness'.)

Bilateral adrenal injury, hemorrhage and infarction — Adrenal insufficiency is a potential complication of blunt trauma; cases have been recognized in the intensive care setting as a result of admission CT examinations [11]. Adrenal crisis can also occur as a result of sudden bilateral adrenal necrosis caused by hemorrhage, emboli, sepsis or very rarely, adrenal vein thrombosis after a back injury [12,13]. These patients do not have evidence of preexisting adrenal insufficiency. Before computed topography (CT) became widely available, the diagnosis of adrenal hemorrhage was usually made at autopsy [13]. (See "Causes of primary adrenal insufficiency (Addison's disease)", section on 'Hemorrhagic infarction'.)

The presenting symptoms and signs (and the frequency with which they occurred in one report) include hypotension or shock (more than 90 percent); abdominal, flank, back, or lower chest pain (86 percent); fever (66 percent), presumably a response to inflammation; anorexia, nausea, or vomiting (47 percent); neuropsychiatric symptoms such as confusion or disorientation (42 percent); and abdominal rigidity or rebound tenderness (22 percent) [12]. Surprisingly, only about half the patients have hypotension before shock. The acute onset does not permit enough time for the patient to become hyperpigmented.

Evidence of occult hemorrhage, such as a sudden fall in hemoglobin and hematocrit, and progressive hyperkalemia, hyponatremia, and volume contraction are other signs that should suggest the diagnosis.

The major risk factors for adrenal hemorrhage or infarction are anticoagulant therapy or coagulopathy, and the postoperative state. In patients treated with an anticoagulant, the results of clotting tests are usually within the therapeutic range and spontaneous bleeding elsewhere is not evident [12].

Because adrenal crisis is difficult to recognize clinically, it must be considered whenever these symptoms develop in a patient with one or more risk factors. Without appropriate therapy, shock progresses to coma and death. If the patient survives, adrenal function may rarely return to normal months later [14].

Adrenal hemorrhage and often death has been associated with meningococcemia (Waterhouse-Friderichsen syndrome) [15], but Pseudomonas aeruginosa was the most common pathogen in 51 children dying of sepsis and bilateral adrenal hemorrhage [16]. (See "Causes of primary adrenal insufficiency (Addison's disease)", section on 'Hemorrhagic infarction'.)

Pituitary apoplexy — Adrenal crisis is rare in patients with secondary (pituitary) or tertiary (hypothalamic) adrenal insufficiency because function of the renin-angiotensin-aldosterone system is usually normal and hypovolemia is rare. These patients may have symptoms and signs of chronic adrenal insufficiency or of deficient secretion of other anterior pituitary hormones. (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.

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 corticotropin (ACTH) secretion, particularly in conjunction with other serious illness, can lead to hypotension and shock [17]. (See "Causes of hypopituitarism",

section on 'Pituitary apoplexy'.)

CHRONIC PRIMARY ADRENAL INSUFFICIENCY — Patients with chronic primary adrenal insufficiency may have symptoms and signs of glucocorticoid, mineralocorticoid, and in women, androgen deficiency. 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 is discussed separately. (See "Causes and clinical manifestations of primary adrenal insufficiency in children".)

Common features — The most common clinical features of chronic primary adrenal insufficiency are listed in the table (table 2) [2,18-20]. Regardless of the immediate complaint, most patients with adrenal insufficiency have the following:

- Chronic malaise
- Lassitude
- Fatigue that is worsened by exertion and improved with bed rest
- Weakness that is generalized, not limited to particular muscle groups
- Anorexia
- Weight loss

The weight loss is primarily due to anorexia, but dehydration may contribute. The amount of weight lost can vary from 2 to as much as 15 kg and may not become evident until adrenal failure is advanced [18].

The patient may also be very sensitive to opioid, analgesic or sedative drugs, or may recover very slowly from illnesses or operations that do not precipitate adrenal crisis.

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 [21], but gastric emptying may be delayed [22]. Peptic ulcer disease is rare [23]. Steatorrhea responsive to glucocorticoid replacement has occasionally been reported [23,24].

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 primarily 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 [25,26]. (See "Pathophysiology of heart failure: Neurohumoral adaptations".)

The contribution of these and other vasoactive agents to the hypotension of primary adrenal insufficiency, if any, is unknown. Glucocorticoids are necessary for adrenal medullary epinephrine synthesis, and patients with adrenal insufficiency have decreased serum epinephrine and compensatory increases in serum norepinephrine concentrations [27]. This may cause slightly lower basal systolic blood pressure and an exaggerated increase in pulse rate in response to upright posture.

Blood pressure control improves in patients with preexisting hypertension. Thus, the presence of hypertension is strong evidence against a diagnosis of adrenal insufficiency [18,19].

Electrolyte abnormalities — Hyponatremia is found in 85 to 90 percent of patients, reflecting both sodium loss and volume depletion caused by mineralocorticoid deficiency and increased vasopressin secretion caused by cortisol deficiency. (See "Hyponatremia and hyperkalemia in adrenal insufficiency".)

Salt craving, sometimes with massive salt ingestion, 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.

Hyperkalemia often associated with a mild hyperchloremic acidosis occurs in 60 to 65 percent of patients due to

mineralocorticoid deficiency.

Hypercalcemia is a rare occurrence. (See "Etiology of hypercalcemia".)

Hypoglycemia — Hypoglycemia may occur after prolonged fasting or, rarely, several hours after a high-carbohydrate meal [18,19]. It is rare in adults in the absence of infection, fever, or alcohol ingestion. Hypoglycemia is more common in infants and children with primary adrenal insufficiency, patients with secondary adrenal insufficiency caused by isolated ACTH deficiency [2,3], and patients with type 1 diabetes mellitus who develop adrenal insufficiency. In the latter patients, sensitivity to insulin is increased because of loss of the gluconeogenic effect of cortisol and the hyperglycemic effects of epinephrine [27,28]. (See "Physiologic response to hypoglycemia in normal subjects and patients with diabetes mellitus".)

Hyperpigmentation — Hyperpigmentation, which is evident in nearly all patients with primary adrenal insufficiency, is the most characteristic physical finding [29]. It is a consequence of cortisol deficiency, and is due to increased production of pro-opiomelanocortin, a prohormone that is cleaved into the biologically active hormones 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 melanin is packaged in secretory granules, called melanosomes, which are phagocytosed by the basal cells [30]. The entire POMC system is present in keratinocytes. In vitro, the POMC peptide, ACTH 1-17, may be a more potent stimulator of melanogenesis than MSH [31,32]. However, the relative roles of ACTH 1-17 and MSH in the hyperpigmentation observed in patients with adrenal insufficiency has not been studied.

The resulting brown hyperpigmentation is generalized, but is most conspicuous in areas exposed to light (such as the face, neck, and backs of hands), 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 [18,19]. 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 sign.

Other patterns of hyperpigmentation include:

- 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 blacks and Native Americans. Hyperpigmentation in general is less noticeable in blacks, 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 (picture 3).
- The hair and nails may become darker, the nails showing longitudinal bands of darkening (picture 4).

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.

Sexual dysfunction — Decreased axillary and pubic hair and loss of libido are common in women, in whom androgen production primarily occurs in the adrenal glands [19]. These changes are unusual in men, in whom most androgen production occurs in the testes. The use of exogenous DHEA in patients with primary adrenal insufficiency is reviewed elsewhere. (See "Dehydroepiandrosterone and its sulfate", section on 'Use in adrenal insufficiency'.)

Amenorrhea develops in about 25 percent of women. It may be due to the effects of chronic illness, weight loss, or autoimmune-mediated primary ovarian failure [19]. (See "Pathogenesis and causes of spontaneous primary ovarian insufficiency (premature ovarian failure)".)

Musculoskeletal symptoms — 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 [33,34]. Serum concentrations of muscle enzymes, muscle biopsy, and electromyography are usually normal. The myalgia and arthralgia disappear rapidly with glucocorticoid and mineralocorticoid replacement, but reversal of the contractures may take months and require orthopedic measures.

Auricular-cartilage calcification — Calcification of the auricular cartilages may occur in long-standing primary or secondary adrenal insufficiency [21,35,36]. This finding occurs exclusively in men; it is thought to result from chronic cortisol deficiency, and does not improve with glucocorticoid replacement [35].

Psychiatric manifestations — Many patients with severe or long-standing adrenal insufficiency have psychiatric symptoms, including [37]:

- 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, paranoid delusions, and bizarre or catatonic posturing.

Perceptual disturbances, with increased sensitivity but impaired recognition and interpretation of auditory, tactile, gustatory, and olfactory stimuli, may also occur.

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.

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 [19,38]. (See "Causes of primary adrenal insufficiency (Addison's disease)".)

Other — Other findings associated with adrenal insufficiency include splenomegaly and lymphoid tissue hyperplasia, particularly of the tonsils. A high incidence of dental caries was reported when tuberculosis was the most common cause of adrenal insufficiency [21].

In addition, patients with polyglandular autoimmune syndrome type I often have chronic moniliasis of the mouth and nails that does not respond to glucocorticoid replacement therapy and responds to antifungal drug therapy poorly.

Relative eosinophilia was reported to be a marker of adrenal insufficiency by George Thorn in 1948 [39]. Small subsequent series suggest that the eosinophil count is greater than 500/mm3 in less than 20 percent of patients [40]. 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 [41].

In patients with AIDS, primary adrenal insufficiency occurs in up to 20 percent [1]. Fatigue is by far the most common presenting symptom. Only about one-third of the patients have hyperpigmentation and one-half have hyponatremia [1]. (See "Pituitary and adrenal gland dysfunction in HIV-infected patients".)

SECONDARY OR TERTIARY ADRENAL INSUFFICIENCY — The clinical features of secondary or tertiary adrenal insufficiency are similar to those of primary adrenal insufficiency, with a few major exceptions. Weakness, fatigability, myalgia, arthralgia, and psychiatric symptoms all can occur in patients with secondary adrenal insufficiency, indicating that these symptoms are caused by glucocorticoid rather than mineralocorticoid deficiency. (See "Clinical manifestations of hypopituitarism".)

The major exceptions are that in secondary or tertiary adrenal insufficiency:

- Hyperpigmentation is not present because ACTH secretion is not increased.
- Dehydration is not present, and hypotension is less prominent [2,3].
- Hyponatremia and volume expansion may be present, caused by an inappropriate increase in vasopressin secretion or action due to cortisol deficiency. The hyponatremia can occur early in the disease and may be the initial manifestation.
- Hyperkalemia is not present, reflecting the presence of aldosterone. (See "Hyponatremia and hyperkalemia in adrenal insufficiency".)
- Gastrointestinal symptoms are less common [2], suggesting that electrolyte disturbances may be involved in their etiology.
- Hypoglycemia is **more common** in secondary adrenal insufficiency [2,42]. This difference 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 [2,3]. 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.
- 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'.)

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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 information: Addison’s disease (The Basics)" and "Patient information: Adrenal crisis (The Basics)")
- Beyond the Basics topics (see "Patient information: Adrenal insufficiency (Addison's disease) (Beyond the Basics)")

SUMMARY — 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.

- After bilateral adrenal infarction or bilateral adrenal hemorrhage.
- 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 'Pituitary apoplexy' 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).

Chronic adrenal insufficiency

Primary — The most common clinical features of chronic primary adrenal insufficiency are listed in the table (table 2). 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.

Other clinical manifestations such as gastrointestinal symptoms, hypotension, electrolyte abnormalities, and hyperpigmentation are reviewed above. (See 'Chronic 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 'Secondary or tertiary adrenal insufficiency' above.)

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

- Hyperpigmentation is not present because ACTH secretion is not increased.
- Dehydration is not present, and hypotension is less prominent.
- Hyponatremia and volume expansion may be present, 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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Topic 159 Version 6.0

GRAPHICS

Clinical and laboratory findings suggesting adrenal crisis

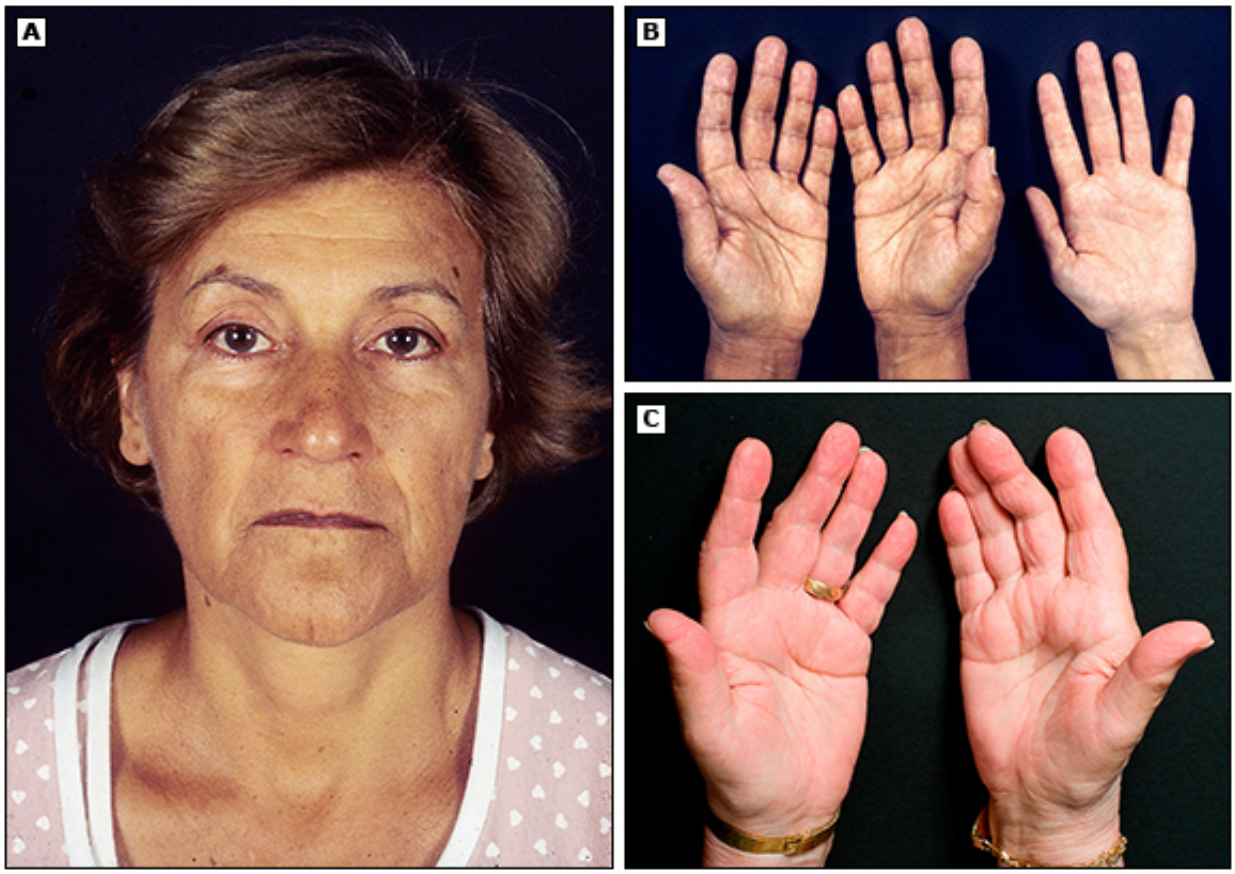
Dehydration, hypotension, or shock out of proportion to severity of current illness
Nausea and vomiting with a history of weight loss and anorexia
Abdominal pain, so-called "acute abdomen"
Unexplained hypoglycemia
Unexplained fever
Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia
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.

Clinical manifestations of chronic adrenal insufficiency

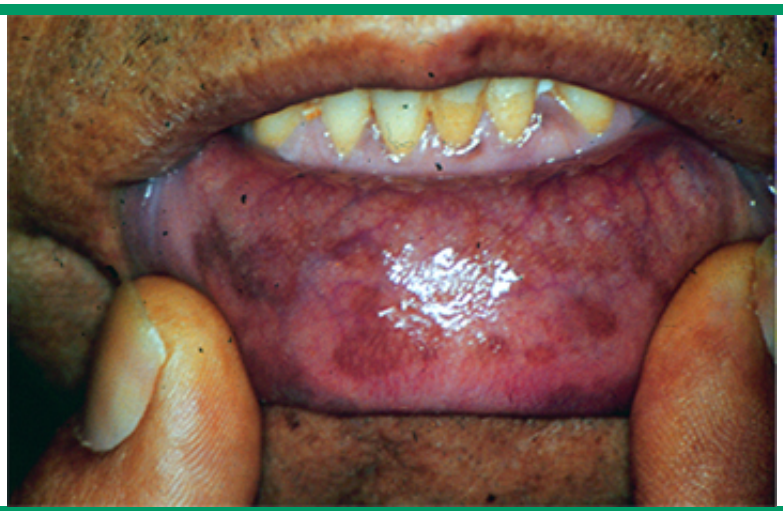
Symptom	Frequency, percent
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	6-13
Sign	
Weight loss	100
Hyperpigmentation	94
Hypotension (systolic BP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

Hyperpigmentation in Addison's disease



(A) A 57-year-old woman presented with symptoms of primary adrenal insufficiency secondary to autoimmune Addison's disease. Diffuse skin hyerpigmentation 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 normal 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.

Buccal hyperpigmentation due to ACTH excess



Lips and gums of a 32-year-old man 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's syndrome or Nelson's syndrome.

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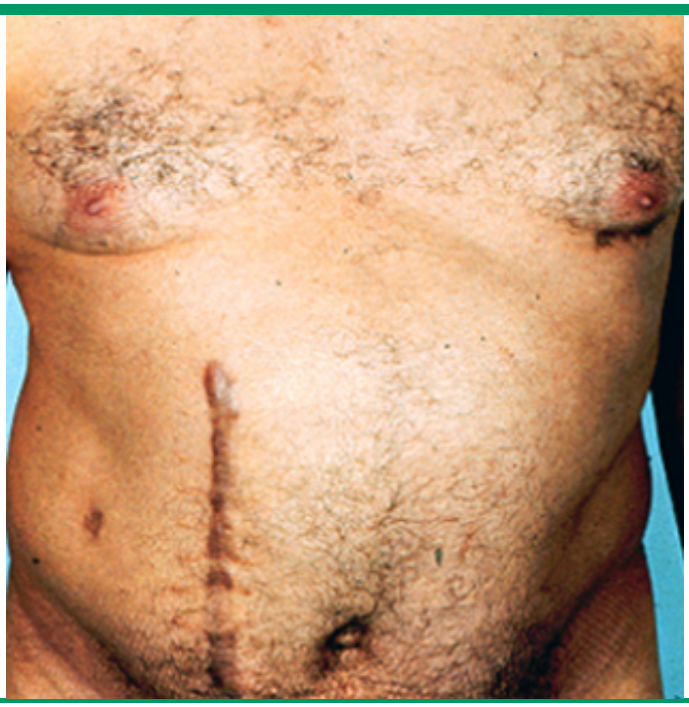
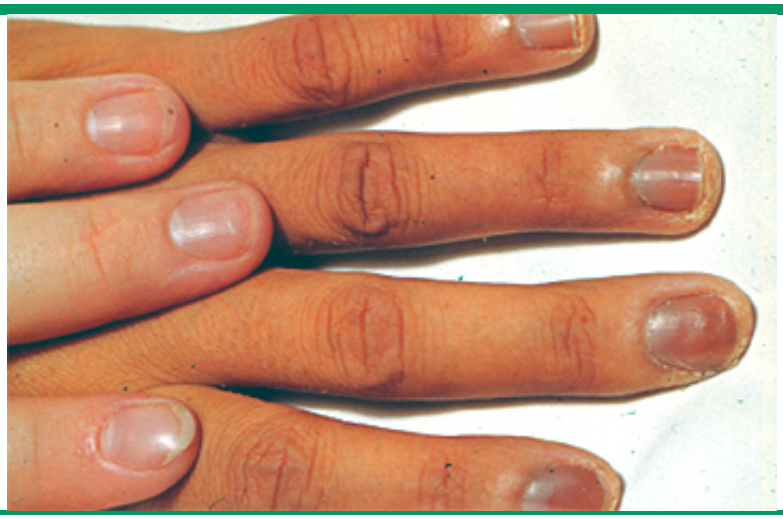
Pigmented scar in Cushing's syndrome



47-year-old man with Cushing's disease who has a pigmented surgical scar from a right adrenalectomy, which did not cure the ACTH excess. Another scar (not seen) from a shrapnel wound received years before the onset of Cushing's disease is nonpigmented.
Courtesy of David N Orth, MD.

Hyperpigmentation of nails in primary adrenal insufficiency



Fingers of a 28-year-old white woman with Addison's disease (underneath) compared to those of a normal woman (top). There is hyperpigmentation of the skin and increased pigmentation of the distal half of the nails that occurred during the period of adrenal insufficiency. The proximal half of the nails are hypopigmented, a reflection of the reduction in ACTH secretion after the institution of glucocorticoid therapy.
Courtesy of David N Orth, MD.