Diagnosis and management of Addison's disease: insights gained from a large South African cohort

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Keywords: Addison's disease, aetiology, management, complications

Abstract

The prevalence of Addison's disease in South Africa is lower than in Western countries. This is concerning, since patients could be dying, undiagnosed. Enhanced awareness of this highly treatable condition is warranted. The epidemiology, aetiology, clinical presentation, screening and management of Addison's disease are discussed. Autoimmunity predominated as the underlying aetiology mostly in patients of European descent. A low threshold is required for screening, intervention and follow-up of all patients for cardiovascular risk factors, given the atherogenic profile observed among Addison's disease sufferers in South Africa.

Background

Although over 60 years have elapsed since the emergence of life-saving glucocorticoid replacement therapy for Addison's disease, multiple challenges relating to its diagnosis and management remain.[1] Several recent studies have confirmed that the survival rate, despite glucocorticoid and mineralocorticoid replacement, is not normal, with the accelerated mortality being attributed to cardiovascular and cerebrovascular disease.[2,3]

Epidemiology

There is a paucity of information as to the epidemiology of Addison's disease from the developing world. Addison's disease occurs in 39-144 people per million people in the Western world.[4-6] However, a recent South African Addison's study that sought to identify every case found the prevalence to be 3.1 per million. Whether patients may be dying with the disease undiagnosed or whether the disease is less common in South Africa is uncertain. In this study of South African Addison's disease patients, autoimmunity as the underlying aetiology occurred in exclusively white and mixed-ancestry patients.[7]

Clinical presentation

Acute primary adrenal insufficiency is characterised by orthostatic hypotension, agitation, confusion, circulatory collapse, abdominal pain and fever. Acute adrenal decompensation is caused by haemorrhage per se or,

rarely, by bleeding into metastases of the adrenal glands, often precipitated by coexistent acute infection leading to death if left untreated.[8,9]

The diagnosis of chronic primary adrenal insufficiency is frequently preceded by a history of prolonged hyperpigmentation, malaise, fatigue, anorexia, weight loss, gastrointestinal disturbance, and joint and back pain. Patients may crave salt and develop unusual food preferences, such as drinking pickling brine.[10]

Hyperpigmentation is the most frequently encountered symptom. It is more easily recognised in the sun-exposed areas of the face, neck and arms, and it also occurs on areas that are subject to trauma, such as the knees and knuckles. However, hyperpigmentation may be more difficult to recognise in darker-skinned races, as the palmar creases and mucous membranes are often normally pigmented.[8] Extensive or progressive hyperpigmentation at any of these sites should alert clinicians to the possibility of Addison's disease. However, increasing pigmentation of the skin is not diagnostic of primary hypoadrenalism.[6] Scalp hair may also become darker, new naevi may be observed[11] and calcification of the cartilage of the ear may occur.[12]

Hyponatraemia, hypoglycaemia, hyperkalaemia, unexplained eosinophilia and mild prerenal azotaemia are, together, highly suggestive of primary hypoadrenalism.[5,13] Although the finding of recurrent hypoglycaemia in a type 1 diabetic should alert a clinician to the possibility of Addison's disease, it is an uncommon cause of recurrent

hypoglycaemia (1%).[14,15] In the South African cohort, similar to other studies, hyperpigmentation, nausea, vomiting and weight loss were the most prominent features.[16,17]

Screening for primary adrenal failure

The adrenal cortex, responsible for the release of cortisol and androgens, is under the negative feedback control of adrenocorticotropic hormone (ACTH), while the release of aldosterone is controlled by the renin-angiotensin II system. Progressive functional deterioration, as in autoimmune destruction of the adrenal cortex, results in diminished functional adrenal reserve, as shown by reduced plasma concentration of cortisol and aldosterone in association with an increased ACTH and renin release.[18]

The short synthetic ACTH stimulation test is regarded as the most reliable diagnostic test for chronic adrenal hypofunction. Synthetic ACTH can be injected intravenously or intramuscularly,[19,20] but the dosage used, whether 1 µg or 250 µg, is vastly supraphysiological. Nevertheless, the 250 µg ACTH stimulation test provides the best sensitivity and specificity for confirmation of primary adrenal insufficiency. Subjects who have either basal or stimulated cortisol levels in excess of 500 nmol/l, do not have overt Addison's disease.[1,20] However, when an early morning (between 07h00 and 09h00) plasma cortisol is less than 165 nmol/l and a simultaneously taken plasma ACTH is elevated, no further confirmatory test is needed.[1]

The short synthetic ACTH stimulation test can also be used to diagnose secondary hypoadrenalism. With regard to the dose of ACTH to be used, a meta-analysis showed that the low-dose (1 µg) and the standard-dose (250 µg) ACTH stimulation test performed similarly, but the receiver operating curves using the 1 µg performed slightly superiorly in ruling out hypothalamic-pituitary adrenal axis insufficiency. However, the differences were clinically unimportant.[21]

Betterle et al proposed that subclinical autoimmune adrenalitis may evolve through three defined stages: stage 1, when both ACTH and basal plasma cortisol levels are normal, with concomitant elevated plasma renin activity and reduced or normal aldosterone levels; stage 2, when ACTH levels are normal but the peak stimulated plasma cortisol level is reduced; and stage 3, when the ACTH level is elevated through compensation but the basal plasma cortisol is reduced. Should stress, surgery, pregnancy, infection or trauma coexist in stage 3 of subclinical disease, overt clinical hypoadrenalism may manifest. Adrenal cortical mass declines throughout these predetermined subclinical stages.[18] Subclinical hypoadrenalism should be considered when the ratio of ACTH (pmol/l) to cortisol (nmol/l) is increased to greater than 0.028.[22] This is evident in early autoimmune primary adrenal insufficiency, when patients exhibit reduced sensitivity to low-dose ACTH stimulation.[23]

Patients with autoimmune polyglandular syndromes (APS) without Addison's disease are at increased risk of subsequently developing Addison's disease. The presence of either adrenocortical autoantibodies (ACA) or 21-hydroxylase autoantibodies in this subgroup represents a good marker of developing subsequent Addison's disease, which was found to be greater in coexistent hypoparathyroidism than either type 1 diabetes mellitus and/or autoimmune thyroid disease.[18] However, the presence of either circulating ACA or 21-hydroxylase antibodies does not invariably indicate that adrenalitis or incipient hypoadrenalism will occur. For example, a baby born to a mother who had ACA and 21-hydroxylase autoantibodies, Addison's disease and coexisting hypothyroidism (APS2) did not develop either clinical or subclinical hypoadrenalism until 34 months of age, suggesting that an additional factor other than positive adrenal autoantibodies is required to induce Addison's disease.[24] In Padua, Italy, the cumulative risk of developing autoimmune Addison's disease was 48.5% among ACA-positive subjects, identifying a subgroup in which screening using 250 µg ACTH stimulation test needs to be performed periodically.[25] It has not been our routine practice to screen for adrenal autoantibodies in patients with APS without Addison's disease, except in the research setting, where only 3% were found to have positive adrenal autoantibodies.

Aetiology

The aetiology of Addison's disease has changed over time. The latter half of the 20th century has seen a decline of Addison's disease attributed to tuberculosis from 33% to 2.6%, and the majority of cases are now thought to be autoimmune in origin. It is only since the discovery of specific adrenal autoantibodies that a definitive diagnosis of autoimmune Addison's disease can be made.[18] Autoimmune Addison's disease is the most common form of primary adrenal insufficiency in Western countries, accounting for 68-94% of cases, even when assessment by adrenal autoantibody assays has occurred in excess of 10 years after the onset of clinical disease. In an Italian study, 70% of patients with previously designated idiopathic Addison's disease of less than 20 years' duration were positive for adrenal autoantibodies, consistent with an autoimmune aetiology. ACA and 21-hydroxylase autoantibodies were reported in up to 90% of patients with recent-onset autoimmune Addison's disease, compared with 0.3% among healthy Italian control subjects.[26] Autoimmune Addison's disease may occur as an isolated condition or

in association with APS. In childhood, APS1 occurs in association with hypoparathyroidism and mucocutaneous candidiasis, and in adulthood APS2 occurs in association with type 1 diabetes mellitus and autoimmune thyroid disease.[11]

A wide variety of infections have been thought to cause Addison's disease. Of these, tuberculosis accounts for the majority, while systemic mycoses, e.g. histoplasmosis, coccidiomycosis and blastomycosis, occur relatively rarely.[8] In most recent Western series, tuberculosis accounts for 15% of all Addison's disease cases.[26] Adrenal insufficiency secondary to histoplasmosis is extremely rare,[27] but asymptomatic infection of the adrenal glands by histoplasmosis occurs more commonly and should be considered in the differential diagnosis of enlarged adrenal glands.[28,29] Adrenal involvement by *Cryptococcus neoformans*, *Toxoplasma gondii*, *Mycobacterium avium-intracellulare* and Kaposi's sarcoma usually occurs in an immunocompromised state, most commonly in the setting of human immunodeficiency virus (HIV) infection.[30] Hyponatraemia may be falsely attributed to gastrointestinal involvement, particularly severe diarrhoea, rather than to hypoadrenalism secondary to HIV infection.[31,32] In one study, frank hypoadrenalism in advanced HIV was reported as remarkably uncommon.[31] End-stage acquired immune deficiency syndrome (AIDS)-associated opportunistic infections, e.g. cytomegalovirus or *M. avium-intracellulare*, may impair adrenal function by direct invasion of the adrenal cortex.[33]

The adrenal glands are frequently infiltrated by metastatic and lymphomatous spread from primary carcinomata of the lung, breast, kidney, urinary bladder, pancreas, melanomata and haematological malignancies, and hypoadrenalism may occur.[34] This was recognised as early as 1855 by Addison, who first suggested that adrenal metastases could induce adrenal insufficiency, but the prevalence of hypoadrenalism in this context is remarkably poorly documented.[35] At least 90% of the adrenal glands need to be replaced by tumours in order that primary hypoadrenalism may result. Although it is mandatory to exclude adrenal dysfunction when there is computerised tomographic evidence for enlarged adrenal glands, normal adrenal function may persist despite significantly enlarged adrenal glands.[36,37] Interestingly, many of these patients demonstrate a paradoxical supranormal cortisol response to ACTH stimulation testing, which is thought to be the result of chronic stress.[38] In a cohort of 30 patients with advanced (stage III or IV) bronchogenic carcinoma not preselected for adrenal metastases, the prevalence of hypoadrenalism using validated diagnostic criteria was 6.7% (95% confidence interval 0.8-22.1%),[38] which was in contrast to the 33 % reported by Redman et al.[39]

Adrenoleukodystrophy (ALD) is a rare X-linked condition (1:20 000 men) characterised by a deficiency of peroxisomal membrane ALD protein, which transports activated acyl-coenzyme A derivates into the peroxisomes, where they are shortened by beta oxidation. The ALD protein, which is similar to the adenosine triphosphate (ATP)-binding cassette transporter superfamily of proteins, is encoded by the ALD gene mapped to Xq28.[40] This deficiency results in accumulation of very long-chain fatty acids (VLCFAs) in the blood, adrenal glands, brain, testes and liver.[41] The ensuing demyelination may evoke an autoimmune reaction.[42] The adrenal glands may sustain damage by VLCFA accumulation, inducing cell membrane microviscosity and subsequent alterations in ACTH action.[43]

The presentation of ALD may vary widely, with six distinct described types ranging in decreasing order of severity, down to asymptomatic individuals. The childhood cerebral type is the most devastating form. It occurs in 31-35% of patients with ALD and is characterised by adrenal insufficiency and progressive relentless neurological dysfunction, often presenting with cognitive and gait disturbances, evolving to a vegetative state within two to four years.[44,45] The adolescent and adult cerebral form occurs in 6-12% of patients with ALD and resembles the childhood type in which spinal cord, peripheral nerve and psychiatric symptoms predominate. However, the progression of the adolescent and adult cerebral form is far slower than that of the childhood cerebral form. Adrenomyeloneuropathy occurs in 40-46% of patients with ALD, and typically the age of onset is between 20 and 40 years of age.[44-46] It has a reduced propensity to affect cortical function and a greater tendency to affect the long ascending and descending tracts of the spinal cord, inducing, inter alia, urinary and erectile dysfunction along with hypoadrenalism.[47] Approximately 10-20% of X-linked ALD patients have primary adrenal insufficiency without neurological involvement, and a proportion may be entirely asymptomatic, despite very high levels of VLCFA. Female carriers may have neurological involvement as a result of non-random X inactivation, with a similar clinical picture to adrenomyeloneuropathy but a slower rate of progression and rare adrenal involvement.[44] A proportion of patients with Addison's disease due to ALD without neurological damage exhibit increased VLCFA, and their brothers also demonstrate increased VLCFA.[41] Although dietary restriction of VLCFA, particularly hexacosanoic acid (C26:0), may normalise plasma VLCFA, it does not produce significant clinical improvement and the ongoing deterioration may be accounted for by an autoimmune process.[42]

Sarcoidosis has previously been suggested as a cause of Addison's disease. However, some reports suggest that the sarcoidosis may have been coincidental, as the Addison's

disease coexisted with another autoimmune gland failure compatible with Schmidt's syndrome.[48]

Triple A or Allgrove's syndrome is an autosomal recessive disorder, characterised by the triad of achalasia cardia, alacrima and ACTH-resistant adrenocortical insufficiency. It is also known as achalasia-Addisonianism-alacrima syndrome (AAAS) and results from mutations on chromosome 12q13.[49] Antiphospholipid syndrome may result in primary hypoadrenalism, either due to adrenal haemorrhage and subsequent haemorrhagic destruction following vascular occlusion of the adrenal vessels or secondary to anticoagulant therapy in the presence of antiphospholipid antibodies. Autoimmune mechanisms may also be causative in association with the antiphospholipid syndrome.[50] Intra-adrenal haemorrhage may hinder normal steroid hormone production within the adrenal cortex, infrequently resulting from long-term anticoagulation therapy.[8] Haemorrhaging of the adrenal cortices has been demonstrated following prophylaxis with anti-coagulation for joint replacements.[51] It has been postulated that a stressed adrenal gland, that is significant ACTH stimulation, may be more predisposed to haemorrhage if anticoagulation is concurrently administered.[52]

Mutations in transcription factors responsible for normal adrenal gland development have been found to induce a familial syndrome of congenital adrenal hypoplasia. These include mutations of any of the following: DAX1 [dosage-sensitive sex reversal, adrenal hypoplasia congenital (AHC), critical region on the X chromosome, gene-1, NR0B1/AHC] and steroidogenic factor-1 (Sf1), NR5A1 and Ad4BP.[53,54] Men with congenital adrenal hypoplasia usually present in infancy or early childhood with salt-losing primary adrenal failure, recognised by profound hyponatraemia, global glucocorticoid deficiency in infancy and arrested puberty

because of associated hypogonadotropic hypogonadism.[54] Duplication of the NR0B1 induces a 46,XY disorder of sex development, resulting in XY "sex-reversal" women.[55]

An analysis of the aetiology of Addison's disease in the South African cohort, using specific diagnostic criteria (Table I), indicated that autoimmune Addison's disease occurred in more than 50%, contradicting an earlier study suggesting that autoimmune Addison's disease is uncommon in South Africa. Despite the burden of two epidemics that South Africa is currently facing, tuberculosis as a cause for Addison's disease was remarkably uncommon and none of the Addison's disease in this cohort was caused by either HIV or AIDS.[7]

Management

Glucocorticoid replacement

Patients with Addison's disease require life-long glucocorticoid replacement therapy. This usually takes the form of oral hydrocortisone, which is widely available in Europe, the USA, the UK and South Africa.[56] The UK, as well as some European countries, especially Norway, also uses cortisone acetate, which requires conversion by 11β-hydroxysteroid dehydrogenase type 1 for activation to cortisol. In instances where hydrocortisone is not available, prednisone and dexamethasone have been used but since they have long half-lives, they may result in excessive night-time concentrations, which may be deleterious.[1]

Endogenous cortisol production, determined by stable isotope dilution mass spectrometry in healthy individuals, is only 6-11 mg/m², but the ideal hydrocortisone replacement dose remains to be determined.[57] Suggested doses vary from 30 mg of hydrocortisone to as little as 12.5 mg per day, divided into two or three daily doses.[58,59] In general, clinicians rely on empiric doses, which vary substantially according

Table I: The underlying aetiology of the South African Addison's disease cohort

Aetiology	Diagnostic criteria	Number (%)
Autoimmune Addison's disease	Presence of 21-hydroxylase autoantibodies or [a]ACA	74 (51)
Adrenoleukodystrophy	Increased plasma [b]VLCFA, irrespective of autoantibody pattern	6 (4)
Tuberculosis	A compatible current or past clinical history of lung, bone, pelvic, peritoneal or genitourinary tuberculosis; radiology compatible with tuberculosis	11 (8)
[c]AIDS (related)	Presence of an AIDS-defining illn ess, e.g. cytomegalovirus, *Mycobacterium avium-intracellulare*, *Cryptococcus neoformans*, *Toxoplasmosis gondii*, Kaposi's sarcoma	0 (0)
Other causes	Malignancy (biopsy proven), sarcoidosis, iron overload	0 (0)
X-linked adrenal hypoplasia	Male patients with primary hypoadrenalism and salt loss in the first few weeks of life; later frequently associated with hypogonadotrophic hypogonadism	8 (6)
[d]ACTH-resistance syndrome	Isolated glucocorticoid insufficiency but normal mineralocorticoid function; may be associated with alacrimia and achalasia	2 (1)
Idiopathic	Adrenal autoantibody negative, normal VLCFA, no history of tuberculosis or genetic form	43 (30)

a = adrenocortical autoantibodies, b = very long-chain fatty acids, c = acquired immune deficiency syndrome, d = adrenocorticotrophic hormone

Table II: Glucocorticoid replacement therapy in South African Addison's disease patients [total number of patients 148; data missing from 22 untraceable patients (15%)]. Equivalent doses derived from Meikle and Tyler.[64]

Preparation	Number (%)	Median daily dose (ªIQR)	ᵇETDHD corrected for body surface area; mg/kg (IQR)	ETDHD corrected for body weight; mg/kg (IQR)[64]
Hydrocortisone	112 (76)	20.0 (20–30.0)	0.33 (0.25–0.44)	12.4 (10.3–16.9)
Cortisone acetate	3 (2.0)	25.0 (25.0–32.5)	0.53 (0.50–0.55)	19.7 (18.3–21.0)
Prednisone	10 (8)	8.75 (5.0–11.9)	0.42 (0.3–0.68)	16.6 (11.36–26.3)
Dexamethasone	1 (0.7)	5	1.31	62

a = interquartile range, b = equivalent total daily hydrocortisone dose

to the practice at a particular centre. Overreplacement with hydrocortisone may result in accelerated bone loss, premature atherosclerosis and metabolic syndrome.[2,60-62] However, insufficient hydrocortisone supplementation results in chronic symptoms of fatigue.[63] There is evidence to support the idea that irrespective of the modality of glucocorticoid replacement, patients have subjective impaired health quality.[64]

In the South African Addison's study, it was observed that several forms of glucocorticoid replacement were used; most patients (76%) received hydrocortisone, with prednisone being the next most common. Both were given in combination with fludrocortisone (Table II). The total median dose of hydrocortisone corrected for body surface area was 12.4 mg/m². The number of daily doses of hydrocortisone also varied: 33% were receiving three daily doses, 52% were receiving two daily doses and 15% were receiving a single daily dose. The proportions of patients using once-daily hydrocortisone, cortisone acetate, prednisone and dexamethasone were 12%, 66%, 40% and 100% respectively. In addition, 38% of patients reported having had at least one lifetime Addisonian crisis, and 58% of patients did not wear any form of medic alert identification. The only patient who used dexamethasone as replacement therapy was receiving a significantly greater glucocorticoid exposure than any of the other patients.

Conventional oral hydrocortisone replacement is nonphysiological, as it is well absorbed in the small and large intestines, inducing high peaks that are followed by rapid elimination. The resultant intermittent low trough levels require two to three doses per day. In addition, because of interindividual differences in the absorption and metabolism of hydrocortisone, uniform doses may not be appropriate for every patient with Addison's disease. Irrespective of the modality of glucocorticoid replacement,[65] normal physiology is not restored.[63] Consequently, there is ongoing research to improve hydrocortisone replacement by prolonging its bioavailability.[66]

Cardiovascular disease has been linked to increased

cortisol levels. Hypertension, increased heart rate, increased total cholesterol and low-density lipoprotein cholesterol, increased fasting insulin and increased glucose have all been reported to correlate with endogenous cortisol levels.[67] Of concern is the fact that the South African Addison study has revealed a significant atherogenic profile among patients. Awareness that these patients may have a tendency to abnormal lipid profiles is required, so that this aspect of patient care is also addressed.

Monitoring of glucocorticoid therapy

In patients with hypoadrenalism, the most significant barrier to monitoring therapy with glucocorticoids is that no single test exists that reliably reflects adequacy, overreplacement or underreplacement. While the 24-hour urine cortisol and plasma ACTH are unreliable in assessing adequacy of glucocorticoid replacement, plasma cortisol day curves have been used, but they require frequent blood sampling and admission to hospital.[68] As salivary cortisol is easily accessible and correlates well with plasma cortisol, it represents an attractive alternative to plasma cortisol measurements. Both, however, demonstrate substantial variability.[69] Both plasma and salivary cortisol monitoring have limited potential to guide dosing replacement therapy. There are no specific recommendations about the frequency of monitoring either plasma or salivary cortisol.

The value of clinical assessment should be emphasised, since a structured scoring system correlated with plasma cortisol concentrations. For each of the clinical features (10 items) that suggested overreplacement, one score point was added, and for each of the features that suggested underreplacement, a point was subtracted. An arbitrary score of between -2 and 2 was considered to be well replaced. Fatigue or loss of energy, nausea, weight loss, hyperpigmentation, hypoglycaemia, hyponatraemia and hyperkalaemia suggest underreplacement, while insomnia, recurrent infections, increased appetite, weight gain, glucose, hyperglycaemia, hypernatraemia, hypokalaemia and elevated blood pressure suggest overreplacement. For the entire scoring system and its correlation with plasma

cortisol, the reader is referred to the paper by Arlt et al.[70] Close attention to clinical symptoms and signs indicative of either under- or overreplacement may be helpful in adjusting dose.

Recent developments in hydrocortisone replacement therapy

Newer formulations of hydrocortisone, focussing on delayed absorption, are being developed to provide a more physiological glucocorticoid exposure for patients requiring such therapy. [71] These are not yet available in South Africa.

Hydrocortisone during periods of stress

At present there is insufficient scientific evidence to guide current practice in this area, and the standard recommendations are based on expert opinion.[1] For example, a Cochrane review showed inadequate evidence to support or refute the use of supplemental perioperative steroids in surgical patients with adrenal insufficiency, and indicated that the maintenance dose may be sufficient.[72] Until further evidence is acquired, it would be best practice to escalate the glucocorticoid dose perioperatively.

Current recommendations are as follows:

- At least a doubling of the dose of hydrocortisone is warranted in most mild illnesses.
- In life-threatening situations, the dose of hydrocortisone should be increased to 100 mg, three times daily, but this may be reduced gradually, depending on a favourable patient response following surgery.

Mineralocorticoid replacement

Mineralocorticoids are essential for the reversal of aldosterone deficiency. Assessment of mineralocorticoid adequacy is possible by evaluating plasma sodium, potassium and renin activity assays. An elevated plasma renin activity in an Addison's patient may indicate inadequate mineralocorticoid substitution, while elevated blood pressure, peripheral oedema and sodium retention may indicate overreplacement. The usual dose of 9-alpha-flouro-hydrocortisone is between 50 µg and 200 µg per day. Patients are at risk of developing hyperkalaemia and hypotension should this be discontinued.[20]

Conclusion

Enhanced awareness of Addison's disease is warranted, since prompt institution of replacement therapy is potentially life-saving. Autoimmune Addison's disease is the most common underlying aetiology in South Africa, despite the very high background prevalence of HIV and tuberculosis. Available forms of glucocorticoid replacement are nonphysiological and novel forms of therapy are in development. As patients with Addison's disease may be at increased risk of cardiovascular disease as a result of atherogenic lipid profiles, surveillance of dyslipidaemia and preparedness to institute appropriate therapy are warranted.

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