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ORIGINAL ARTICLE

Co-morbidities, management and clinical outcome of auto-immune Addison's disease

Lalantha Leelarathna · Louise Breen · James K. Powrie · Stephen M. Thomas · Rustom Guzder · Barbara McGowan · Paul V. Carroll

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Abstract There are no consensus guidelines on the optimum long-term care of patients with primary adrenal failure. Published data suggest increased morbidity and mortality in patients treated with current therapy. Investigations of bone mineral density (BMD) in adults with adrenal failure have reported conflicting results. The objectives of this study were to determine the prevalence of auto-immune and other co-morbidities, describe the treatment regimens and to assess the BMD of adults with auto-immune Addison's disease (AAD). A retrospective, cohort study of adults with primary adrenal failure was used. Electronic and paper records were used to collect demographic, biochemical, BMD data and details of other co-morbidities. 48 patients (35% male; 65% female; 50 ± 16, years, mean ± SD) with primary adrenal failure were identified. There was high prevalence of other auto-immune co-morbidities (hypothyroidism 58%, vitamin B_{12} deficiency 29%, type 1 diabetes 10%). The presence of cardiovascular risk factors including dyslipidaemia (65% had total cholesterol >5 mmol/l) and excess weight (65% had a BMI >25 kg/m^2) were high. Using WHO criteria, 17.9 and 53.5% of patients had spinal osteoporosis and osteopenia, respectively, at the spine. This did not relate to the duration or dose of glucocorticoid replacement. Our data shows a high prevalence of both auto-immune and non-autoimmune co-morbidities in patients with AAD. In addition to common auto-immune diseases, patients should be screened for other cardiovascular risk factors. Further studies are needed to assess the cause of the observed increased prevalence of reduced BMD at the lumbar spine. There is a need for internationally agreed long-term management guidelines.

Keywords Addison's disease · Adrenal insufficiency · Bone density

L. Leelarathna · L. Breen · J. K. Powrie · S. M. Thomas · R. Guzder · B. McGowan · P. V. Carroll (✉)
Department of Endocrinology, Guy's & St Thomas' NHS Foundation Trust, DEDC 3rd Floor Lambeth Wing, St. Thomas' Hospital, London SE1 7EH, UK
e-mail: paul.carroll@gstt.nhs.uk

Introduction

Addison's disease has a prevalence of 93–140 cases per million people and an annual incidence of 4.7–6.2 cases per million people in Western populations [1, 2]. A recent epidemiological study suggests that the incidence of Addison's disease is rising in the developed world [2]. Primary adrenal failure often presents insidiously, and we have recently highlighted the use of modern biochemical tests in the early diagnosis of the condition [3].

There are still significant challenges in the long-term management of the patient with adrenal insufficiency. First of all, current oral replacement therapy regimens do not mimic the physiological pattern of cortisol secretion. Second, a reliable bio-marker of in vivo glucocorticoid action and therefore adequacy of replacement therapy has yet to be identified. Finally, no consensus guidelines exist on the optimum long-term treatment and surveillance of the patient with auto-immune Addison's disease (AAD).

Published data indicates that current replacement regimes fail to restore a normal quality of life in adults with primary adrenal failure [4–6]. Studies have also shown that patients on currently accepted optimum replacement regimes have a more than a twofold increase in the standardized mortality ratio [7, 8]. The cause of this increased

mortality is not clear, but both under- and over-replacement with glucocorticoid has the potential to cause significant harm. Chronic glucocorticoid over-replacement has the potential to cause impaired glucose tolerance, central adiposity and adverse consequences on skeletal mineralisation. Patients with auto-immune adrenal failure are also at an increased risk of developing other auto-immune diseases.

The objectives of this study were to determine the prevalence of auto-immune and other co-morbidities, describe the treatment regimens and to assess the BMD of adults with AAD attending a university teaching hospital in United Kingdom (UK).

Methods

A retrospective study was conducted by analysing the adult patient population attending the endocrine clinics at Guy's & St. Thomas' NHS Foundation Trust. Patients with primary adrenal failure were identified using our electronic coding systems (Diabeta3®) and paper records. All patients identified as having primary adrenal failure attending clinics between 01/01/2007 and 31/12/2008 were eligible to participate. Demographic, biochemical and bone densitometry (DEXA) data were collected from electronic and paper records. The most recent steroid replacement dose, biochemistry and BMD results were used included in the analysis. SPSS (Ver 14.0) was used in the statistical analysis. The rates of common auto-immune conditions in men and women were compared using independent samples *t* tests. The relationship between spinal BMD and duration of treatment was assessed using the Pearson product movement correlation co-efficient.

Results

The clinical and demographic details of the patients ($n = 48$) are summarised in Table 1. The male to female ratio was 1:1.8, and the average age at the time of the study was 50 (SD ± 16) years. The duration of adrenal failure was 17 (SD ± 14) years, with age of diagnosis/onset 33 (SD ± 16) years. Sixty-five percent of the sample had a BMI ≥25 kg/m^2 and 23% were obese with a BMI ≥30 kg/m^2. Males had a higher BMI than females (29.4 vs. 25.8 kg/m^2, $P = 0.029$). Nineteen percent of patients were either on treatment for hypertension or had a systolic BP ≥140 mmHg. The mean systolic BP for the whole cohort was 122 (SD ± 15) mmHg (range 90–159 mmHg). The mean diastolic BP was 74 (SD ± 7) mmHg (range 59–88 mmHg).

Plasma renin activity (PRA) measurements were available for all 48 patients. The median plasma renin activity was 2.45 (range <0.4–34) p/ml/H; reference range 2.8–4.5 p/ml/H. Five patients (10%) had plasma renin activity ≥15p/ml/H (≥30 p/ml/H in three patients). Four had undetectable (<0.4 p/ml/H) plasma renin activity. PRA was measured on their current replacement therapy.

The total serum cholesterol concentration for the entire group was 5.3 ± 0.8 mmol/l. Sixty-five percent of the sample had total cholesterol ≥5.0 mmol/l and 15% of the sample had a total cholesterol ≥6.0 mmol/l. Twenty-one percent of the sample had been prescribed HMGCoA reductase "statin" treatment.

Adrenal replacement (Tables 2, 3)

The vast majority of patients (>90%) were on hydrocortisone replacement with a mean dose of 24.0 ± 5.5 mg/d

Table 1 Demographic characteristics of the study population (N = 48)

Characteristic	Number (%)/mean (±SD)	Range
Male	17 (35%)	
Female	31 (65%)	
Current age (Years)	50.3 (±16.0)	25–82
Age at diagnosis (Years)	32.8 (±15.6)	4–72
Duration of treatment (Years)	17.3 (±14.0)	1–52
BMI (kg/m^2)	27.1 (±5.5)	17.5–42.8
BP (mmHg)	122/74 (±15/±7)	159–90/88–59
Plasma renin activity (p/ml/H) (nr 2.8–4.5 p/ml/H)	5.7 (±8.2)	<0.2–34
Total cholesterol (mmol/l) ($N = 34$)	5.3 (±0.8)	3.2–7.1
HDL (mmol/l) ($N = 27$)	1.7 (±0.5)	0.91–2.60
LDL(mmol/l) ($N = 27$)	2.9 (±0.8)	0.67–4.10
Triglycerides (mmol/l) ($N = 29$)	1.5 (±0.7)	0.46–3.69

Table 2 Adrenal replacement

Mean ± SD values
Hydrocortisone dose equivalent 24 (±6) mg
Hydrocortisone, $n = 44$
Cortisone acetate, $n = 2$
Prednisolone, $n = 2$
Fludrocortisone dose 119 (±42) μg
DHEA replacement dose 25 (±4.7) mg
15 Females: 10 on maintenance, 5 discontinued
5 Males: 4 on maintenance, 1 discontinued
Glucocorticoid education, $n = 48$
Education on parental hydrocortisone, $n = 36$

Table 3 Total daily doses of hydrocortisone replacement

Hydrocortisone dose equivalent (mg)	Number (%)
15	4 (8.3%)
20	20 (41.7%)
25	11 (22.9%)
30	10 (20.8%)
>35	3 (6.3%)
Total	48 (100%)

(range 15–38 mg/d). Thirty-five percent of patients were on a twice daily regimen and the remaining subjects were prescribed a three times a day regimen.

All patients were prescribed fludrocortisone with a median prescribed dose of 119 ± 42 μg/day. Fifty-six percent of patients were using 100 μg/day, 23% 150 μg/day and 13% 200 μg/day of fludrocortisone.

It is standard clinical practice in our Department to consider supplemental dihydroepidandrosterone (DHEA) in patients with primary adrenal failure and this was offered to patients with AAD for a trial period of 12 months. Twenty-nine percent of the sample was taking DHEA replacement. A further 12.5% had discontinued DHEA due to side effects. The entire sample had received specific education about steroid replacement therapy and sick day rules and all patients were issued with a steroid card. Seventy-five percent of patients (36/48) had received additional education and training in the use of intra-muscular hydrocortisone.

Auto-immune and other co-morbidities (Table 4)

Over 50% of patients had primary hypothyroidism, and approximately 30% had vitamin B_{12} deficiency. The rates of primary hypothyroidism for men and women were similar (59 and 58%, respectively). The prevalence of vitamin B_{12} deficiency was similar in both men and women (29 and 23%, respectively). Similarly there were no statistically significant difference in the proportion of men and women with positive thyroid and gastric parietal cell antibodies (Table 4).

The cohort included five patients (10%) with type 1 diabetes and two patients (4%) with type 2 diabetes mellitus. Control of diabetes was sub-optimal in type 1 patients with a mean HBA1c of 8.4%.

There were six patients (13%) with premature gonadal failure (one male and five female). None of these patients were receiving sex hormone replacement therapy. Overall, 35 of 48 patients (73%) with AAD had an associated auto-immune co-morbidity, predominantly hypothyroidism, requiring replacement therapy.

Bone mineral density

Dual energy X-ray absorptiometry (DEXA) data were available in 28 patients (19 females and seven males) out of the 48 subjects (58%). Using WHO criteria [9], five patients (17.9%) had osteoporosis (T score ≤ -2.5) at the lumbar spine and 15 patients (53.5%) had osteopenia (T score ≤ -1.0). Overall, 71.4% of the sample had evidence of reduced spinal BMD. In contrast, there was no

Table 4 Common auto-immune conditions and antibody status

Common auto-immune co morbidities				
	On treatment	Positive antibodies[a]	Negative antibodies	Antibody status not known
Adrenal Insufficiency	48	20	7	21
	100%	42%	14%	44%
Hypothyroidism	28	24	12	12
	58%	50%	25%	25%
B_{12} deficiency (on replacement or level <190 pmol/l)	14	14	13	21
	29%	29%	27%	44%

[a] Adrenocortical antibodies (ACA) were measured using indirect immunofluorescence techniques

evidence of osteoporosis at the hip, but 12 patients (42.9%) had osteopenia at this site. Age and sex-adjusted BMD (*Z* score) also showed reduced BMD at spine with 37% patients having a *Z* score ≤ -1 and 7.4% having a *Z* score ≤ -2.5. In comparison, *Z* scores at hip showed 18.5% of patients with a score of ≤ -1 and no patients with *Z* score ≤ -2.5.

The relationship between the duration of replacement therapy, weight-adjusted hydrocortisone doses and spinal bone mineral density (BMD; *Z* score) was investigated using the Pearson product-movement correlation coefficient. No association were evident between lumbar spine *Z* score and duration of glucocorticoid replacement ($P = 0.72$) or weight adjusted hydrocortisone dose ($P = 0.37$).

Discussion

This study reports the clinical outcome and associated co-morbidities present in adults with AAD attending a university teaching hospital in UK. The diagnosis of adrenal failure was confirmed using the short synacthen test (Cosyntropin test). The diagnosis of Addison's disease was made clinically, after excluding obvious non-autoimmune causes of primary adrenal failure, such as tuberculosis. For majority in this cohort, at the time of diagnosis, performing CT/MRI scan of adrenal gland was not routine practice for antibody negative patients unless there was clinical suspicion of an alternative cause. The data show a high prevalence of other autoimmune diseases mostly primary hypothyroidism and pernicious anaemia. Over 50% of patients had concomitant primary hypothyroidism and approximately one-third had vitamin B_{12} deficiency. Interestingly, the rates of these conditions were very similar between males and females suggesting that, in patients with primary adrenal failure, the rates of other auto immune diseases are similar between men and women. In addition, 13% of the patients had premature gonadal failure and 10% of the patients had type 1 diabetes mellitus. A recent publication from Norway has looked at the largest cohort of Addison's disease published to date [6]. Rates of auto-immunity in this cohort were broadly similar to our study but the rates for hypothyroidism and vitamin B_{12} deficiency were even higher in our UK population. In the Norwegian study, overall autoimmune co-morbidity was observed in 66%, while in our cohort this figure was 73%. Rates of common auto-immune co-morbidities between the Norwegian and our study were—thyroid disease 47 vs. 58%, vitamin B_{12} deficiency 10 vs. 29% and type 1 diabetes 12 vs. 10%, respectively. Routine screening for hypothyroidism and vitamin B_{12} status is performed widely in many centres and these data strongly supports this practice. We suggest that testing for thyroid and B_{12} status is performed annually and testing for other auto-immune diseases is guided by clinical assessment.

In this cohort, obesity and dyslipidaemia were common. Although the cause of reported excess mortality in AAD is not entirely clear (and may represent historic data), cardiovascular disease is considered the leading cause of death [8]. It is therefore important to assess and treat modifiable cardiovascular risk factors such as body composition, blood pressure, hyperglycaemia and lipids in these patients. Furthermore, these cardiovascular risk factors are adversely affected by chronic over-replacement with glucocorticoid.

There are concerns regarding the deleterious effects of long term glucocorticoid therapy on BMD especially at the spine. Published studies on BMD in adrenal failure have shown conflicting results. BMD has been reported variously to be reduced only in post menopausal women [10], only in men [11] and also to be normal in both sexes [12, 13]. In our cohort, there was a high proportion of preferential bone mineral loss at the spine. We cannot ascertain the cause of this from the available data, but long-term excessive glucocorticoid replacement and a lack of adrenal androgens may be contributory. In a recent randomised trial [14] to assess the efficacy of DHEA replacement ($N = 106$) baseline data showed that at the lumbar spine, 39% of males and females were osteopenic and 7% of males and 5% of females were osteoporotic; in the femoral neck, 39% of males and females were osteopenic and 2% of females were osteoporotic. During the 12 months of this study, there was progressive reduction in BMD. Current data are probably not sufficient to recommend routine BMD measurements in all patients but this should certainly be considered in selected patients, perhaps including those who have been on relatively large replacement doses, with a long-duration of disease and those with amenorrhoea or premature menopause. We were not able to find any published data on fracture rates in this group of patients.

Achieving optimal glucocorticoid replacement therapy remains clinically challenging. Under physiological conditions, cortisol secretion follows a distinct circadian rhythm which cannot be mimicked by current oral replacement therapy. Moreover, there is no robust way of assessing the adequacy of replacement therapy. Modified release hydrocortisone preparations are in development and early studies have shown some promise in addressing these issues [15, 16]. At present, efforts should be made to maintain patients on the minimum required dose while avoiding under-replacement.

Study limitations

We made every effort to collect all relevant data but due to the very long duration of Addison's disease in this cohort

(mean 17 years, range 1–52 years) and the retrospective nature of the study, we were not able to collect full dataset for all participants. BMD data was only available for 58% and adrenal antibody status was only available for 56% of the cohort. Adrenocortical antibodies (ACA) was measured using "older" indirect immunofluorescence techniques on cryostatic sections of adrenal gland tissue. Reported sensitivity for this test is between 60 and 80% of patients with Addison's disease at diagnosis [17] and this may at least in part be responsible the negative antibody status in some of our patients. Adrenocorticotrophic hormone (ACTH) and Dehydroepiandrosterone sulphate (DHEAS) levels were not available for the majority of the cohort. Until recently, measurement of ACTH and DHEAS levels were not routinely available, and it is unlikely that these tests were done at the time of diagnosis for the majority of the patients in this cohort.

In summary, patients with auto-immune adrenal failure may have a variety of other co-morbidities and all patients should be screened for the presence of these associations. In addition to auto-immune conditions, it seems appropriate to assess body composition, blood pressure, lipid levels and BMD in these patients. Such a holistic approach may reduce the excess mortality and morbidity reported in previous studies and may to lead to improved quality of life. There is a need for larger prospective studies to improve our understanding of the aetiology and pathophysiology of excess mortality and morbidity as well as internationally agreed consensus guidance on long-term surveillance and management of this rare but important endocrinopathy.

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