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Original Study

Occult Adrenal Insufficiency in Renal Amyloidosis Patients

Renal Amiloidoz Hastalarında Gizli Adrenal Yetmezlik

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ABSTRACT

Objective: *Systemic amyloidosis may affect many organs, and may cause endocrinologic problems which may result in adrenal insufficiency. However, assessment of adrenocortical reserve is challenging in amyloidosis patients with renal involvement. We aimed to evaluate adrenocortical reserve with various methods of cortisol measurement to determine any occult clinical condition.*
Methods: *Patients with renal amyloidosis and healthy subjects were evaluated in this cross-sectional study. Basal cortisol, corticosteroid-binding globulin (CBG), and albumin levels were measured. Serum free cortisol (cFC) level was calculated. Cortisol response tests performed after ACTH stimulation test (250 µg, intravenously) were evaluated, and free cortisol index (FCI) was calculated.*
Results: *Twenty renal amyloidosis patients, and 25 healthy control subjects were included in the study. Patients and control subjects had similar median serum baseline cortisol levels [258 (126-423) vs 350 (314-391) nmol/L, p=0.169)] whereas patients' stimulated cortisol levels at the 60th minute were lower [624 (497-685) vs 743 (674-781) nmol/L, p=0.011)]. The 60th-minute total cortisol levels of 8 of the 20 (40%) amyloidosis patients were <500 nmol/L, but only three of these 8 patients had stimulated FCI <12 nmol/mg suggesting an adrenal insufficiency (15%).*
Conclusion: *ACTH stimulation test and cortisol measurements should be considered in renal amyloidosis patients with severe proteinuria to avoid false positive results if only ACTH stimulation test is used. It will be appropriate to evaluate this group of patients together with estimated measurements as FCI.*

Keywords: *Adrenocortical insufficiency, albumin, CBG, cortisol, renal amyloidosis*

ÖZ

Amaç: *Sistemik amiloidoz birçok organı etkileyebilir ve adrenal yetmezlikle sonuçlanabilecek endokrinolojik problemlere sebep olabilir. Renal tutulumlu amiloidoz hastalarında ise adrenokortikal rezervi değerlendirmek zordur. Biz bu çalışmada farklı kortizol ölçüm yöntemleri ile renal tutulumlu amiloidoz hastalarında gizli adrenal problemlerini tespit etmeyi planladık.*
Yöntem: *Bu kesitsel çalışmada renal tutulumu olan amilodoz hastalarını ve sağlıklı kontrol grubunu adrenal yetmezlik testleri açısından değerlendirdik. Bazal kortizol ve kortizol bağlayıcı globulin (KBG) ölçüldü. Serum serbest kortizol düzeyi hesaplandı. 250 mcg ACTH stimulasyon testi sonrası kortizol yanıt testleri değerlendirildi ve serbest kortizol indeksi (SKI) hesaplandı.*
Bulgular: *Çalışmaya 20 amilodoz hastası ve 25 sağlıklı kontrol grubu dahil edildi. Bazal serum kortizol düzeyleri hasta ve kontrol grubunda benzerdi [258 (126-423) vs 350 (314-391) nmol/L, p=0.169)]. Ancak amiloidoz grubunda ACTH stimulasyon testi sonrası 60. dk. kortizol yanıtı daha düşüktü [624 (497-685) vs 743 (674-781) nmol/L, p=0.011)]. 20 hastanın 8'inde (40%) bu değer <500 nmol/L olarak bulundu. Ancak sadece bu sekiz hastanın üçünde (15%) SKI <12 nmol/mg olarak bulundu. Bu üç hasta klinik olarak da adrenal yetmezlikle uyumlu olabilecek bulgular taşıyordu.*
Sonuç: *Ağır proteinürisi olan renal tutulumlu amiloidoz hastalarında, adrenal yetmezlik araştırılırken sadece ACTH stimulasyon testinin kullanılması yanlış pozitifliklere sebep olabilir. Bu grup hastaları SKI gibi hesaplanmış ölçümlerle birlikte değerlendirmek daha uygun olacaktır.*

Anahtar kelimeler: *Adrenal yetmezlik, albumin, KBG, kortizol, renal amiloidoz*

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INTRODUCTION

Amyloid A (AA) amyloidosis is a result of the deposition of serum amyloid A (SAA) protein fragments and related to a chronic inflammatory disease of either infectious or noninfectious etiology[1]. Renal involvement is frequent[2], but endocrine system involvement has been extensively demonstrated at autopsies[3]. Detecting adrenal system problems in AA amyloidosis together with heavy proteinuria is a problem because interpretation of adrenal function tests is complicated. Urinary losses of albumin and hormone-binding proteins such as corticosteroid-binding globulin (CBG) results in an increased percentage of the unbound cortisol. Serum cortisol levels, if measured, would be at a healthy level in case of adrenal insufficiency[4].

Reliable assessments of adrenal function in this patient group require realization of stimulation tests to prevent misdiagnosis of any adrenal problem before they become apparent. Adrenal insufficiency findings might be overlooked because autonomic involvement causes similar symptoms. A short adrenocorticotropin (ACTH) test (250 µg) is the gold standard diagnostic tool for establishing adrenal insufficiency in the general population[5]. Beyond stimulation tests, other metrics can estimate subtle adrenal insufficiency: Corrected measured hormone levels in proportion to CBG and albumin-calculated free cortisol (cFC) as well as mathematical models (e.g., free cortisol index (FCI), which is the ratio between total serum cortisol and CBG[6], and ΔCortisol). In this study, we investigated adrenocortical reserve in AA amyloidosis patients who also had impaired renal function or heavy proteinuria using the ACTH stimulation test, cFC, and FCI after ACTH stimulation test.

MATERIAL and METHODS

Study Population:

Twenty patients with renal AA amyloidosis who were being followed at Ankara Education and Research Hospital and 25 healthy subjects as the control group were included in the study. The patient group had amyloidosis secondary to Familial Mediterranean Fever. The healthy control group had no known kidney or health problem. The diagnosis of AA amyloidosis was based on a kidney biopsy that was performed to document the etiology of proteinuria or impaired renal function. Exclusion criteria consisted of the following parameters: (1) previously documented adrenal insufficiency; (2) hypopituitarism; (3) pregnancy; (4) Cushing's syndrome; (5) malignancy; (6) type 2 diabetes mellitus; (7) use of corticosteroid medication within the previous year of the study; (8) ACTH allergy; and (9) age <18, or >75 years old.

Informed consents were obtained from all individual participants included in the study. All procedures involving human participants were in compliance with the ethical standards of the Institutional Ethics Committee of Ankara Education and Research Hospital and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (Committee decision no: 2011-126; 09.07. 2011).

Measurement of adrenocortical reserve:

All study subjects were analyzed for their serum creatinine, serum albumin, and 24-h urinary protein levels with an automated clinical chemistry analyzer. After eight hours of overnight fasting, a short ACTH test (250 µg) was administered intravenously (i.v.) to all patients and subjects of the healthy control group. Before ACTH injections, blood samples for basal serum cortisol and CBG were drawn at 8:00 AM. After ACTH injection, the 30th and 60th min blood samples for measurement of serum cortisol levels were drawn. Serum total cortisol was measured using an enzyme-linked immunosorbent assay (ELISA) technique (DRG, Cortisol ELISA). Serum CBG was measured by ELISA (Biovendor, human corticosteroid binding globulin ELISA).

A rational response to the (250 µg iv bolus) ACTH stimulation test is accepted as a rise in serum cortisol concentration after 60 min to a peak of ≥500 nmol/l (≥20 ug/dl)[5]. The change in cortisol increment (ΔCortisol) was calculated as the difference between the 0th minute and 60th min serum cortisol levels. Relative adrenal insufficiency was defined as an increase of <250 nmol/l in cortisol levels in the case of the highest cortisol level which was below 500 nmol/l[7].

Free cortisol levels were calculated from Coolen's equation (recently discovered mathematical models): $U= \sqrt{(Z^2+0.0122T)} - Z$ [U: plasma free cortisol (µmol/L) (after the statistical analysis it is converted and expressed as nmol/L), Z: 0.0167 + 0.182 (G-T), G:

CBG (µmol/L), T: total cortisol (µmol/L)[8]. cFC <20 nmol/L was considered adrenal insufficiency.

Corrected total cortisol was calculated with the equation of [(40-CBG) x 0.7] + [(40-albumin) x0.2] + measured cortisol[9]. The free cortisol index (FCI) was calculated by serum total cortisol/CBG (nmol/milligrams). A FCI response (after the ACTH test) of ≥12 is accepted as a normal (healthy) adrenal response[9].

Statistical Analyses:

Data were expressed as means with standard deviation, frequencies (percentages), or medians with interquartile ranges (IQRs) as appropriate. The Shapiro-Wilk test was used to test the normality of the variables. Comparisons between AA amyloidosis patients and control subjects were performed with X^2 (for categorical variables), independent samples t test, or the Mann-Whitney U test (for continuous variables as appropriate). Correlation analysis was performed with Spearman's correlation coefficient.

All statistical tests were set at significance level of $p<0.05$. In the power analysis, we computed the required α value as 0.05, hence our sample size in the patient group consisted of 20 patients. The difference between two independent groups, with a power $1-\beta=0.80$ and 0.75 effect size, sample size in the control group consisted of 25 subjects. All statistical analyses were done with SPSS 22.0 software (SPSS Inc, Chicago, IL) for Windows.

RESULTS

Baseline Characteristics

Twenty patients with AA amyloidosis and 25 healthy control subjects were included in the study. Seventeen (85%) patients had nephrotic range proteinuria, and eight (40%) patients had glomerular filtration rate (GFR) of 45-60 ml/min/1.73 m^2. The remaining subjects had GFR >60 ml/min/1.73 m^2. Beyond exclusion criteria, none of the patients had any liver problem or any cardiac disease.

The clinical and laboratory characteristics of these patients are shown in Table 1. No gender differences were observed between groups, and their serum fasting glucose, serum sodium (Na), and serum potassium (K) levels were comparable. The AA amyloidosis group patients had higher serum creatinine levels and heavy proteinuria; and lower serum albumin, CBG, and GFR as expected.

Table 1. Comparison of baseline characteristics of patients and control groups.

	Amyloidosis patients (n=20)	Control (n=25)	p-value
Age	43.4±16.5	34.5±11.5	0.089
Male n, %	11 (55%)	12 (48%)	0.641
Laboratory			
Fasting glucose (mg/dL)	80±11	88±7.9	0.902
Serum creatinine (mg/dL)	1.43±0.66	0.79±0.14	0.002
GFR (ml/min/1.73 m^2)	55 (32.7)	99 (17)	0.001
Serum albumin (mg/dL)	28.5 (22.5)	41 (3.5)	<0.001
CBG (mg/L)	15.6 (19.3)	40.0 (2.6)	<0.001
24-h urinary protein (mg/day)	5175 (6480)	100 (33.5)	<0.001
Serum Na (meq/L)	139.3±1.9	138.6±2.0	0.605
Serum K (mEq/L)	4.59±0.74	4.52±0.41	0.512

CBG: Cortisol binding globulin, GFR: Glomerular filtration rate, Na: sodium, K: potassium

Results of adrenocortical reserve assessment

Baseline and stimulated adrenal gland cortisol results are shown in Table 2. Although baseline cortisol levels and ΔCortisol after ACTH stimulation were similar between the groups, stimulated serum cortisol (60^{th} min) levels were significantly lower in the patient group when compared to the control group (p=0.011).

Table 2. Comparison of baseline adrenal tests and serum cortisol response to ACTH stimulation test.

	Amyloidosis patients (n=20)	Control (n=25)	p value
Cortisol 0^{th} min (nmol/L)	258 (297.2)	350 (120.8)	0.169
Cortisol 60^{th} min (nmol/L)	624 (187.3)	743 (157.9)	0.011
ΔCortisol (nmol/L)	282 (205.8)	392 (121.5)	0.169
cFC, baseline (nmol/L)	31.0 (16.3-69.5)	23.3 (21.6-27.3)	0.475
FCI	8.0 (3.4-10.9)	17.7 (14.2-16.4)	0.008
Cortisol response <500 nmol/l (%)	8 (40%)	0 (0)	
FCI response, corrected < 12 (nmol/mg)	3 (15%)	0 (0)	

cFC: Calculated free cortisol, FCI: Free cortisol index, ΔCortisol: Cortisol increments after ACTH stimulation

Table 3. Comparison of baseline adrenal tests and serum cortisol response to ACTH stimulation test.

	Amyloidosis patients (n=20)	Control (n=25)
Cortisol response <500 nmol/l (n)	8 (40%)	0
ΔCortisol <250 nmol/L (n)	7 (35 %)	4 (16%)
cFC, baseline, <20 nmol/L (n)	3 (15%)	0
FCI response, corrected <12 nmol/mg (n)	3 (15%)	0

cFC: Calculated free cortisol, FCI: Free cortisol index, ΔCortisol: Cortisol increments after ACTH stimulation.

Eight of 45 participants in the study group had 60th min cortisol response <500 nmol/l. All eight subjects were in the amyloidosis group. Any suspected adrenal insufficiency in patients according to different criteria is summarized in Table 3. These eight patients have adrenal insufficiency at first glance and were evaluated in more detail. Three of those 8 AA patients had FCI levels <12 nmol/mg. Similarly, cFC (estimated using wCoolen's equation) was lower than 20 nmol/l in these three patients. All control group subjects had both FCI >12 nmol/mg and cFC >20 nmol/l. The ΔCortisol levels were <250 nmol/l in four subjects of the control group. Finally, adrenal insufficiency was suggested in these three patients (15%) with low stimulated cortisol (<500 nmol/L), low FCI (<12 nmol/mg), and low cFC levels. The results of eight patients are shown in Table 4. When these three patients were questioned for signs of adrenal insufficiency, anorexia, nausea, vomiting, diarrhea, and hypotension were found and could be attributed to amyloidosis. They have been advised to go to the endocrinology and metabolism department for follow-up.

Table 4. Amyloidosis patients' characteristics who had cortisol response <500nmol/l to ACTH stimulation test.

	Cortisol 0th min (nmol/L)	Cortisol 60th min (nmol/L)	Δ Cortisol (nmol/L)	cFC (nmol/L)	FCI (nmol/mg)
Case 1	226.49	497.2	270.71	24	22
Case 2*	88.82	242	153.8	16.3	11.6
Case 3	176.03	484	307.97	31.6	21.3
Case 4	451.4	499.8	48.4	29.3	32.7
Case 5*	104.31	270.3	165.99	16.5	10.6
Case 6	305.42	495.50	190.08	28.6	26.7
Case 7*	84	342.16	258.16	14.7	10.9
Case 8	399	499	100	22	17.6

*cFC: Calculated free cortisol, FCI: Free cortisol index, ΔCortisol: Cortisol increments after ACTH stimulation.*Patients with clinically compatible adrenal problems.*

DISCUSSION

In our study, patients with amyloidosis had similar serum baseline cortisol but lower stimulated cortisol levels when compared to the control group. Stimulated total cortisol levels of 40% of AA patients were <500 nmol/L, which was interpreted as adrenal insufficiency for the general population. When considering the FCI, three patients had <12 nmol/mg. All three patients had stimulated total cortisol levels of <500 nmol/L suggesting adrenal insufficiency (15%). The cFC also demonstrated similar results.

Evaluation of the adrenal gland requires measurement of the relevant hormones or their metabolites together with symptoms of adrenal insufficiency. However, it is not known to what extent the fibrils invaded the adrenal gland in amyloidosis and when it will cause clinically significant adrenal insufficiency. Widespread abnormalities of the autonomic nervous system might overlap with the same symptom patterns. In AA amyloidosis with heavy proteinuria, serum total cortisol measurements are likely to underestimate cortisol production because patients have lower CBG levels. In such patients, reduced serum cortisol concentrations may not correlate with decreases in free cortisol levels[10-12]. Here, all patients with amyloidosis had an acceptedly lower median serum CBG level of 15.6 (9.3-28.4: normal: 40 mg/l) mg/l[13]. The available literature reports that the correlation between plasma levels of CBG and clinical symptoms is weak; low CBG levels are observed in asymptomatic patients. Conversely, elevated levels can occur in symptomatic patients[14].

We also found that baseline serum cortisol and base-

line calculated free cortisol levels were comparable in the patient and control groups. Brennan et al.[10] and Davidson et al.[15] reported cases of nephrotic syndrome due to amyloidosis with abnormal adrenal response to ACTH stimulation test. They attributed the subnormal response to the stimulation test as secondary to low CBG levels caused by urinary loss with heavy proteinuria[11] as speculated in our study.

Borderline results after the ACTH stimulation test and abnormal CBG results must be reevaluated indirectly by using mathematically calculated cortisol measurements like FCI[16]. The strong correlation between serum free cortisol and FCI suggests that the FCI may be a useful surrogate marker for serum free cortisol[6]. As Dhillo et al. reported in their study, low cortisol levels appear to be related to low CBG levels in the settings of hypoalbuminemia. They applied 250 µg short ACTH tests to 30 healthy individuals and analyzed cortisol and CBG levels at the -30th, 0th, and +30th min. Thirteen subjects who had +30th min cortisol <550 nmol/l had significantly lower CBG levels. When they used FCI values, there was no significant differences in FCI values between subjects with +30th minute >550 nmol/l and subjects with <550 nmol/l[9]. In our study, amyloidosis patients had lower FCI levels (p=0.008). Three of eight AA patients with cortisol response <500 nmol/l had FCI <12 nmol/mg, which is considered as an abnormal adrenal response with unclear clinical symptoms[17]. The cortisol/CBG ratio should be used to evaluate adrenal secretory capacity in amyloidosis patients with massive proteinuria and hypoproteinemia in addition to serum cortisol and the ACTH stimulation tests.

In critical illnesses, the diagnostic criteria for adrenal insufficiency include assessment of random cortisol level[18], cortisol increment (Δcortisol) after cosyntropin stimulation test[19], and/or free cortisol or total cortisol levels stratified by serum albumin levels[20,21]. In studies of critically ill patients, ΔCortisol values of <9 mg/dl (248 nmol/l) were accepted as non-responders to ACTH and they were associated with vasopressor hypo-responsiveness, higher risk of death, and improved response to prolonged corticosteroid supplementation[22]. In our study, there was no statistical difference between the patient and control groups as for ΔCortisol, but patients had statistically lower ΔCortisol compared to controls in abnormal adrenal response (eight patients). When we separately checked the ΔCortisol levels of subjects, four of eight had <250 nmol/l. Lower ΔCortisol levels in the control group were seen in four patients. But none of them demonstrated decreased 60th minute response. Thus, we did not accept them as adrenal insufficiency. As limitations, our limited number of patients did not allow determination of a cut-off level for ΔCortisol. We did not measure CBG binding capacity or ACTH levels that may be considered to estimate adrenal gland problems. Further studies with a larger population would be required to address the use of cortisol increment after stimulation tests in amyloidosis patients.

In conclusion, an optimal assessment of the adrenal gland is essential in the management of patients with amyloidosis and heavy proteinuria. Failure to recognize the differences between adrenal insufficiency and disease-related symptoms can have potentially life-threatening effects in these patients. Beyond this, unnecessary steroid replacement therapy may cause significant morbidity in terms of glucocorticoid side effects. ACTH stimulation tests and calculated FCI would guide clinicians not to skip adrenal insufficiency in amyloidosis patients with complex underlying problems.

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