PEER REVIEWED

Addison's disease

A diagnosis not to be missed

JASNA ALEKSOVA MB BS(Hons), BMedSc
CAROLINE JUNG MB BS(Hons), FRACP, PhD

Addison's disease is a potentially life-threatening disorder caused by deficiencies of all adrenocortical hormones. A high index of suspicion is needed because the presentation is often nonspecific and can mimic other medical and psychiatric conditions. Prompt recognition and treatment is essential and life saving.

Key points

- **Addison's disease should be suspected in patients presenting with hyperpigmentation of skin and oral mucosa, unexplained weight loss, persistent hyponatraemia or other autoimmune diseases associated with polyendocrinopathy syndrome.**
- **The initial test in patients with suspected Addison's disease is the measurement of basal morning plasma cortisol and adrenocorticotrophic hormone (ACTH) levels. A basal morning plasma cortisol level of less than 100 mmol/L is diagnostic of adrenal insufficiency. Plasma ACTH levels are elevated in patients with Addison's disease.**
- **The short Synacthen test should be performed if basal plasma cortisol levels are nondiagnostic.**
- **Treatment should not be delayed in patients with suspected adrenal crisis while awaiting diagnostic confirmation.**
- **Referral of the patient to an endocrinologist is essential in cases of equivocal diagnostic tests with high clinical suspicion of adrenal insufficiency and for long-term management of diagnosed Addison's disease.**

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Dr Aleksova is an Endocrinology Registrar and Dr Jung is an Endocrinologist, Department of Endocrinology and Diabetes at St Vincent's Hospital, Melbourne, Vic.

Primary adrenal insufficiency (PAI), also known as Addison's disease,[1] is a rare but life-threatening disorder caused by disease or destruction of the adrenal cortex, resulting in deficiency of all adrenocortical hormones.[2,3] The major hurdle for clinicians is to consider PAI as a diagnostic possibility in patients presenting with nonspecific symptoms. Prompt recognition and treatment is essential and life saving. This article addresses the clinical features and biochemical tests that can assist clinicians in the diagnosis of PAI.

Normal production of adrenocortical hormones

The three main types of hormones produced by the adrenal cortex are: mineralocorticoids (aldosterone, deoxycorticosterone) from the zona glomerulosa; glucocorticoids (cortisol) from the zona fasciculata; and adrenal androgens (dehydroepiandrosterone [DHEA] and androstenedione) from the zona reticularis.[4]

Mineralocorticoids

Aldosterone is secreted in low amounts (150 µg/day),[5] predominantly under the control of the renal–angiotensin system. It regulates sodium and potassium balance and intravascular volume.[6]

Glucocorticoids

Glucocorticoids are produced under the regulation of the hypothalamic–pituitary–adrenal (HPA) axis (Figure 1).

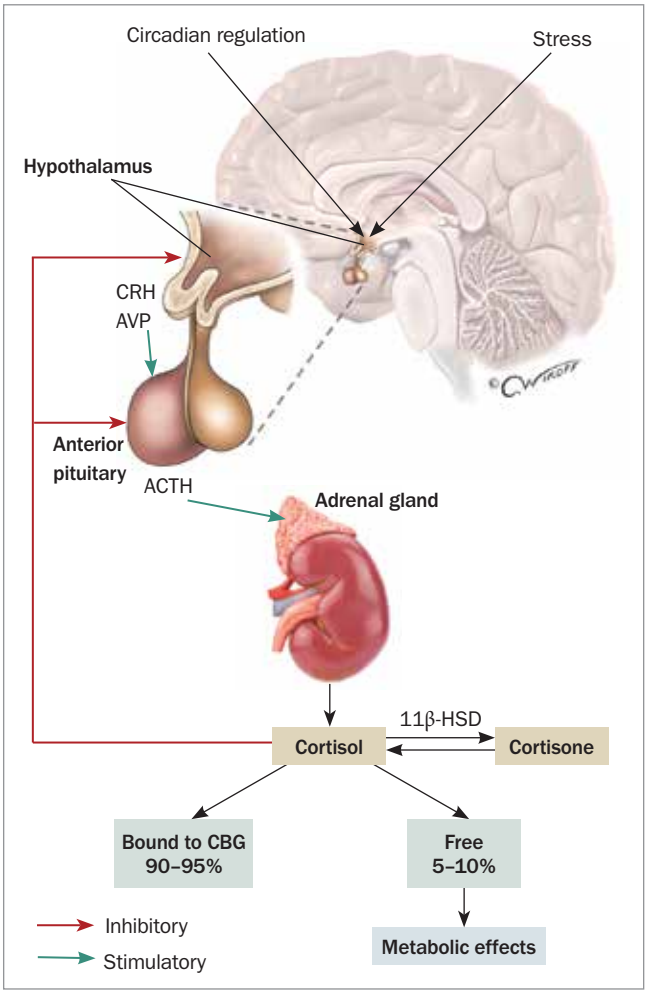

Figure 1. Hypothalamic–pituitary–adrenal axis.
Abbreviations: ACTH = adrenocorticotrophic hormone; AVP = arginine vasopressin; CBG = corticosteroid-binding globulin; CRH = corticotrophin-releasing hormone; 11β-HSD = 11β-hydroxysteroid dehydrogenase.

Corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), which are synthesised in the hypothalamus, stimulate the secretion of adrenocorticotropic hormone (ACTH),[7] resulting in the production of cortisol, the main endogenous glucocorticoid. Cortisol exerts negative feedback at the level of both the hypothalamus and the pituitary gland.[8] Cortisol circulates in the plasma both in the free form (5 to 10%) and protein-bound (90 to 95%), predominantly to corticosteroid-binding globulin (CBG).[9] Cortisol is interconverted to inactive cortisone by the 11β-hydroxysteroid dehydrogenase enzymes.[10]

Normal cortisol secretion follows a distinct circadian rhythm with peak levels in the morning within one hour of waking, and then declining throughout the day to reach a nadir around midnight.[11,12] The mean cortisol production rate is 5.7 mg/m^2/day or about 10 mg/day.[13,14] Cortisol binds to the intracellular glucocorticoid receptor resulting in many important metabolic and endocrine changes that are essential for human survival, particularly during stress. Cortisol is required for the metabolism of carbohydrates, lipids and proteins.[15-17] It also potentiates the vasoconstrictor actions of catecholamines,[18] and has anti-inflammatory effects on the immune system.[19]

Adrenal androgens

DHEA is the major precursor of more potent androgens (such as testosterone) and oestrogens. DHEA secretion is decreased or absent in adrenal insufficiency, the clinical significance of which has been much debated.[20] A recent meta-analysis concluded that the evidence does not support the routine administration of DHEA in women with adrenal insufficiency.[21]

Adrenal insufficiency

Primary adrenal insufficiency

PAI is a rare disease and has a prevalence of 100 to 150 per million,[2,22-25] with an estimated incidence of 4.4 to 6.0 new cases per million population per year.[22,24,25] PAI affects all three layers of the adrenal cortex, resulting in glucocorticoid, mineralocorticoid and adrenal androgen deficiencies. However, isolated aldosterone or cortisol deficiencies may occur in PAI. The most common cause of PAI in developed countries in the adult population is autoimmune adrenalitis, which accounts for 80 to 90% of cases.[3,22] Autoimmune adrenalitis is a cell-mediated immune destruction of the adrenal cortex, which can arise in isolation (40%) or as part of an autoimmune polyendocrinopathy syndrome (60%).[26] Other causes of PAI include infections, genetic disorders, bilateral adrenal haemorrhage, infiltration, surgery and use of medications (Table 1).[2,3,27,28]

Secondary or tertiary adrenal insufficiency

Secondary adrenal insufficiency results from any disease process that interferes with ACTH secretion from the pituitary gland. Tertiary adrenal insufficiency results from processes that involve the hypothalamus and interfere with secretion of CRH, AVP or both.[3] The most common cause of tertiary adrenal insufficiency is suppression of the HPA axis by exogenous glucocorticoid therapy in pharmacological doses.[8,29] Central adrenal insufficiency is the collective name for the secondary and tertiary types.[3] Deficiency of ACTH or CRH leads to atrophy of the zona fasciculata, resulting in cortisol insufficiency. Mineralocorticoid deficiency does not occur in central adrenal insufficiency because the renin–angiotensin–aldosterone system remains intact.

Clinical presentation of PAI

Acute adrenal insufficiency (adrenal crisis)

The first presentation of adrenal insufficiency can be a life-threatening adrenal crisis, which primarily manifests with severe hypotension and hypovolaemia. Associated features include nausea, vomiting, abdominal pain, fever and confusion,[27,30] and the acute presentation can be mistaken for acute abdomen or sepsis. Adrenal crisis can be precipitated by infection, surgery, trauma or severe psychological stress.[31,32] Adrenal crisis is a medical emergency that requires urgent transfer of the patient to hospital for intravenous fluid resuscitation and administration of a high-dose glucocorticoid.[28,30,33] Blood samples

for measurement of cortisol and ACTH levels, as well as for other tests, can be collected at the time of intravenous cannulation in the emergency department. Treatment should not be delayed while waiting for test results. Adrenal crisis can be the presenting complaint in half of the patients eventually diagnosed with PAI. It is pertinent to recognise the earlier clinical features of PAI to prevent presentations with an adrenal crisis. Frequency of adrenal crisis among patients diagnosed with PAI is six to eight cases per 100 patient years.[2]

Chronic adrenal insufficiency

Many of the symptoms of chronic adrenal insufficiency (fatigue, loss of energy, weight loss, dizziness, nausea, anorexia) are nonspecific and occur insidiously.[27,28] In some patients, adrenal insufficiency may be initially misdiagnosed as depression, an eating disorder or gastrointestinal disease. A specific sign of chronic PAI is hyperpigmentation, which is most evident on palmar creases, knuckles, elbows, scars and oral mucosa (Figure 2).[27] Hyperpigmentation is caused by enhanced stimulation of skin melanocortin-1 receptor by high plasma ACTH concentrations as a result of decreased cortisol feedback.[27,28,34] Hypotension is more pronounced in primary than central adrenal insufficiency because of combined glucocorticoid and mineralocorticoid deficiencies.[28] Mineralocorticoid deficiency accounts for salt craving. Clinical features of PAI (pathophysiological mechanisms and frequencies of symptoms and signs at diagnosis) are summarised in Table 2.[25,27]

In a patient with fatigue or other nonspecific symptoms, screening laboratory tests are often performed for serum biochemistry and full blood count. Mineralocorticoid deficiency in PAI causes hyponatraemia (90%) and hyperkalaemia (65%).[27] Other abnormalities in laboratory tests may include acidosis, elevated plasma creatinine levels, hypoglycaemia, hypercalcaemia (6%), mild normocytic anaemia, lymphocytosis and eosinophilia.[3,28]

Table 1. Causes of primary adrenal insufficiency[2,3,27,28]

Aetiology	Pathogenesis or comments	Aetiological diagnosis
Autoimmune adrenalitis	T- and B-cell autoimmunity against adrenocortical cells	Antibodies to adrenal cortex or 21-hydroxylase
– Isolated	No other autoimmune diseases	
– Autoimmune polyendocrinopathy syndrome (APS)	APS type 1: chronic mucocutaneous candidiasis, hypoparathyroidism, other autoimmune diseases APS type 2: thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases. Autosomal recessive, mutations in the *AIRE* gene	Assess for other autoimmune diseases
Infectious adrenalitis	Tuberculosis Fungal, HIV/AIDS	Culture, Quantiferon test Adrenal CT: enlarged adrenal glands, calcifications in later stages of tuberculosis
Bilateral adrenal haemorrhage	Meningococcal sepsis (Waterhouse-Friederichsen syndrome), antiphospholipid syndrome, anticoagulants	Culture Adrenal CT: bleeding
Adrenal infiltration	Metastases (cancers of the lung, stomach, breast, colon), primary adrenal lymphoma, amyloidosis, haemochromatosis, sarcoidosis	Adrenal CT: enlarged adrenal glands, tumours Evidence of systemic disease
Bilateral adrenalectomy	Bilateral adrenal masses, bilateral phaeochromocytoma, unresolved Cushing's syndrome	
Genetic disorders	Congenital adrenal hyperplasia: autosomal recessive Most common cause of primary adrenal insufficiency in children Deficiency of one of the enzymes required for cortisol synthesis, most commonly 21-hydroxylase	17-hydroxyprogesterone, urine steroid profile, sequencing of steroidogenic genes
	Adrenoleukodystrophy: X-linked Cerebral form (demyelination of CNS) Adrenomyeloneuropathy (demyelination of spinal cord or peripheral nerves)	Measure plasma concentrations of very-long-chain fatty acids
Drug-induced	Ketoconazole, etomidate, aminoglutethimide, mitotane, metyrapone: inhibits cortisol synthesis	

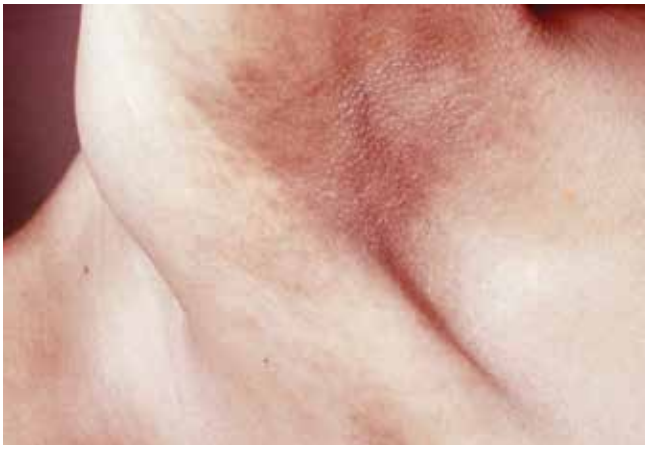

Figure 2. Hyperpigmentation on the underarm of a patient with Addison's disease.

Subclinical presentation

Autoimmune adrenalitis has a long, silent subclinical period, but may be detected in patients who are tested for the presence of adrenal cortex autoantibodies because of a history of other autoimmune diseases. In autoimmune adrenalitis, zona glomerulosa is first affected by immune-mediated destruction and subsequently the zona fasciculata. The first stage of subclinical adrenalitis is characterised by high plasma renin and low aldosterone concentrations, followed by progressive glucocorticoid deficiency, initially with inadequate cortisol response to stressful stimuli and then overt adrenal failure with low basal cortisol concentrations.[26]

Diagnosis of PAI

Numerous tests, both static and dynamic (stimulatory), are available to assess HPA function in patients with suspected adrenal insufficiency. This article focuses on the use of basal morning cortisol and ACTH measurements, and the standard-dose short Synacthen test (SST). Table 3 outlines the diagnostic tests for PAI. Insulin tolerance test (ITT) is widely regarded as the gold standard for assessing the HPA axis in the setting of pituitary disease, but is contraindicated if there is a strong suspicion of PAI.

It should be emphasised that currently accepted basal and dynamic tests measure total plasma cortisol levels, which includes CBG-bound and free cortisol. Total plasma cortisol levels are elevated in women taking the combined oral contraceptive pill (OCP) and during pregnancy because of the oestrogen-stimulated increase in CBG concentrations,[35] and therefore this can lead to false-negative results in women with adrenal insufficiency. Women taking the OCP who have low-normal total plasma cortisol levels may have clinical relevant deficiency of free cortisol. The OCP should therefore be ceased for at least six weeks, if possible, before measurement of total plasma cortisol levels. Conversely, patients with low CBG levels due to chronic liver disease or nephrotic syndrome have low total plasma cortisol levels, but may have normal free cortisol levels (false-positive results in total plasma cortisol).[3,36]

Importantly, in patients who present in suspected adrenal crisis, it is crucial that treatment be given immediately (after a blood sample is collected for spot cortisol and ACTH measurements), and further investigations are performed after clinical improvement.[33]

Table 2. Clinical features of primary adrenal insufficiency

	Pathophysiology[27]	Frequency (%) at diagnosis[25]
Symptoms		
Fatigue	GC and AA deficiency	95
Weight loss	GC deficiency	73
Loss of appetite	GC deficiency	67
Salt craving	MC deficiency	64
Nausea, vomiting or abdominal pain	GC and MC deficiency	62
Postural dizziness	MC and GC deficiency	56
Muscle or joint pain	GC deficiency	40
Signs		
Hyperpigmentation	High ACTH levels	74
Low blood pressure	MC and GC deficiency	68

Abbreviations: AA = adrenal androgen; ACTH = adrenocorticotrophic hormone; GC = glucocorticoid; MC = mineralocorticoid.

Basal morning cortisol and ACTH

Screening for adrenal insufficiency is performed by taking a morning plasma cortisol level, with a blood sample drawn before 9 am. We advocate that a blood sample for measurement of ACTH levels is taken at the same time in patients with suspected adrenal insufficiency to distinguish between primary and central types.

Morning plasma cortisol level of less than 100 nmol/L is strongly suggestive of true cortisol deficiency and further dynamic testing is generally not required.[37-40] However, the morning cortisol level that reliably predicts normal pituitary–adrenal function is less well established. Different plasma cortisol cutoffs between 300 and 500 nmol/L have been proposed based on studies that evaluated the correlation between basal morning cortisol and the response to ITT.[37,39,41] After review of the literature, Inder and Hunt concluded that morning plasma cortisol levels of more than 350 nmol/L predict normal response to ITT in 96% of individuals (Table 3).[37,39,41,42] For clinicians seeking a higher specificity, a basal cortisol level cutoff of 450 nmol/L predicts normal response to ITT (using peak cortisol criterion of 550 nmol/L) in 100% of individuals.[39,43]

The major drawback of the basal morning cortisol measurement is that many patients have indeterminate levels and may require additional dynamic testing.[44] Other limitations include the wide variability in a single measurement of cortisol, affected by factors such as diurnal rhythm, pulsatile secretion and stress.[36] Morning salivary free cortisol has been evaluated for the diagnosis of adrenal insufficiency,[40] but this test has not been fully validated as the only diagnostic test.[3]

Table 3. Diagnostic tests for primary adrenal insufficiency

Screening test: basal plasma cortisol and ACTH (before 9 am)	**Interpretation**
Cortisol	<100 nmol/L = definite adrenal insufficiency 100 to 350 nmol/L = indeterminate, adrenal insufficiency not excluded >350 nmol/L = excludes adrenal insufficiency in most (96%) individuals
ACTH	Elevated in primary adrenal insufficiency, usually >22 pmol/L
Confirmatory test: short Synacthen test	**Interpretation**
Peak cortisol response to Synacthen (250 µg) at 30 minutes and/or 60 minutes	>500 nmol/L (or preferably >550 nmol/L) = normal response

Measurement of the basal morning plasma ACTH concentration can generally distinguish between primary and central adrenal insufficiency.[3] In healthy people, the upper end of the normal range for ACTH is 12 pmol/L. In PAI, plasma ACTH concentrations are increased, usually higher than 22 pmol/L (Table 3).[27,28] Low cortisol with high ACTH levels should prompt urgent specialist referral of the patient and treatment of PAI. Low cortisol with low or normal ACTH levels indicates secondary or tertiary adrenal insufficiency and should prompt investigation of pituitary or hypothalamic disease.

Mineralocorticoid deficiency in PAI is characterised by high plasma renin and low or low-normal aldosterone concentrations.[27,28]

Short Synacthen test

Standard dose SST is the most commonly used dynamic test for the diagnosis of PAI.[28] This test involves stimulation of the adrenal glands by using a pharmacological dose (250 µg) of synthetic ACTH 1-24 (Synacthen), which has the full biological activity of endogenous 39-aminoacid ACTH.[45] Synacthen is administered intramuscularly or intravenously, and plasma cortisol levels are measured at baseline, and then 30 and 60 minutes after stimulation. Adrenal function is considered to be normal if the post-Synacthen plasma cortisol level is at least 500 nmol/L[44,46] or, preferably, at least 550 nmol/L[32,47] (Table 3). A peak cortisol response to Synacthen is a more useful measure of adrenal function than the incremental response, which depends on the basal cortisol value at the time of day SST is performed.[43,44]

It is important to exercise clinical judgement because SST cannot differentiate all patients with adrenal insufficiency from normal individuals. There are cases of people with PAI presenting with adrenal crisis months to years after initially normal SST, which may reflect isolated mineralocorticoid deficiency initially with subsequent development of glucocorticoid deficiency resulting in clinical deterioration.[48] Conversely, healthy individuals can show mildly abnormal responses to SST (post-Synacthen cortisol levels between 350 and 500 nmol/L), which are often normal on repeat testing.[3,44,47]

GPs can refer patients to an endocrinologist to organise an SST or refer them directly to private pathology providers that offer this service. However, patients with marked symptoms should not have their diagnosis delayed while waiting for an SST, but should be referred to an appropriate hospital for investigation and management.

The low dose (1 µg) Synacthen test has been studied in the investigation of central adrenal insufficiency,[49] and will not be discussed in this article.

Establishing the aetiological cause of PAI

Autoantibodies to the adrenal cortex or 21-hydroxylase are present in more than 90% of patients with autoimmune adrenalitis of recent onset.[3]

In patients without adrenal autoantibodies, investigations for nonimmune causes of PAI should be undertaken, firstly with CT of the adrenal glands to exclude tumours, infiltration, haemorrhage or calcifications typical of tuberculosis.[2,26] In clinical situations in which the cause of PAI is unclear, a CT-guided fine-needle biopsy of adrenal masses may be helpful in the differential diagnosis.[28] Men should be screened for adrenoleukodystrophy by measuring plasma concentrations of very-long-chain fatty acids. Table 1 summarises an approach to the aetiological diagnosis.

Management

Annual follow up by an endocrinologist is recommended for patients with diagnosed adrenal insufficiency. The management of PAI is beyond the scope of this article, and further information can be obtained from recent review articles.[2,3]

Conclusion

PAI is a potentially life-threatening, but treatable disorder, caused by deficiencies of all adrenocortical hormones. A high index of suspicion is required because the presentation is often nonspecific and can mimic other medical and psychiatric conditions. The screening test for PAI is measurement of basal morning cortisol and ACTH levels. SST should be performed in patients with indeterminate basal cortisol levels. Patients should be referred to an endocrinologist in cases of equivocal or normal diagnostic tests with high clinical suspicion of adrenal insufficiency, and also for long-term management of adrenal steroid replacement therapy and to screen for other autoimmune diseases. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

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CAROLINE JUNG MB BS(Hons), FRACP, PhD

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