Adrenal insufficiency

Abstract

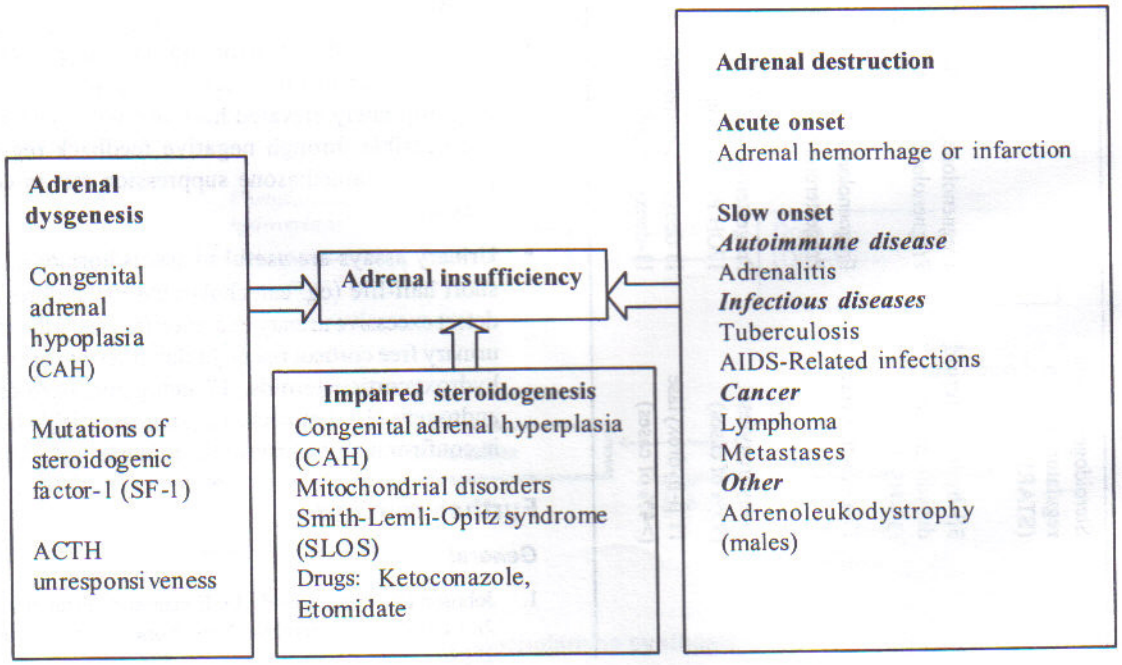
Adrenal insufficiency can be due to disease of the adrenal gland itself (primary adrenal deficiency) or of the hypothalamic or pituitary regulation of the adrenal gland (secondary adrenal insufficiency). This article discusses its causes, clinical features, diagnosis and treatment.

Adrenal insufficiency (AI) develops when a large part of the function of the adrenal glands is lost. Primary AI is caused by processes that affect the adrenal glands, whereas secondary AI results from reduced secretion of ACTH by the pituitary gland due to a pituitary or hypothalamic pathology. The last, due to deficit of corticotrophin-releasing hormone (CRH), is sometimes called tertiary AI.

Primary AI

The various causes of primary AI can be grouped into three categories (panel 1). The relative frequencies of these different disorders vary markedly according to the

Panel 1. **Causes of primary AI**



gender and age of the patients at clinical presentation. In developed countries, the most frequent cause of primary AI is autoimmune adrenalitis, whereas in the developing world tuberculosis probably remains the more common cause of adrenal failure.

Secondary AI

The commonest cause of secondary AI is exogenous glucocorticoid use. Causes of secondary AI are given in panel 2. In the failing pituitary gland, ACTH secretion is usually the last function to be lost but exceptions can occur as in post-irradiation hypopituitarism. Both primary and secondary AI may develop slowly, over several weeks or months, or acutely, with cardiovascular collapse.

Panel 2. **Causes of secondary AI**

Acute onset

Pituitary apoplexy
Pituitary or hypothalamic surgery
Traumatic brain injury

Slow onset

Autoimmune disease
Lymphocytic hypophysitis

Infectious disease
Tuberculosis

Cancer
Pituitary or hypothalamic tumours
Lymphoma

Trauma or other injury
Traumatic brain injury
Subarachnoid haemorrhage
Radiation

Drugs
Megestrol acetate

Other
Discontinuation of exogenous glucocorticoids
Sarcoidosis
Empty sella syndrome

Clinical presentation

Acute AI should be considered as a possible cause in every patient with unexplained deterioration of cardiovascular status. Adrenal hemorrhage or infarction occurs in patients who are severely ill from underlying conditions, such as sepsis, pulmonary embolism, acute renal failure, acute myocardial infarction, and heart failure.

Patients with slow onset AI usually have non-specific symptoms (panel 4). There are differences between primary and secondary adrenal deficiency (panel 3). Patients with primary AI have more severe symptoms than patients with secondary AI. Patients with secondary AI are often able to function reasonably well during unstressed periods, but may manifest cardiovascular instability or hypoglycaemia in the presence of physical stress.

Diagnosis of AI

Once AI is suspected, a variety of tests may be used to evaluate adrenal function. A stepwise approach is recommended.

The cutoff levels for the ACTH stimulation test that are useful in the outpatient setting cannot be projected to the critical care setting. Recent recommendations are that the patients should be considered to have adrenal insufficiency if the basal serum level is less than 15 μg/dl. Decreased adrenal reserve is diagnosed if basal levels are 15-34μg/dl but the response to ACTH is less than 9μg/dl. Adequate function is present if basal levels are more than 35μg/dl or response to ACTH >9μg/dl.

Figure 1 is an algorithm for the laboratory diagnosis of patients with suspected primary or secondary adrenal insufficiency. The evaluation begins with the 250μg cosyntropin stimulation test.

Panel 3. **Clinical differences between primary and secondary AI**

Feature	*Primary AI*	*Secondary AI*
Skin and mucosae	Dark	Pale
Potassium	High	Normal
Sodium	Low	Normal
Associated diseases	Primary hypothyroidism, type 1 diabetes mellitus, vitiligo, neurological deficit (adrenoleukodystrophy, males only)	Central hypogonadism or hypothyroidism, growth hormone deficiency, diabetes insipidus, headache, visual abnormalities

Panel 4. **Clinical features of Addison disease**

Symptoms	*Signs*	*Biochemical abnormalities*
Fatigue	Postural hypotension	High (supine) plasma renin and/or increased
Muscular weakness	Weight loss	nighttime ACTH levels
Abdominal pain	Generalised pigmentation	Low ACTH stimulated cortisol responses
Vomiting	Darkened skin creases	At the time of crisis: normo- or hyponatremia,
Diarrhoea	Pigmented buccal mucosa and nail beds	hyperkalaemia, hypoglycaemia
Salt craving	Associated vitiligo and/or goitre	Eosinophilia
Behaviour changes		Lymphocytosis
Headache		
Sweating		
Depression		
Muscle and joint pain		

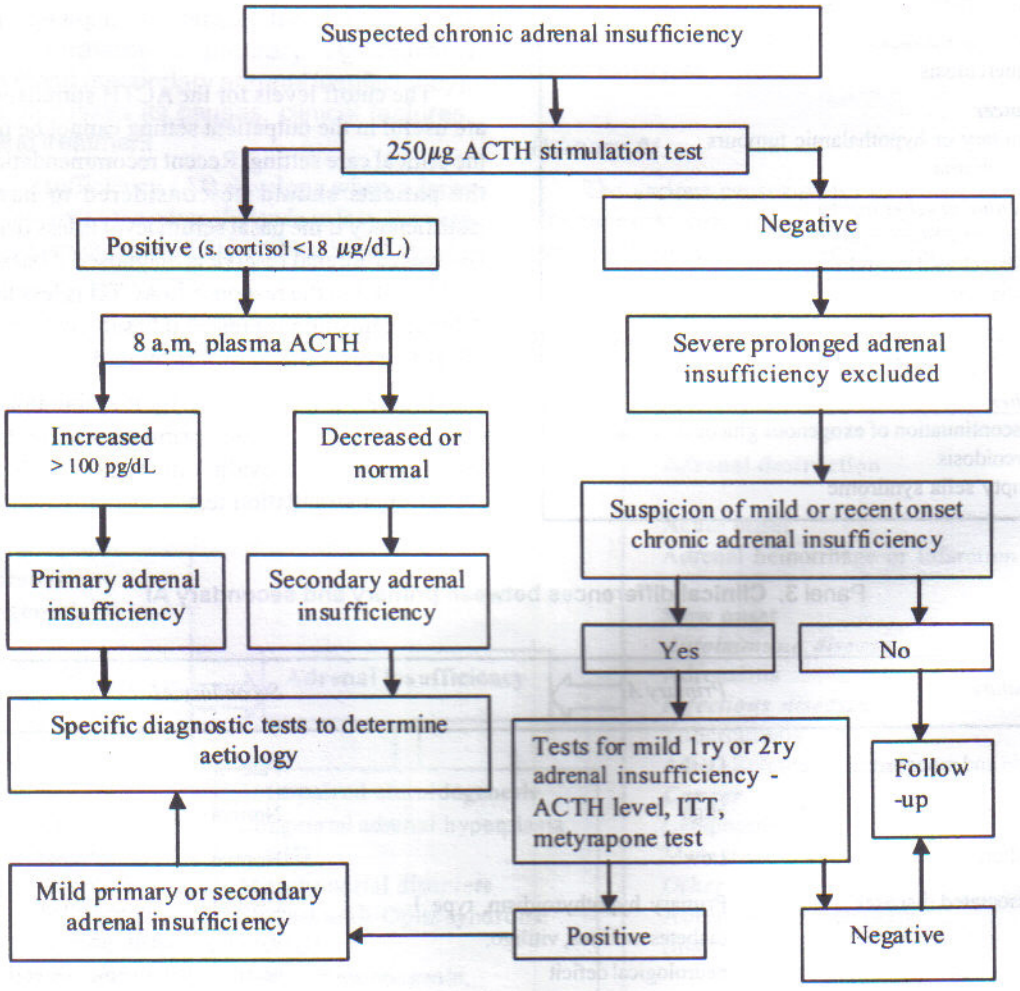


Figure 1. **Algorithm for laboratory diagnosis of AI**

Identifying the cause of AI

Once the diagnosis of AI is made, its aetiology needs to be established. Clinical features and ACTH level will distinguish primary from secondary AI. In primary AI, the age of the patient, associated morbidities, clinical picture, and medical history must guide further investigations. Measurement of anti-adrenal antibodies may help the diagnosis of autoimmune adrenalitis. This test is highly specific but not 100% sensitive. Measurement of very long chain fatty acids must be obtained if adrenoleukodystrophy is suspected. Computed tomography imaging of the adrenals will determine whether the glands are small (autoimmune adrenalitis or adrenoleukodystrophy) or enlarged (all the other causes). Adrenal biopsy may occasionally be needed. In secondary AI, in the absence of a history of exogenous glucocorticoid exposure, patients should undergo magnetic resonance imaging of the sellar region, and be screened for other pituitary hormone deficiencies.

Therapy

Glucocorticoids. Glucocorticoids are indicated in all forms of AI. Although different preparations are available, hydrocortisone (10-12.5 mg/m^2 per day) is preferred because its short half-life most closely mimics the normal cortisol circadian rhythm. In patients who are also hypothyroid, thyroid hormones should never be started before administering glucocorticoids as this may trigger an adrenal crisis by accelerating the metabolism of cortisol. Similarly, growth hormone therapy can accelerate cortisol metabolism, requiring adjustment of hydrocortisone dosing. Dose adjustment is generally not required during pregnancy, but in prolonged first trimester vomiting, parenteral administration may be required.

Every patient with AI should ideally wear a medical alert bracelet or necklace stating the need for glucocorticoids in case of an emergency. An emergency glucocorticoid injection kit should be prescribed to patients who live in or travel to remote areas, where medical assistance may not be promptly available.

Mineralocorticoids. Patients with primary AI also need mineralocorticoid therapy. The only drug available is fludrocortisone. Its dose ranges in most cases between 0.05 and 0.2 mg/d, usually in a single dose. The dose is adjusted according to the patient's symptoms, including orthostatic dizziness and salt craving, and to serum potassium and plasma renin activity.

Androgen. In women with AI, dehydroepiandro-sterone replacement (50 mg/d) improves well-being and sexuality.

Therapy during stress. During illnesses, the glucocorticoid dose should be increased. One approach is to double the maintenance dose in fever (temperature >38°C), major dental procedures (tooth extractions or root canal work), or invasive diagnostic procedures (gastroscopy, colonoscopy, cystoscopy or broncho-scopy). Patients with AI are more likely to develop cardiovascular instability when they have vomiting or diarrhoea and parenteral glucocorticoids are indicated.

The glucocorticoid dose recommended is 50 mg hydrocortisone every 8 hours. There is no need to prescribe fludrocortisone even in patients with primary AI, because the high doses of hydrocortisone will activate the mineralocorticoid receptor.

Further reading

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Bandula Wijesiriwardene[1] and **Deepthi C de Silva**[2]. [1]*Physician, Colombo South Teaching Hospital, Kalubowila, Sri Lanka, and* [2]*Senior Lecturer, Department of Physiology, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka.*

Correspondence: BW, *e-mail <bandulawije@lycos.com>. Competing interests: none declared.*