Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2010 June ; 17(3): 217–223. doi:10.1097/MED.0b013e328338f608.

Adrenal Insufficiency- etiology, diagnosis and treatment

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Abstract

Purpose of review—Adrenal insufficiency, first codified in 1855 by Thomas Addison, remains relevant in 2010 because of its lethal nature.

Recent findings—Reports illuminate features of adrenal insufficiency etiology, diagnosis and treatment, and the role of glucocorticoids in critical illness.

Summary—Progress has been made in identifying HLA and MHC alleles that predispose to the development of adrenal insufficiency in patients with antibodies to 21-hydroxylase, but their role in clinical care is not established. Reports of HIV-associated infections and medication-induced hypocortisolism are reminders that autoimmune adrenal destruction does not underlie all cases. The diagnosis is adequately established by the 250 µg ACTH stimulation test in most patients; the 1 µg test carries the risk of misdiagnosis of healthy individuals as adrenally insufficient. Glucocorticoids provide life saving treatment, but long-term quality of life is impaired, perhaps because therapy is not given in a physiologic way. The current recommended total daily dose is lower than that often prescribed. DHEA replacement may be useful in pubertal girls, but not in adults. Supraphysiologic hydrocortisone doses may aid in the reversal of septic shock independent of underlying adrenal function.

Keywords

adrenal insufficiency; ACTH stimulation; autoimmunity; glucocorticoids

Introduction

The features of primary adrenal insufficiency (AI) that Thomas Addison eloquently described in 1855 [1] (weakness, fatigue, anorexia, salt craving and orthostatic hypotension) remain important to recognize because treatment may be life saving. Recent publications shed light on the cause, diagnosis, and treatment of AI, and continue the controversy about “relative adrenal insufficiency” in critical illness.

Causes of primary adrenal insufficiency

In primary AI, there is failure of production of all hormones from the adrenal cortex; it is most often caused by autoimmune destruction in developed countries [2,3] (Table 1). AI 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 AIRE gene [6].

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The authors declare no conflicts of interest.

There is considerable interest regarding genetic predispositions to develop autoimmune adrenal insufficiency, in addition to the known association of the HLA genotype DR3/4-DQB1*0302 with type 1 diabetes and AI. In two recent studies, the DRB1*0404 allele was more common in patients with AI than in control subjects [7**,8**]. In a study of 63 patients with type 1 diabetes and their relatives, who had positive 21-hydroxylase antibodies, this haplotype was not associated with progression to frank adrenal insufficiency. However, the allele frequency of another major histocompatibility complex gene, MICA5.1, was increased in those who progressed, with a hazards ratio 8.628 (95% confidence interval 2.029–36.696) [8]. This allele encodes a truncated protein and has an increased frequency in other autoimmune disorders [9,10]. A clinical role for determination of the MICA5.1 status in patients with 21-hydroxylase antibodies is not established, as some without the allele develop AI. Patients at higher risk, such as those with type 1 diabetes, should continue to undergo ACTH stimulation testing based on annual clinical assessment.

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 [5]. 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. As AI can be the initial feature, adrenoleukodystrophy should be considered in young males with AI and confirmed biochemically with elevated plasma VLCFAs.

Recent reports drew attention to infectious and drug-related causes of adrenal insufficiency. HIV-associated immunosuppression has led to resurgence in infectious causes (e.g. tuberculous and CMV adrenalitis) [11*]. Agents that may significantly reduce cortisol synthesis include anti-fungal agents and as little as a single dose of the anesthetic etomidate [12*]. Novel tyrosine kinase targeting drugs, such as sunitinib, may cause AI in animals [13]; human reports are awaited.

Diagnosis

Traditionally, AI is diagnosed biochemically by measuring serum cortisol before and 30, 45 and/or 60 minutes after intravenous administration of 250µg synthetic ACTH. Any value $\geq$ 18µg/dl usually defines a normal response [14]. This test can diagnose secondary AI resulting from insufficient endogenous ACTH, which ultimately results in adrenal atrophy and a reduced cortisol response. However ACTH stimulation testing should not be used before adrenal atrophy has occurred (e.g. after recent pituitary surgery). 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 1µg dose was proposed and initially was reported to perform similarly to the 250µg test [15]. In 2008, Kazluoskaite et al. reported that the 1µg test was superior based on a meta-analysis of 679 patients with suspected secondary adrenal insufficiency, using a cortisol diagnostic threshold of 16µg/dl [16**]. However, as Stewart and Clarke point out in their response letter, this superiority required exclusion of five studies that used a fluorescence immunoassay, with correction of plasma cortisol values to their expected serum values, thus reducing its generalizability [17**].

Significant proportions of healthy children [18*] and adults [19,20*] fail the 1 µg test if a cortisol criterion of 18 µg/dl is used. This may be explained in part by incomplete delivery of the dose [20]. Such low specificity may lead to unnecessary lifelong glucocorticoid replacement. Moreover, there is more experience regarding marginal test responses to the 250µg dose [17,21]. Therefore, we currently favor the use of the 250µg ACTH stimulation test for diagnosis.

The 10% of total serum cortisol not bound to corticosteroid binding globulin (CBG) is thought to be biologically active, so measurement of this free fraction may better reflect underlying cortisol physiology [22]. In a recent study, salivary (free) cortisol performed similarly but not better than serum (total) cortisol during a 250 µg ACTH-stimulation test in patients with secondary AI [23*]. If free serum and salivary cortisol assays become more widely available and characterized, they may prove helpful, particularly in patients with abnormal CBG concentrations.

Treatment

Improved assay techniques show that daily physiological production of cortisol, 5-6mg/m² body surface area (BSA), is lower than initially estimated [24]. Consequently, current recommendations for oral replacement doses of hydrocortisone are lower at 10-12 mg/m² BSA, although many patients receive higher equivalent doses [7]. Swedish patients with primary AI had over a 2-fold increase in mortality compared with age-matched controls [25]. The excess deaths were due to cardiovascular, malignant and infectious diseases, which might be attributable to supra-physiological glucocorticoid doses. Patients with secondary AI and hypopituitarism also have increased mortality [26]. However there was no evidence that patients with corticotroph deficiency requiring glucocorticoid treatment had higher mortality than those with other pituitary hormonal deficiencies. (GH deficiency was not assessed in all patients and may have been a confounding factor) [26]. Therefore the excess mortality associated with hypopituitarism may not be attributable to supra-physiological steroid dosing.

Glucocorticoid excess may decrease bone mineral density (BMD). Løvas et al reported small reductions in BMD in patients with primary AI (compared to a reference population, mean Z scores at femoral neck and lumbar spine ranged from -0.57 to -0.17) [27*]. On average, the patients were taking higher than recommended glucocorticoid doses. These findings support recommendations to use lower doses. Low circulating levels of adrenal androgens may also contribute to the lower bone mineral density seen in AI [28].

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 [29]. 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 [29] suggests that inappropriate mineralocorticoid replacement is unlikely to be the cause.

We currently cannot reproduce the circadian rhythm of endogenous cortisol production. Normally cortisol levels peak before waking and fall to a nadir during nighttime sleep [30]. 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 [31*]. 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 a study that did not address the effect of dose equivalence [32*].

Hydrocortisone administration via a subcutaneous pump is a novel strategy for glucocorticoid replacement, with the potential to provide the early morning cortisol surge. A total daily dose of 10mg/m² hydrocortisone restored normal circadian rhythm in most patients [33]. In a recent pilot study Harbeck et al. administered a single infusion of hydrocortisone from midnight to 0800h to 14 patients [34*]. 0800h cortisol levels were normal to increased following the infusion, but low a few weeks later. There were no differences between post-infusion and basal QOL or cognition measures, apart from impaired memory in those with highest post-infusion

cortisol levels. A larger study with longer treatment duration is needed to investigate this strategy further.

New hydrocortisone modified-release formulations, a preparation by DuoCort and Chronocort® (Phoqus Pharmaceuticals Ltd) are in development [35*,36*]. These formulations may provide more physiological pharmacokinetics with higher levels of cortisol on waking, and long-term studies of effects on QOL and other parameters are awaited.

Dehydroepiandrosterone (DHEA) replacement continues to be controversial, with conflicting reports regarding quality of life [37,38]. DHEA levels are low at birth, increase beginning around age of 6-10 years, peak around age 24 and decline thereafter [39]. 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.

A 50mg daily dose of DHEA has been reported to provide physiological replacement [40]. Alkatib et al. performed a meta-analysis of 10 trials lasting three months or more, which quantified QOL, depression, anxiety and sexual function in adult women with primary or secondary adrenal insufficiency [41**]. In eight studies using a 50mg daily dose, all women achieved normal serum DHEA levels and most women had normal levels in the other studies with doses of 20-30mg. There was a small overall improvement in quality of life and a small reduction in depression scores in women receiving DHEA compared with placebo, but no significant effect on anxiety or sexual well-being. The authors concluded that the small effect size did not justify routine supplementation.

DHEA treatment may have a role in pubertal females, however. Binder et al. examined the effect of 25mg DHEA or placebo for 12 months in females of mean age 23 years (range 13-25) with secondary adrenal insufficiency, two or more additional pituitary hormone deficiencies, and a low DHEA level [42**]. The main endpoints were pubic hair stage score and psychometric evaluation. There was significant improvement in pubic hair development only in the DHEA group (from Tanner stage I-III to Tanner stage II-V; mean change +1.5 stages). Using the SCL-90-R measures of psychological distress, the DHEA group improved from baseline to 12 months in all 10 scores whereas the placebo group worsened. Thus, supplementation of DHEA when levels are normally highest may be beneficial, and deserves further study.

DHEA has been reported to improve markers of endothelial function in middle-aged men with hypercholesterolemia [43], and in post-menopausal women [44]. Given the increased cardiovascular mortality in AI [25,26], Rice et al. hypothesized that 50mg DHEA daily for 12 weeks would improve endothelial function [45*]. They reported a small reduction in HDL cholesterol but no changes in markers of endothelial function in men and women with AI who received DHEA compared with placebo. The relatively short treatment period might explain the lack of an effect. A similar, but uncontrolled, study in women showed a significant reduction in total and HDL cholesterol, and larger HDL particles, resulting in a less favorable lipid profile [46]. These data suggest that DHEA should not be given with the aim of reducing cardiovascular risk.

Statin therapy was proposed as a treatment for the underlying high levels of very long chain fatty acids (VLCFAs) in adrenoleukodystrophy (ALD) following an early report that lovastatin reduced the plasma VLCFAs concentrations in five patients [47]. This finding was not subsequently reproduced with simvastatin [48]. Recently, Engelen et al. compared a 22-week course of 40mg lovastatin daily to placebo in 14 men with adrenoleukodystrophy [49*]. The expected LDL cholesterol reduction was associated with decreases in plasma but not erythrocyte or lymphocyte VLCFA levels. Therefore the authors recommend that lovastatin

should not be prescribed to treat ALD. We agree that current evidence does not support the use of lovastatin, or indeed simvastatin or other statins as treatment for ALD. However patients with adrenoleukodystrophy require standard adrenal hormonal replacement if there is evidence of adrenal insufficiency.

An alternative approach to adrenocorticoid hormone replacement was described in a fascinating case report of adrenal transplantation [50**]. A previously healthy 5-year-old girl developed renal and adrenal insufficiency due to meningococcal septicemia, requiring hemodialysis, and glucocorticoid and mineralocorticoid replacement. She later received a living-donor one haplotype matched kidney and adrenal gland. The adrenal gland was divided into small pieces and these were then transplanted into the rectus abdominus muscle. Three years later she was well on low dose immunosuppression without glucocorticoids. The 30-minute cortisol value after 250 µg ACTH administration was normal (30.1 µg/dl). The suprarenal area showed no uptake of radiolabeled octreotide, suggesting continued lack of eutopic adrenal gland function. This successful outcome motivates consideration of adrenal gland transplantation in the rare situation of renal transplantation in a patient with AI.

Critical Illness

Part of the physiological response to critical illness is an increase in serum cortisol [51]. 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 200mg hydrocortisone parenterally on the day of major surgery. However, as Loriaux and Fleseriu argue [52*], the rise in serum cortisol may be a biomarker of severe stress rather than a necessary level for recovery.

Clinicians and scientists have postulated since the 1970s that an inadequate increase in endogenous glucocorticoids in critically ill but previously healthy patients, so called “relative adrenal insufficiency”, could contribute to morbidity and mortality. Based on this hypothesis, up to 8000mg equivalent daily doses of hydrocortisone were given to patients with severe sepsis in the 1980s [53]. Although an initial study was promising [53], a larger study showed that the treatment achieved earlier shock reversal but no reduction in mortality [54]. More recently such patients have received lower so-called ‘physiological stress’ doses of hydrocortisone (200mg/day) [55].

There is no consensus regarding the clinical or biochemical definition (or importance) of relative adrenal insufficiency. In the intensive care setting, a cortisol increase after ACTH administration from baseline (Δ cortisol) of $<9\mu\text{g/dl}$ is often regarded as diagnostic [56]. Important confounding factors for test interpretation are the variable cortisol baselines and CBG and albumin concentrations, which tend to fall in critical illness, reducing total without necessarily reducing free cortisol levels [57].

In a prospective study by the CORTICUS group, 499 patients with septic shock were randomized within 24 hours to receive 50mg hydrocortisone every 6 hours or placebo for 5 days regardless of their response to ACTH [58]. Hydrocortisone was then tapered over 6 days. About 50% of patients ‘responded’ to ACTH with a Δ cortisol $>9\mu\text{g/dl}$. Shock reversal occurred earlier with hydrocortisone treatment, perhaps because of improved blood pressure response to vasopressor agents [59]. There was no significant difference in mortality at 28 days, in contrast with a previous study by Annane et al. [55]. There are possible explanations for these conflicting results: the CORTICUS patients were less sick with a lower mean simplified acute physiologic II (SAPS II) score, which is a measure of disease severity in the intensive care setting; the patients in the CORTICUS study received glucocorticoids later while patients in the Annane study also received daily fludrocortisone.

A subsequent consensus statement by the American College of Critical Care Medicine suggested that hydrocortisone therapy should be considered in patients with septic shock, particularly for those who respond poorly to fluid resuscitation and vasopressor agents, regardless of a random total cortisol value or the response to ACTH [60*].

In a further study, Bendel et al. examined free serum cortisol levels in patients with septic shock [61*]. Interestingly, survivors had lower total and free cortisol than non-survivors and there were no differences in mortality between those who did and did not receive glucocorticoids. These patients had better overall outcomes than patients in other studies and the authors suggested that the reason could be that more severe cases were treated with glucocorticoids and therefore excluded. Overall, the role of endogenous and exogenous glucocorticoids in recovery from critical illness is not understood and deserves further study.

Conclusion

Patients with autoimmune diabetes are at risk of developing adrenal insufficiency. Certain HLA genotypes and MHC alleles increase the probability of adrenal insufficiency. However their role in clinical care is not established and testing for these genes should not be used in routine clinical practice at this time. The 250 µg ACTH stimulation test provides the diagnosis of adrenal insufficiency in most patients. Measurement of free serum or salivary cortisol may be useful when CBG is low, but requires standardization. Adrenal insufficiency is associated with reduced quality of life that may be caused by non-physiological glucocorticoid replacement. DHEA insufficiency is unlikely to play a major role in quality of life of adults, and routine replacement is not warranted. In critical illness, glucocorticoids may reverse hemodynamic shock independent of adrenal function but do not improve mortality.

Acknowledgments

This work was supported by the intramural program of the National Institute of Child Health and Human Development, NIH

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data support the concept that the rise in serum cortisol in critical illness is a marker of stress rather than being an important factor in recovery.

Table 1

Causes of primary adrenal insufficiency

Cause	Prevalence (if known)
Autoimmune destruction	1 in 10,000 [2,3]
Congenital adrenal hyperplasia	1 in 15,000 [4]
X-linked adrenoleukodystrophy	1 in 20,000 men [5]
Drugs inhibiting steroidogenesis	
Infectious	
Hemorrhagic	