Seminar

Adrenal insufficiency

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Adrenal insufficiency is caused by either primary adrenal failure (mostly due to autoimmune adrenalitis) or by hypothalamic-pituitary impairment of the corticotropic axis (predominantly due to pituitary disease). It is a rare disease, but is life threatening when overlooked. Main presenting symptoms such as fatigue, anorexia, and weight loss are non-specific, thus diagnosis is often delayed. The diagnostic work-up is well established but some pitfalls remain, particularly in the identification of secondary adrenal insufficiency. Despite optimised life-saving glucocorticoid-replacement and mineralocorticoid-replacement therapy, health-related quality of life in adrenal insufficiency is more severely impaired than previously thought. Dehydroepiandrosterone-replacement therapy has been introduced that could help to restore quality of life. Monitoring of glucocorticoid-replacement quality is hampered by lack of objective methods of assessment, and is therefore largely based on clinical grounds. Thus, long-term management of patients with adrenal insufficiency remains a challenge, requiring an experienced specialist. However, all doctors should know how to diagnose and manage suspected acute adrenal failure.

In 1855, Thomas Addison described a clinical syndrome characterised by wasting and hyperpigmentation, and identified its cause as destruction of the adrenal gland. However, life-saving glucocorticoid-replacement therapy for the condition did not become available until 1949, when Kendall, Sarett, and Reichstein first synthesised cortisone. Furthermore, despite this breakthrough, 150 years on there are still many advances and challenges with respect to the management of individuals with adrenal insufficiency.

Epidemiology

There are two types of adrenal insufficiency, primary and secondary (figure 1). Chronic primary adrenal insufficiency has a prevalence of 93–140 per million and an incidence of 4·7–6·2 per million in white populations.[1–4] These recent numbers are higher than those reported during the 1960s and 1970s,[5,6] despite a continuous decline in tuberculous adrenalitis in the developed world, suggesting an increasing incidence of autoimmune adrenalitis.[3,4] The age at diagnosis peaks in the fourth decade of life, with women more frequently affected than men.[1–4]

Secondary adrenal insufficiency has an estimated prevalence of 150–280 per million,[3,7–10] and also affects women more frequently than men. Age at diagnosis peaks in the sixth decade of life.[8,9] Therapeutic glucocorticoid administration is thought to be the most common cause of secondary adrenal insufficiency, since chronic administration exogenous glucocorticoids induces atrophy of pituitary corticotroph cells. However, iatrogenic adrenal insufficiency becomes potentially relevant only during or after glucocorticoid withdrawal. Because iatrogenic adrenal insufficiency is transient in most cases,[11] we suspect its prevalence to be lower than that of endogenous adrenal insufficiency.

Lancet 2003; **361:** 1881–93

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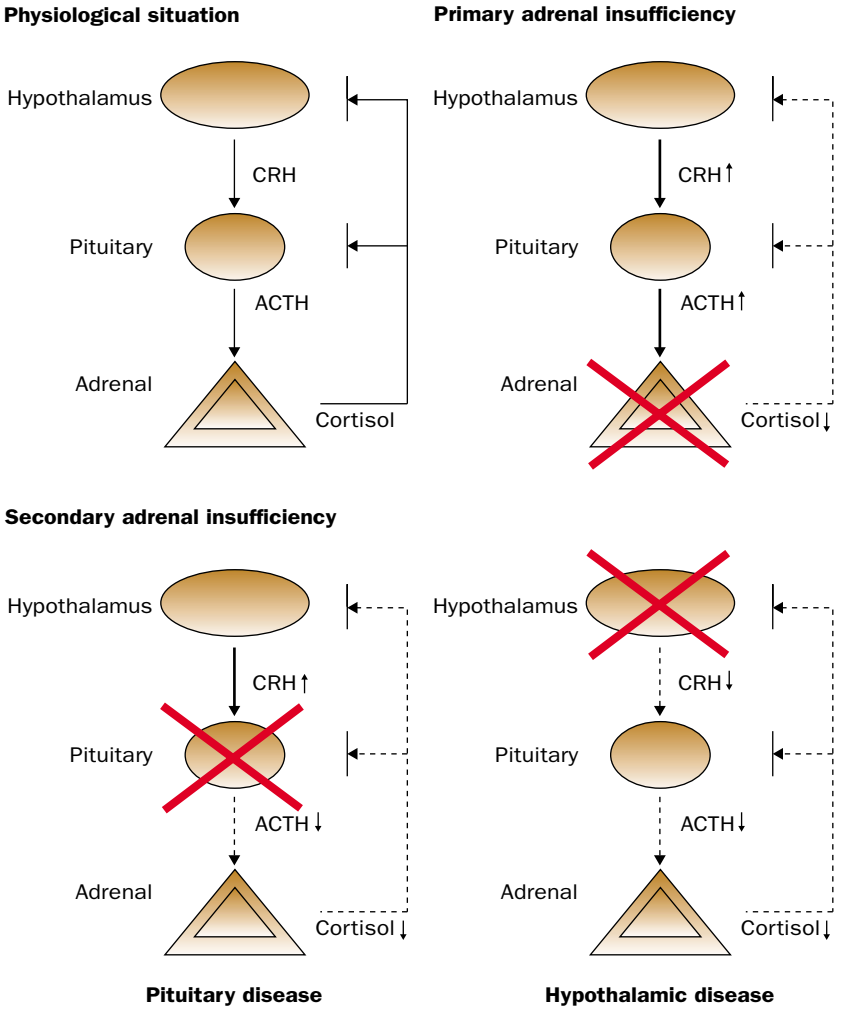
Cause

Primary adrenal insufficiency (panel 1)[12–38]

During the times of Thomas Addison, tuberculous adrenalitis was by far the most prevalent cause of adrenal insufficiency and, in the developing world, it remains a major factor.[39] In active tuberculosis, the incidence of adrenal involvement is 5%.[40] In developed countries, 80–90% of patients with primary adrenal insufficiency have autoimmune adrenalitis, which can arise as isolated (40%; slight male preponderance) or as part of an autoimmune polyendocrine syndrome ([APS]; 60%; female preponderance).[12,41] APS type 1, also termed autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), arises in up to 15% of patients with autoimmune adrenalitis. It is characterised by adrenal insufficiency, hypoparathyroidism, and chronic mucocutaneous candidiasis with onset during childhood.[12,42] APECED might also comprise the autoimmune disorders seen in APS type 2, and in addition, childhood alopecia (40% of APECD patients), chronic active hepatitis (20%), and malabsorption (15%).[12] APECED is caused by mutations in the autoimmune regulator (*AIRE*) gene[13,14] and is inherited in an autosomal-recessive fashion. APS type 2 is the most frequently seen APS and comprises adrenal insufficiency and autoimmune thyroid disease. The clinical spectrum also includes primary gonadal failure, type 1 diabetes mellitus, and other autoimmune diseases such as vitiligo, chronic atrophic gastritis, or coeliac disease. APS type 2 occurs with autosomal-dominant inheritance with incomplete

Search strategy

We searched Medline and PubMed for reviews and original articles related to adrenal insufficiency and published between 1966 and December, 2002. Keywords used included adrenal insufficiency and incidence, prevalence, cause, origin, diagnosis, function test, imaging, hydrocortisone, glucocorticoid, mineralocorticoid, dehydroepiandrosterone, management, treatment, therapy, replacement, surveillance, crisis, bone mineral density, quality of life, well-being, disablement, pregnancy, prognosis, morbidity, and mortality. Citations were chosen on the basis of relevance to the specific topics covered.



Primary and secondary adrenal insufficiency
CRH=corticotropin-releasing hormone.

penetrance, and shows a strong association with HLA-DR3[12,43] and CTLA-4.[44,45] The combination of adrenal insufficiency with other autoimmune disorders, but without thyroid disease, is classified as APS type 4, and APS type 3 involves autoimmune thyroid disease but not adrenal insufficiency.

X-linked adrenoleukodystrophy is caused by a mutation in the *ABCD1* gene,[46] which encodes a peroxisomal membrane protein (adrenoleukodystrophy protein),[47] leading to accumulation of very-long-chain fatty acids (>24 carbon atoms). The clinical picture comprises adrenal insufficiency and neurological impairment due to white-matter demyelination. The two major forms are cerebral adrenoleukodystrophy (50% of cases; early childhood manifestation; rapid progression) and adrenomyeloneuropathy (35% of cases; onset in early adulthood; slow progression) with restriction of demyelination to spinal cord and peripheral nerves.[16] Adrenal insufficiency can precede the onset of neurological symptoms and is the sole manifestation of disease in 15% of cases.[16]

Other causes of primary adrenal insufficiency—eg, adrenal infiltration or haemorrhage—are rare. Congenital or neonatal primary adrenal insufficiency accounts for only 1% of all cases. However, the elucidation of the genetic basis of underlying diseases has emphasised the importance of specific genes for adrenal development and steroidogenesis (panel 1).

Secondary adrenal insufficiency (panel 2)[48–55]

The most frequent cause of secondary adrenal insufficiency is a tumour of the hypothalamic-pituitary region, usually associated with panhypopituitarism caused by tumour growth or treatment with surgery or irradiation. Autoimmune lymphocytic hypophysitis is less frequent, mostly affecting women during or shortly after pregnancy. Isolated adrenocorticotropic hormone (ACTH) deficiency could also be of autoimmune origin since some patients concurrently have other autoimmune disorders, most frequently thyroid disease.[49] The differential diagnosis of postpartum autoimmune hypophysitis includes Sheehan's syndrome, which results from pituitary apoplexy, mostly due to pronounced blood loss during delivery. Very rarely mutations of genes important for pituitary development or for synthesis and processing of the corticotropin precursor pro-opiomelanocortin cause secondary adrenal insufficiency (panel 2).

Pathophysiology and clinical presentation (panel 3)

Glucocorticoids are secreted from the adrenal zona fasciculata under the control of hypothalamic corticotropin-releasing hormone and pituitary corticotropin. Cortisol secretion is diurnal with maximum concentrations measured early in the morning and trough concentrations noted around midnight.[56] Mineralocorticoids are produced by the zona glomerulosa, mainly under the control of the renin-angiotensin system. Thus, mineralocorticoid secretion is preserved in secondary adrenal insufficiency. Dehydroepiandrosterone secretion by the zona reticularis is also diurnal and is acutely increased by ACTH. However, although cortisol secretion varies little throughout life, dehydroepiandrosterone secretion is age dependent, with an increase noted at age 6–10 years (adrenarche), which continues until age 20–30 years. Thereafter, dehydroepiandrosterone concentrations steadily fall. This pattern suggests the existence of ACTH-independent factors, controlling release of dehydroepiandrosterone.[57]

Patients with acute adrenal insufficiency—ie, life-threatening adrenal crisis—typically present with severe hypotension or hypovolaemic shock, acute abdominal pain, vomiting, and often fever. Such individuals are, therefore, sometimes misdiagnosed as having an acute abdomen. In a series of 91 patients with Addison's disease,[58] adrenal crisis led to the initial diagnosis of adrenal insufficiency in half of them. In children, acute adrenal insufficiency often presents as hypoglycaemic seizures. Deterioration of glycaemic control with recurrent hypoglycaemia can be the presenting sign of adrenal insufficiency in patients with pre-existing type 1 diabetes. In APS type 2, onset of autoimmune hyperthyroidism (or thyroxine replacement for newly diagnosed hypothyroidism) can precipitate adrenal crisis due to enhanced cortisol clearance.

Panel 1: **Causes of primary adrenal insufficiency**

Diagnosis	Clinical features in addition to adrenal insufficiency	Pathogenesis or genetics
Autoimmune adrenalitis		
Isolated autoimmune adrenalitis	No other features	Associations with HLA-DR3, CTLA-4
Auotimmune adrenalitis as part of APS[12]		
APS type 1 (APECED)	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders	*AIRE* gene mutations (21q22.3)[13,14]
APS type 2	Thyroid disease, type 1 diabetes mellitus other autoimmune diseases	Associations with HLA-DR3, CTLA-4
APS type 4	Other autoimmune diseases, excluding thyroid disease or diabetes	Associations with HLA-DR3, CTLA-4
Infectious adrenalitis		
Tuberculous adrenalitis	Other organ manifestations of tuberculosis	Tuberculosis
AIDS	Other AIDS-associated diseases	HIV-1, cytomegalovirus[15]
Fungal adrenalitis	Mostly in immunosuppressed patients	Cryptococcosis, histoplasmosis, coccidoidomycosis
Genetic disorders leading to adrenal insufficiency		
Adrenoleukodystrophy, adrenomyeloneuropathy	Demyelination of CNS (cerebral adrenoleukodystrophy), spinal cord, or peripheral nerves (adrenomyeloneuropathy)	Mutation of the *ABCD1* gene encoding for the peroxisomal adrenoleukodystrophy protein[16]
Congenital adrenal hyperplasia		
21-hydroxylase deficiency	Ambiguous genitalia in girls	*CYP21* mutation
11β-hydroxylase deficiency	Ambiguous genitalia in girls and hypertension	*CYP11B1* mutation[17]
3β-HSD type 2 deficiency	Ambiguous genitalia in boys, postnatal virilisation in girls	*HSD3B2* mutation[18]
17α-hydroxylase deficiency	Ambiguous genitalia in boys, lack of puberty in both sexes, hypertension	*CYP17* mutation
Congenital lipoid adrenal hypoplasia	XY sex reversal	Mutations in the steroidogenic acute regulatory protein (*StAR*) gene;[19] mutations in *CYP11A* (encoding P450scc)[20]
Smith-Lemli-Opitz syndrome	Mental retardation, craniofacial malformations, growth failure	7-dehydrocholesterol reductase mutations in gene *DHCR7*[21,22]
Adrenal hypoplasia congenita		
X-linked	Hypogonadotropic hypogonadism	Mutation in *NROB1*[23]
Xp21 contiguous gene syndrome	Duchenne muscular dystrophy and glycerol kinase deficiency (psychomotor retardation)	Deletion of the Duchenne muscular dystrophy, glycerol kinase, and *NROB1* genes[24]
SF-1 linked	XY sex reversal	Mutation in *NR5A1*[25]
IMAGe syndrome	Intrauterine growth retardation, metaphyseal dysplasia, adrenal, insufficiency, and genital anomalies (IMAGe)	Unknown[26]
Kearns-Sayre syndrome	External ophthalmoplegia, retinal degeneration, and cardiac conduction defects; other endocrinopathies	Mitochondrial DNA deletions[27,28]
ACTH insensitivity syndromes (familial glucocorticoid deficiency)	Glucocorticoid deficiency, but no impairment of mineralocorticoid synthesis	
Type 1	Tall stature	ACTH receptor (MC2R) mutations[29]
Type 2	No other features	Unknown[30]
Triple A syndrome (Allgrove's syndrome)	Alacrimia, achalasia; additional symptoms—eg, neurological impairment, deafness, mental retardation, hyperkeratosis	Mutations in triple A gene (*AAAS*) encoding for a WD-repeat protein[31,32]
Bilateral adrenal haemorrhage	Symptoms of underlying disease	Septic shock, specifically meningococcal sepsis (Waterhouse-Friderichsen syndrome); primary antiphospholipid syndrome[33]
Adrenal infiltration	Symptoms of underlying disease	Adrenal metastases[34] primary adrenal lympoma sarcoidosis, amyloidosis, haemochromatosis
Bilateral adrenalectomy	Symptoms of underlying disease	Unresolved Cushing's syndrome
Drug-induced adrenal insufficiency	No other symptoms	Treatment with mitotane,[35] aminoglutethimide, etomidate,[36,37] ketoconazole, suramin,[38] mifepristone

HSD=hydroxy-Δ-5-steroid dehydrogenase.

Panel 2: **Causes of secondary adrenal insufficiency**

Diagnosis	Comment
Pituitary tumours	Secondary adrenal insufficiency mostly as part of panhypopituitarism, additional symptoms (visual-field impairment): generally adenomas, carcinoma is a rarity; consequence of tumour growth, surgical treatment, or both
Other tumours of the hypothalamic-pituitary region	Craniopharyngioma, meningioma, ependymoma, and intrasellar or suprasellar metastases
Pituitary irradiation	Craniospinal irradiation in leukaemia, radiation for tumours outside the hypothalamic-pituitary axis, irradiation of pituitary tumours
Lymphocytic hypophysitis	
Isolated	Autoimmune hypophysitis; most frequently in relation to pregnancy (80%[48]); mostly hypopituitarism, but also isolated adrenocorticotropic hormone deficiency
As part of APS	Associated with autoimmune thyroid disease and, less frequently, with vitiligo, primary gonadal failure, type 1 diabetes, and pernicious anaemia[49]
Isolated congenital ACTH deficiency	Pro-opiomelanocortin cleavage enzyme defect?[50]
Pro-opiomelanocortin-deficiency syndrome	Pro-opiomelanocortin gene mutations;[51] clinical triad adrenal insufficiency, and early-onset obesity, red hair pigmentation
Combined pituitary-hormone deficiency	Mutations in the gene encoding the pituitary transcription factor Prophet of Pit1 (*PROP1*),[52] progressive development of panhypopituitarism in the order GH, PRL, TSH, LH/FSH, (ACTH) Mutations in the homeo box gene *HESX1*,[53] combined pituitary hormone deficiency, optic-nerve hypoplasia, and midline brain defects (septo-optic dysplasia)
Pituitary apoplexy	Onset mainly with abrupt severe headache, visual disturbance, and nausea or vomiting[54]
Sheehan's syndrome	Pituitary apoplexy or necrosis with peripartal onset—eg, due to high blood loss or hypotension
Pituitary infiltration or granuloma	Tuberculosis, actinomycosis, sarcoidosis, histiocytosis X, Wegener's granulomatosis
Head trauma	For example pituitary stalk lesions
Previous chronic glucocorticoid excess	Exogenous glucocorticoid administration for more than 4 weeks[55] endogenous glucocorticoid hypersecretion due to Cushing's syndrome

GH=growth hormone. PRL=prolactin. TSH=thyrotropin. LH=luteinising hormone. FSH=follicle stimulating hormone.

The main symptom of chronic adrenal insufficiency is fatigue, accompanied by lack of stamina, loss of energy, reduced muscle strength, and increased irritability. Additionally, chronic glucocorticoid deficiency leads to weight loss, nausea, and anorexia (anorexia or failure to thrive in children), and can account for muscle and joint

Panel 3: **Clinical manifestations of adrenal insufficiency**

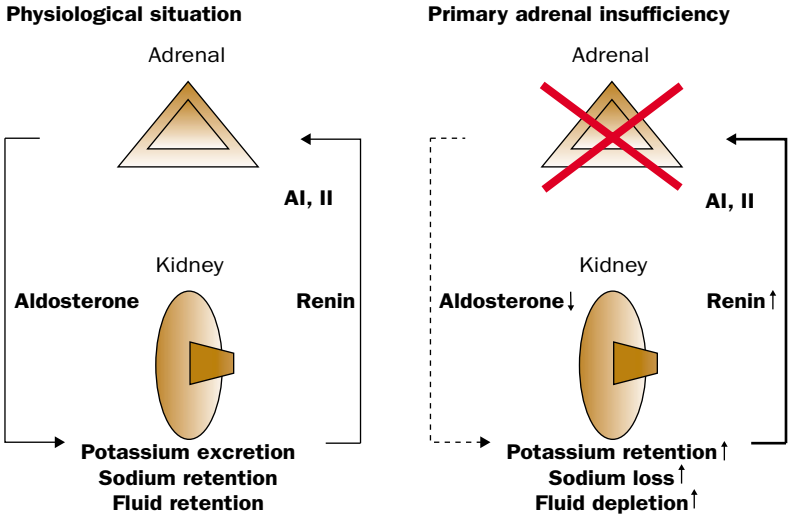
Symptoms	Pathophysiology
Fatigue, lack of energy or stamina, reduced strength	Glucocorticoid deficiency, adrenal androgen deficiency
Anorexia, weight loss (in children failure to thrive)	Glucocorticoid deficiency
Gastric pain, nausea, vomiting (more frequent in primary adrenal insufficiency)	Glucocorticoid deficiency, mineralocorticoid deficiency
Myalgia, joint pain	Glucocorticoid deficiency
Dizziness	Mineralocorticoid deficiency, glucocorticoid deficiency
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Dry and itchy skin (in women)	Adrenal androgen deficiency
Loss or impairment of libido (in women)	Adrenal androgen deficiency
Signs	
Skin hyperpigmentation (primary adrenal insufficiency only)	Excess of pro-opiomelanocortin-derived peptides
Alabaster-coloured pale skin (secondary adrenal insufficiency only)	Deficiency of pro-opiomelanocortin-derived peptides
Fever	Glucocorticoid deficiency
Low blood pressure (systolic RR <100 mm Hg), postural hypotension (pronounced in primary adrenal insufficiency)	Mineralocorticoid deficiency, glucocorticoid deficiency
Raised serum creatinine (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Hyponatraemia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to SIADH)
Hyperkalaemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Anaemia, lymphocytosis, eosinophiliia	Glucocorticoid deficiency
Increased thyroid stimulating hormone (primary adrenal insufficiency only)	Glucocorticoid deficiency (or autoimmune thyroid failure)
Hypercalcaemia (primary adrenal insufficiency only)	Glucocorticoid deficiency (mostly concurrent hyperthyroidism)
Hypoglycaemia	Glucocorticoid deficiency
Loss of axillary or pubic hair (in women), absence of adrenarche or pubarche in children	Adrenal androgen deficiency

RR=R-R interval. SIADH=syndrome of inappropriate antidiuretic hormone secretion.

pain. Unfortunately, most of these symptoms are non-specific. Thus, 50% of patients have signs and symptoms of Addison's disease for more than 1 year before diagnosis is established.[58] In secondary adrenal insufficiency, diagnosis is generally prompted by a history of pituitary disease, but can also be delayed—eg, in isolated ACTH deficiency. A more specific sign of primary adrenal failure is hyperpigmentation, which is most pronounced in areas of the skin exposed to increased friction—eg, palmar creases, knuckles, scars, oral mucosa. Hyperpigmentation is caused by enhanced stimulation of skin MC1-receptor by ACTH and other pro-opiomelanocortin-related peptides. Accordingly, patients with secondary adrenal insufficiency often have pale, alabaster-coloured skin. Laboratory findings in glucocorticoid deficiency can include mild anaemia, lymphocytosis, and eosinophilia. Cortisol physiologically inhibits thyrotropin release. Thus, concentration of thyrotropin is often increased at initial diagnosis of primary adrenal insufficiency, but returns to normal during glucocorticoid replacement unless there is coincident autoimmune thyroid dysfunction.[59] In rare cases, glucocorticoid deficiency can result in hypercalcaemia, which is due to increased intestinal absorption and decreased renal excretion of calcium and generally coincides with autoimmune hyperthyroidism, facilitating calcium release from bone.[60]

Mineralocorticoid deficiency, which is present only in primary adrenal insufficiency (figure 2), leads to dehydration and hypovolaemia, resulting in low blood pressure, postural hypotension, and sometimes even in prerenal failure. Deterioration can be sudden and is often due to exogenous stress such as infection or trauma. Combined mineralocorticoid and glucocorticoid replacement in primary disease reconstitutes the diurnal rhythm of blood pressure[61] and reverses cardiac dysfunction.[62] Glucocorticoids contribute to this improvement not only by mineralocorticoid receptor binding, but also by permissive effects on catecholamine action.[63] The latter could account for the relative unresponsiveness to catecholamines in patients with unrecognised adrenal crisis. Mineralocorticoid deficiency accounts for hyponatraemia (90% of patients with primary adrenal insufficiency), hyperkalaemia (65%), and salt craving (15%).[1,6] Low serum sodium values can also be present in secondary adrenal insufficiency due to syndrome of inappropriate antidiuretic hormone secretion, which results from the loss of physiological inhibition of pituitary vasopressin release by glucocorticoids.[64]

Adrenal insufficiency inevitably leads to dehydroepiandrosterone deficiency. Dehydroepiandrosterone is the major precursor of sex-steroid synthesis and loss of its production results in pronounced androgen deficiency in women. As a consequence, women with adrenal insufficiency frequently show loss of axillary and pubic hair (absence of pubarche in children), dry skin, and reduced libido. Dehydroepiandrosterone also exerts direct action as a neurosteroid with potential antidepressant properties.[57] Thus dehydroepiandrosterone deficiency could contribute to the impairment of wellbeing noted in patients with adrenal insufficiency despite adequate glucocorticoid and mineralocorticoid replacement.[65]



Mineralocorticoid production
AI, II=Angiotensin I and II.

Laboratory assessment of adrenal function (panel 4)

Concentrations of ACTH and cortisol vary throughout the day due to their closely related pulsatile release, which follows a diurnal rhythm. Therefore, the diagnostic usefulness of random samples is limited. Moreover, total cortisol, but not the biologically active free fraction, can increase as a result of hepatic cortisol-binding globulin production, which is increased, for example, by oestrogens.[66] Finally, differences in cortisol assays can affect normative data and interpretation of dynamic tests.[67]

Primary adrenal insufficiency

The combined measurement of early morning serum cortisol and plasma ACTH separates patients with primary adrenal insufficiency from healthy individuals and from those with secondary disease.[68] Plasma ACTH is usually greatly increased and invariably higher than 22·0 pmol/L, with serum cortisol generally lower than the normal range (<165 nmol/L) but sometimes in the lower normal range. Serum aldosterone concentrations are subnormal or within the lower normal range, with plasma renin activity concurrently increased above the normal range.[68] In patients who have adrenal insufficiency, serum dehydroepiandrosterone is consistently low,[69,70] and in women is often lower than the limit of detection.

The impaired ability of the adrenal cortex to respond to ACTH is readily demonstrated by the standard short corticotropin test,[71] which involves measurement of serum cortisol before and after 30 or 60 min intravenous or intramuscular injection of 250 μg 1-24 ACTH.[66,72] In healthy individuals, this challenge leads to a physiological increase in serum cortisol to peak concentrations of greater than 500 nmol/L.[67] In those with primary adrenal insufficiency, in whom the adrenal cortex is already maximally stimulated by endogenous ACTH,[68] exogenous hormone administration usually does not evoke any further increase in serum cortisol.

Adrenal cortex autoantibodies or antibodies against 21-hydroxylase are present in more than 80% of patients with recent onset autoimmune adrenalitis.[73] Although 21-hydroxylase has been identified as the major autoantigen in autoimmune adrenalitis,[74] autoantibodies

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