Review Article

Adrenal Insufficiency - Aetiology, Diagnosis and Treatment

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Abstract

Adrenal insufficiency is caused by either primary adrenal failure or by hypothalamic-pituitary impairment of the corticotrophic axis. Adrenal insufficiency, first codified in 1855 by Thomas Addison, remains relevant in 2014 because of its lethal nature. Though, it is a rare disease but is life threatening when overlooked. Main presenting symptoms such as fatigue, anorexia and weight loss are nonspecific, thus diagnosis is often delayed. The diagnostic work-up is well established but some pitfalls remain. The diagnosis is adequately established by the 250 μg ACTH (adrenocorticotropic hormone) stimulation test in most cases. Glucocorticoids provide life saving treatment but long-term quality of life is impaired, perhaps because therapy is not given in a physiologic way. Dehydroepiandrosterone-replacement therapy has been introduced that could help to restore quality of life. It may be useful in pubertal girls, but not in adults. Monitoring of glucocorticoid-replacement is difficult due to 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.

Search strategy

We searched Medline and PubMed for reviews and original articles related to adrenal insufficiency.

Keywords used included adrenal insufficiency and incidence, prevalence, cause, origin, diagnosis, function test, imaging, hydrocortisone, glucocorticoid, mineralocorticoid, dehydroepiandrosterone, management, treatment, therapy, replacement, crisis, quality of life, well-being, pregnancy, prognosis, morbidity and mortality.

Keywords: Adrenal insufficiency; glucocorticoid.

Introduction

The cardinal clinical symptoms of adrenocortical insufficiency, as first described by Thomas Addison in 1855,¹ include weakness, fatigue, anorexia and abdominal pain, with orthostatic hypotension, salt craving and characteristic hyperpigmentation of the skin occurring with primary adrenal failure. The acute syndrome constitutes a medical emergency since it may result in a severe hypotensive crisis and clouded sensorium, together with pain in the muscles, joints or abdomen and fever.²³ However, life saving glucocorticoid replacement therapy for the

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condition did not become available until 1949, when Kendall, Sarett, and Reichstein first synthesized cortisone. Furthermore, despite this breakthrough, there are still many advances and challenges with respect to the management of individuals with adrenal insufficiency.2

**Epidemiology**

There are two types of adrenal insufficiency, primary and secondary. Chronic primary adrenal insufficiency has a prevalence of 93-140 per million worldwide and an incidence of 4.7-6.2 per million in white populations.4-7 These recent numbers are higher than those reported during the 1960s and 1970s,4,5 despite a continuous decline in tuberculous adrenalitis in the developed world that suggests an increase in incidence of autoimmune adrenalitis.6,7 The age at diagnosis peaks in the fourth decade of life, with women more frequently being affected than men.4-7 Secondary adrenal insufficiency has an estimated prevalence of 150-280 per million and also affects women more frequently than men.6,8-11 Age at diagnosis peaks in the sixth decade of life.7,8 Therapeutic glucocorticoid administration is thought to be the most common cause of secondary adrenal insufficiency. However, iatrogenic adrenal insufficiency becomes potentially relevant only during or after glucocorticoid withdrawal. Because iatrogenic adrenal insufficiency is transient in most cases,12 we suspect its prevalence to be lower than that of endogenous adrenal insufficiency.

**Cause**

Primary adrenal insufficiency -

During the times of Thomas Addison, tuberculous adrenalitis was by far the most prevalent cause of adrenal insufficiency. In the developing world, it remains a major factor.13 In active tuberculosis, the incidence of adrenal involvement is 5%.14

In primary adrenal insufficiency (AI), there is failure of production of all hormones from the adrenal cortex. It is most often caused by autoimmune destruction in developed countries (Table I).5,6 Adrenal insufficiency may occur alone, with other autoimmune diseases (polyglandular autoimmune syndrome type 2 and polygenic inheritance) or with hypoparathyroidism and mucocutaneous candidiasis (polyglandular autoimmune syndrome type 1) due to autosomal recessive inheritance of mutations in the autoimmune regulator (AIRE) gene.15

### Table I: Causes of primary adrenal insufficiency

<table>
<thead>
<tr>
<th>Cause</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune destruction</td>
<td>1 in 10,000 5,6</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>1 in 15,000 16</td>
</tr>
<tr>
<td>X-linked adrenoleukodystrophy</td>
<td>1 in 20,000 men 17</td>
</tr>
<tr>
<td>Drugs inhibiting steroidogenesis</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
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<tr>
<td>Hemorrhagic</td>
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Autoimmune polyglandular syndrome (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.18,19 Autoimmune polyglandular syndrome 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. Autoimmune polyglandular syndrome type 2 occurs with autosomal-dominant inheritance with incomplete penetrance, and shows a strong association with HLA DR3,20 and CTLA-4 (cytotoxic T lymphocyte antigen-4).21,22 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.23

Adrenoleukodystrophy (ALD) is an X-linked recessive disorder caused by mutations in the ABCD1 gene, resulting in defective oxidation of very long chain fatty acids (VLCFAs) and membrane and organelle dysfunction.17 The clinical features include spastic paralysis and
primary AI which may present in infancy or childhood. The milder ALD phenotype typically presents in adolescence or early adulthood. Other causes of primary adrenal insufficiency e.g. adrenal infiltration or haemorrhage are rare. Congenital or neonatal primary adrenal insufficiency accounts for only 1% of all cases.24

Secondary adrenal insufficiency -

The most frequent causes of secondary adrenal insufficiency are hypothalamic-pituitary-adrenal (HPA) axis suppression by chronic glucocorticoid therapy, tumour growth or treatment with surgery or irradiation of the hypothalamic-pituitary region. The condition if often associated with panhypopituitarism. Autoimmune lymphocytic hypophysitis is less frequent, mostly affecting women during or shortly after pregnancy. The differential diagnosis of postpartum autoimmune hypophysitis includes Sheehan’s syndrome, which results from pituitary apoplexy, mostly due to pronounced blood loss during delivery.25

Pathophysiology and clinical presentation

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.26 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.27

Patients with acute adrenal insufficiency - i.e. 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.28 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.

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 (failure to thrive in children), and can account for muscle and joint 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.28 In secondary adrenal insufficiency; diagnosis is generally prompted by a history of steroid intake or pituitary disease, but often delayed e.g. 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 e.g. palmar creases, knuckles, scars and oral mucosa.

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.29

Mineralocorticoid deficiency, which is present only in primary adrenal insufficiency, leads to dehydration and hypovolaemia, resulting in low blood pressure, postural hypotension, and sometimes even in pre renal 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 pressure30 and reverses cardiac dysfunction.31 Glucocorticoids contribute to this
improvement not only by mineralocorticoid receptor binding, but also by permissive effects on catecholamine action. Mineralocorticoid deficiency accounts for hyponatraemia (90% of patients with primary adrenal insufficiency), hyperkalaemia (65%), and salt craving (15%). 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. 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. Thus dehydroepiandrosterone deficiency could contribute to the impairment of wellbeing noted in patients with adrenal insufficiency despite adequate glucocorticoid and mineralocorticoid replacement.

Diagnosis

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.

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. 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. The impaired ability of the adrenal cortex to respond to ACTH is readily demonstrated by the standard short corticotropin test. Traditionally, AI is diagnosed biochemically by measuring serum cortisol before and/or 60 minutes after intravenous administration of 250 μg synthetic ACTH. Any value ≥ 18 μg/dL usually defines a normal response. It has been suggested that ACTH stimulation testing could also lack sensitivity in chronic secondary adrenal insufficiency, because it achieves supra-physiological levels of ACTH. Instead, a 1 μg dose was proposed and initially was reported to perform similarly to the 250 μg test. Such low specificity may lead to unnecessary lifelong glucocorticoid replacement. Moreover, there is more experience regarding marginal test responses to the 250 μg dose. Therefore, we currently favor the use of the 250 μg ACTH stimulation test for diagnosis. Adrenal cortex auto antibodies or antibodies against 21-hydroxylase are present in more than 80% of patients with recent onset autoimmune adrenalitis.

Secondary adrenal insufficiency-

Baseline hormone measurements differ little between patients with secondary adrenal insufficiency and healthy individuals. However, a morning cortisol value below 100 nmol/L indicates adrenal insufficiency whereas a serum cortisol greater than 500 nmol/L is consistent with an intact HPA axis. Thus, in most instances, dynamic tests of the hypothalamic-pituitary-adrenal axis are required to establish a diagnosis of secondary adrenal insufficiency. The insulin tolerance test is regarded as the gold standard in the assessment of suspected secondary adrenal insufficiency, since hypoglycaemia (blood glucose <2.2 mmol/L) is a powerful stressor that results in rapid activation of the hypothalamic-pituitary-adrenal axis. An intact axis is indicated by a peak cortisol of more than 500 nmol/L at any time during the test. Occasionally, however, a patient will pass the insulin tolerance test despite exhibiting clinical evidence for adrenal insufficiency that responds to hydrocortisone substitution. A higher cut-off value (550 nmol/L) for peak cortisol in the insulin tolerance test could help to reduce...
misclassification. During the test, close supervision is mandatory and cardiovascular disease or history of seizures are contraindications. Sustained secondary adrenal insufficiency leads to adrenal atrophy and also to reduce ACTH receptor expression in the adrenal gland, since ACTH up-regulates its own receptor. Thus adrenal responsiveness to an acute exogenous ACTH challenge is impaired also in secondary disease, facilitating the use of the standard short corticotropin test for the assessment of axis integrity. Since the administration of 250 μg ACTH represents a massive supraphysiological challenge, a low-dose corticotropin test that uses only 1 μg ACTH has been proposed as a more sensitive test for the diagnosis of secondary adrenal insufficiency. The test has been successfully used to monitor recovery of adrenal function after withdrawal of oral glucocorticoids and to detect subtle impairment of adrenal reserve during inhaled steroid therapy. However, the intravenous administration of 1 μg ACTH still results in hormone concentrations greater than those required for maximum cortisol release.

Special diagnostic situations -

**Adrenal insufficiency after pituitary surgery**

Screening for adrenal insufficiency with the standard short corticotropin test or with the low-dose corticotropin test should be done 4-6 weeks or more after surgery for pituitary surgery, since adrenal atrophy can develop only gradually after onset of ACTH deficiency. Until then, patients with a morning cortisol not excluding secondary adrenal insufficiency (< 450 nmol/L at 3 days and < 350 nmol/L at 7 days after surgery) should receive hydrocortisone replacement, and withheld for 24 h before scheduled testing of adrenal function.

**Adrenal insufficiency in critically ill patients**

In critically ill patients, the corticotropic axis is greatly activated. Moreover, patients in intensive care are less sensitive to dexamethasone suppression and achieve higher peak ACTH and cortisol concentrations after administration of corticotropin-releasing hormone. Critically ill patients also have fairly low serum concentrations of aldosterone with concurrently raised plasma renin activity.

Unfortunately, no consensus exists about how to diagnose adrenal insufficiency in these individuals. In patients with primary or severe secondary adrenal insufficiency the standard short corticotropin test will establish a diagnosis by indicating a low baseline cortisol (< 165 nmol/L) not responding to corticotropin (peak cortisol < 500 nmol/L).

**Imaging**

Adrenal imaging is not indicated in patients with an unequivocal diagnosis of autoimmune adrenalitis or adrenomyeloneuropathy. If infection, haemorrhage, infiltration, or neoplastic disease is suspected, abdominal CT scans should be done. In adrenal tuberculosis, bilateral enlargement is present in the subacute phase, whereas calcifications develop during later stages. In secondary adrenal insufficiency of unknown origin, MRI of the hypothalamic-pituitary region is the method of choice to reveal a space-occupying lesion. Only pituitary adenomas with a diameter of greater than 1 cm will cause secondary adrenal insufficiency; smaller microadenomas are coincident. Lymphocytic hypophysitis might initially present as pituitary enlargement, sometimes leading to the misdiagnosis of a pituitary tumour, whereas the long-term course leads to pituitary atrophy and subsequent empty sella.

**Treatment**

Current recommendations for oral replacement doses of hydrocortisone are lower at 10-12 mg/m² BSA, although many patients receive higher equivalent doses. Glucocorticoid replacement is usually given in two or three daily doses, with a half to two-thirds of the daily dose administered in the morning to mimic the physiological cortisol secretion pattern. Findings of studies indicate that daily cortisol production rates vary between 5
mg/m² and 10 mg/m², equivalent to the oral administration of 15-25 mg hydrocortisone (cortisol) or 25.0-37.5 mg cortisone acetate. Initial glucocorticoid treatment provides great symptomatic improvement in AI. However, patients taking chronic adrenal hormone replacement report reduced quality of life (QOL) compared with healthy controls. Possible explanations include non physiological glucocorticoid replacement and lack of adrenal androgen replacement. The observation that patients with primary and secondary adrenal insufficiency experience similar impairments suggests that inappropriate mineralocorticoid replacement is unlikely to be the cause.

Normally cortisol levels peak before waking and fall to a nadir during night time sleep. However, even three daily doses of hydrocortisone cannot approximate this rhythm, and a recent study reported no differences in QOL between two or three daily doses. Another option is to use a longer acting glucocorticoid, such as prednisolone or prednisone, in a more convenient single morning dose. However, no differences in QOL were reported between patients taking hydrocortisone or prednisolone. In general, if a twice daily regimen is applied, the second dose should be administered about 6-8 h after the first. Long-acting glucocorticoids are also used for replacement (1 mg hydrocortisone = 1.6 mg cortisone acetate = 0.2 mg prednisolone = 0.05 mg dexamethasone). Prednisolone and dexamethasone have much longer biological half lives than hydrocortisone and cortisone acetate, which could result in unfavourably high night time glucocorticoid activity.

Dehydroepiandrosterone (DHEA) replacement continues to be controversial, with conflicting reports regarding QOL. Some postulate that DHEA insufficiency explains the impaired QOL in AI, particularly in women. Healthy men derive most androgens from the testes so that the androgenic effects of DHEA are presumably less important. Mineralocorticoid replacement (only required in primary adrenal insufficiency) consists of oral administration of 0.05-0.2 mg fludrocortisone. Monitoring includes measurement of blood pressure, serum sodium, and potassium and plasma renin activity, aiming at concentrations within the middle or upper normal.

Treatment surveillance of chronic glucocorticoid replacement is mainly based on clinical grounds because no objective assessment has proven to be reliable for monitoring replacement quality. ACTH cannot be used as a criterion for glucocorticoid dose adjustment, since in primary adrenal insufficiency it is invariably high before the morning dose and rapidly declines with increasing cortisol concentrations after glucocorticoid ingestion. Thus, in the absence of objective variables to measure replacement quality, the doctor has to rely primarily on clinical judgment, taking into account signs and symptoms potentially suggestive of glucocorticoid over replacement or under-replacement. Under replacement bears the risk of incipient crisis and severe impairment of wellbeing. Conversely, chronic over replacement can lead to substantial morbidity, including impaired glucose tolerance, obesity, and osteoporosis. With recommended replacement doses of 15-25 mg hydrocortisone osteoporosis is not to be expected. Therefore, bone-mineral-density measurements are not required for regular monitoring in adrenal insufficiency.

Critical illness

Part of the physiological response to critical illness is an increase in serum cortisol. To mimic this increase, patients with AI are advised to double or even triple their glucocorticoids dose for febrile illness and are usually given at least 200 mg hydrocortisone parenterally on the day of major surgery.

Prevention and management of adrenal crisis

Risk of crisis was much higher in primary adrenal insufficiency (3.8 per 100 vs 2.5 per 100 years) and in women (4.4 per 100 vs 1.6 per 100 years) with the highest overall risk in women with autoimmune adrenalitis (6.5 per 100 years). Most
crises were due to glucocorticoid dose reduction or lack of stress related dose adjustment by patients or family practitioners. All patients and their partners should receive regular crisis prevention training, including verification of steroid emergency card or bracelet and instruction on stress-related glucocorticoid dose adjustment. Patients should add 5-10 mg hydrocortisone to their normal regimen shortly before strenuous activities e.g., hiking. More severe physical stress such as fever requires doubling of daily doses until recovery. In instances of vomiting or diarrhoea, glucocorticoids should be administered parenterally. For major surgery, trauma, and diseases that require monitoring in intensive care, patients should receive intravenous infusions of 100-150 mg hydrocortisone in 5% glucose per 24 h. Management of acute adrenal crisis consists of immediate intravenous administration of 100 mg hydrocortisone followed by 100-200 mg per 24 h and continuous infusion of larger volumes of physiological saline solution (initially 1 L/h) under continuous cardiac monitoring. With daily hydrocortisone doses of 50 mg or more, mineralocorticoid replacement in primary adrenal insufficiency can be reduced because this dose is equivalent to 0.1 mg fludrocortisone.

Special therapeutic situations - Thyroid dysfunction

Hyperthyroidism increases cortisol clearance. In patients with adrenal insufficiency and unresolved hyperthyroidism, glucocorticoid replacement should be doubled or tripled. To avoid adrenal crisis, thyroxine replacement for hypothyroidism should only be initiated after concomitant glucocorticoid deficiency has either been excluded or treated.

Pregnancy

Pregnancy is physiologically associated with a gradual increase in cortisol-binding globulin and, during the last term, also in free cortisol. Serum progesterone concentrations also increase, exerting antimineralocorticoid action. Therefore, during the third trimester, hydrocortisone replacement should be increased by 50%. Mineralocorticoids should be adjusted according to blood pressure and serum potassium. Peripartum hydrocortisone replacement should follow the requirements for major surgery - i.e., 100 mg per 24 h starting with labour and continuing until 48 h after delivery, followed by rapid tapering.

Conclusion

Prospective data indicate excess mortality in hypopituitarism, including secondary adrenal insufficiency, mainly due to vascular and respiratory disease. However, deficiencies of other hormonal axes could also contribute. Despite adequate glucocorticoid and mineralocorticoid replacement, health-related quality of life is greatly impaired in patients with primary and secondary adrenal insufficiency. Predominant complaints are fatigue, lack of energy, depression, and anxiety. In addition, affected women frequently complain about impaired libido. However, fine-tuning of glucocorticoid replacement leaves only a narrow margin for improvement, and changes in timing or dose do not result in improved wellbeing. Dehydroepiandrosterone replacement in adrenal insufficiency can improve wellbeing, mood, and - in women - libido, and opens up the prospect of improving quality of life for patients with chronic adrenal insufficiency. In critical illness, glucocorticoids may reverse hemodynamic shock independent of adrenal function but do not improve mortality.

References


