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RESEARCH ARTICLE

Evaluation of anterior pituitary hormone levels in patients with atrial fibrillation

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ABSTRACT

Aim: The risk of ischemic stroke is increased 5-fold in patients with atrial fibrillation (the most common reason for cardiac arrhythmia). The aim is to investigate whether insufficiency in anterior pituitary hormones develops in patients diagnosed with atrial fibrillation and no history of cerebrovascular accident.

Method: A group of 65 patients with chronic /paroxysmal atrial fibrillation without a history of cerebrovascular accident and a group of 65 healthy controls without arrhythmia were included in this study. Atrial fibrillation was diagnosed by electrocardiography or 24-hour rhythm holter. Demographic data, biochemical tests, echocardiography findings were compared between the groups. P<0.05 was considered statistically significant.

Results: There was no statistical difference in gender and age distribution between groups (p<0.05). (Patient group: Mean age 68 ± 7 years (16 (24.6%) male and 49 (75.4%) female) / Control group: Mean age 67 ± 6 years (18 (27.7%) male and 47 (72.3%) female). Serum insulin-like growth factor-1, adrenocorticotropic hormone and cortisol levels were significantly lower in the patient group compared to the control group (p=0.048, p=0.005, p=0.023). There was no significant difference in serum thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, and prolactin levels between groups. Left atrial diameter and left ventricular end-diastolic diameter were higher in the patient group (p<0.0001). The left ventricular ejection fraction value was lower in the patient group (p<0.0001).

Conclusion: It was thought that the reason for the low level of insulin-like growth factor-1 in the setting of normal liver and kidney functions and simultaneous cortisol and adrenocorticotropic hormone deficiency, in patients with atrial fibrillation with no history of cerebrovascular accident might be due to silent cerebral ischemia leading to pituitary dysfunction.

Keywords: Anterior pituitary hormones, atrial fibrillation, embolism

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1-2% of the general population (1). Atrial fibrillation is associated with more than a 2-fold increment in the odds for silent cerebral infarctions and a 5-fold increase in the risk of ischemic stroke and is responsible for one-fifth of all strokes (2,3). The main risk factors that lead to the development of atrial fibrillation are age, hypertension, heart failure, rheumatic heart disease, hypertrophic cardiomyopathy, mitral valve prolapse and thyrotoxicosis. Epidemiological and clinical studies have shown that AF is an independent risk factor for stroke (3). Apart from major thromboembolism, cerebral infarcts due to microembolism have been described in AF patients (4,5).

The pituitary gland is a well-blooded organ and very sensitive to ischemia. Anterior pituitary gland insufficiency, 'hypopituitarism', is a clinical syndrome that develops as a result of the insufficiency of one or more hormones produced in this gland. In this study, we aimed to investigate whether insufficiency in anterior pituitary hormones develops in patients with AF who did not have an obvious clinical finding of stroke.

MATERIALS AND METHODS

This is an IRB (Institutional Review Board) approved single-institution study (B.10.4.İSM.4.06.68.49/2012). Patients between the ages of 50 and 85 who applied to the internal medicine outpatient clinic were included in the study. The patient group was composed of patients with a diagnosis of chronic AF or who have a paroxysmal AF attack shown in previous electrocardiography (ECG) or 24-hour rhythm Holter tests. Patients who did not have AF or any other rhythm problem were included in the control group. Patients with cerebrovascular disease, malignancies, acromegaly, chronic liver disease, chronic kidney disease, and patients using glucocorticoids, oral contraceptives (OCS), estrogens and androgens were excluded from the study. All females in both groups were in the postmenopausal period.

Biochemical tests of all patients included lipid profile, liver and kidney function tests, complete blood count, serum insulin, C-peptide, free triiodothyroxine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), brain natriuretic peptide (BNP), adrenocorticotropic hormone (ACTH), cortisol, total testosterone (TT), follicle-stimulating hormone (FSH), Luteinizing hormone (LH), sex hormone binding globulin (SHBG), Insulin-like growth factor-1 (IGF-1), prolactin (PRL), estradiol (E2), HbA1c, D-dimer were measured. In principle, in diagnosing central hormone deficiencies (secondary or tertiary deficiencies), both basal pituitary and target gland hormone levels should be measured. The target hormone for ACTH is basal cortisol and for GH, IGF-1. However, stimulation tests are required for the definitive assessment of ACTH and GH insufficiency. Stimulation tests are not performed in AF patients because they are contraindicated. GH measurement was not available, so serum IGF-1 levels were measured. Patients with chronic liver and kidney diseases, which may affect serum IGF-1 levels, were excluded from the study. Peripheral venous blood samples were taken from the patients after 10-12 hours overnight fast. These blood samples were centrifuged at 3000 rpm for 4 minutes in a refrigerated centrifuge without waiting and stored at -80°C. To avoid undesirable variations, samples were run with the same batch on the same day. Echocardiography (ECHO) measurements were performed on the patients using the Vivid 3 cardiac ultrasound device (GE Vingmed Ultrasound, Horten, Norway) and a 2.5 - 3.5-MHz probe.

In statistical analysis, normal distribution analysis was tested with the Kolmogorov-Smirnov test. For normally distributed data, differences between groups were compared with the Student t-test, and for non-normally distributed data, differences between groups were compared with the Mann-Whitney U test. Categorical variables were compared with the Chi-square test. Correlation analyses were performed with the Pearson correlation test for normally distributed data, and with the Spearman correlation test for non-normally distributed data. The results were evaluated within the 95% confidence interval, and $p<0.05$ was accepted for statistical significance.

RESULTS

Of the 130 patients participating in the study, 34 were men and 96 were women. The atrial fibrillation group consisted of 65 patients and the control group consisted of 65 patients. Gender, age, and BMI (body mass index) were found to be similar in both groups.

In the patient group, 31 (47.7%) of the patients were using warfarin, 26 (40%) were using acetylsalicylic acid (ASA), and 3 (4.6%) were using clopidogrel. In the control group, there were no patients using warfarin, 5 (7.7%) were using ASA and 1 (1.5%) was using clopidogrel. The characteristics of the patient and control groups are shown in Table 1.

Table 1. The characteristics of the patient and control groups

	Patient Group		**Control Group**		**P**
Age (year)	68 ± 7		67 ± 6		>0.05
	Female	Male	Female	Male	>0.05
	49 (%75.4)	16 (%24.6)	47 (%72.3)	18 (%27.7)	
HbA1c (%)	6.28 ± 0.88		6.25 ± 0.64		>0.05
BMI (kg/m^2)	26 (18-38)		26.5 (18.2-36.5)		>0.05
Waist Circumference (cm)	88.15 ± 7.13		86.95 ± 6.13		>0.05

*Data were expressed as mean ± standard deviation, median (interquartile range), or n (%).

P value was calculated using the T test, Mann–Whitney U test, and chi-square test.

BMI: Body mass index.

Table 2. The comparison of hormone levels of the patient and control group

Parameter (normal range)	**Patient Group**	**Control Group**	**P**
Insulin (1.9-25 µIU/mL)	13.7 ± 14.1	11.4 ± 6.3	>0.05
C-peptide (1.1-3.2 ng/mL)	4.5 ± 3.1	2.9 ± 1.36	<**0.0001**
Free T3 (2.5-5 pg/mL)	2.6 ± 0.6	2.8 ± 0.41	**0.039**
Free T4 (0.9-1.7 ng/dL)	1.17 ± 0.37	1.14 ± 0.42	>0.05
TSH (0.4-4 µIU/L)	1.94 ± 2.16	2.42 ± 2.38	>0.05
BNP (0-125 pg/mL)	1600.7 ± 1565.7	125 ± 80.3	<**0.0001**
ACTH (9-25 pg/mL)	16.6 ± 12.7	22.88 ± 15.9	**0.005**
Cortisol (5-20 µg/dL)	11.4 ± 5.1	13.4 ± 5.6	**0.023**
TT (300-1000 ng/mL)	0.9 ± 1.4	1.44 ± 1.97	>0.05
FSH (30-118 mIU/mL)	49 ± 30.3	52.8 ± 41.5	>0.05
LH (12-55 mIU/mL)	20.1 ± 13.2	20.9 ± 15.5	>0.05
SHBG (10-57 nmol/L)	59.7 ± 28.3	34.4 ± 15.8	<**0.0001**
IGF-1 (10-1000 ng/mL)	88.8 ± 36.1	109.6 ± 55.9	**0.048**
PRL (< 25 ng/mL)	9.41 ± 5.90	7.5 ± 3.9	>0.05
E2 (0-30 pg/mL)	22.8 ± 19.1	29.8 ± 24.8	>0.05

Data were expressed as mean ± standard deviation.

P value was calculated by T test or Mann–Whitney U test.

C-peptide, FT3: Free triiodothyroxine, FT4: Free thyroxine, TSH: Thyroid stimulating hormone, BNP: Brain Natriuretic Peptide, ACTH: adrenocorticotropic hormone, cortisol, TT: Total testosterone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, SHBG: Sex hormone binding globulin, IGF-1: Insulin-like growth factor-1, PRL: Prolactin, E2: Estradiol.

Hormone levels of the patient and control groups are shown in Table 2. There was no significant difference in the comparison of serum TSH, insulin, FSH, LH, PRL, E2, TT levels between groups. Serum C-peptide, BNP, SHBG levels were significantly higher in the patient group than in the control group (p<0.0001). Serum FT3, ACTH, cortisol and IGF-1 levels were lower in the patient group than in the control group (p<0.05). There was also a significant positive correlation between serum BNP and C-peptide levels (r=0.288, p:0.003) and SHBG levels (r=0.305, p:0.002).

ECHO findings of the patient and control groups were evaluated. The left atrial diameter (LAD) and left ventricular end-diastolic diameter (LVEDD) of the two groups were higher in the patient group (p<0.0001). The left ventricular ejection fraction (LVEF) value was lower in the patient group (p<0.0001). There was a strong positive correlation between LAD and BNP levels (r=0.666, p<0.0001) and SHBG levels (r=0.406, p<0.0001).

Biochemical and hematological findings of both groups are shown in Table 3. There was no significant difference between the two groups in serum fasting blood glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), low-density lipoprotein (LDL), triglyceride, total cholesterol, hemoglobin, hematocrit, erythrocyte sedimentation rate (ESR) values (Table 3). Serum total protein, albumin and high-density lipoprotein cholesterol (HDL) levels were found to be significantly lower in the AF group compared to the control group (p<0.05) (Table 3). Serum urate, lactate dehydrogenase (LDH), D-dimer levels were found to be higher in the AF group than in the control group, and the difference was statistically significant (p <0.05) (Table 3).

Table 3. The comparison of biochemical and complete blood count tests of the patient and control group

Parameter (normal range)	Patient Group	Control Group	P
FBG (100-125 mg/dL)	117.3 ± 37.9	105.2 ± 17.8	>0.05
Urea (10-20 mg/dL)	36.1 ± 19.37	30.5 ± 8.2	>0.05
Serum creatinine (0.50-1.30 mg/dL)	0.89 ± 0.2	0.8 ± 0.1	>0.05
AST (15-50 IU/L)	23.3 ± 10.1	20.6 ± 6.8	>0.05
ALT (10-40 IU/L)	23.4 ± 17.6	19.4 ± 8.3	>0.05
LDH (140-280 IU/L)	261 ± 109.4	180 ± 33.2	**<0.0001**
Total Protein (6.4-8.3 g/dL)	7.09 ± 0.54	7.3 ± 0.6	**0.007**
Albumin (3.5-5.5 g/dL)	3.95 ± 0.37	4.1 ± 0.4	**0.001**
HDL (35-55 mg/dL)	43 ± 10.2	47.4 ± 9.2	**0.028**
LDL (30-130 mg/dL)	116.9 ± 39.1	109.9 ± 30.3	>0.05
Triglyceride (0-149 mg/dL)	132.6 ± 66.5	153.4 ± 88.7	>0.05
Total cholesterol (0-200 mg/dL)	187 ± 47.6	198.4 ± 38.1	>0.05
Urate (2.6-6 mg/dL)	5.4 (3.2-5.9)	3.4 (2.2-4.8)	**0.007**
Hemoglobin (13-17.5 g/dL)	13.2 ± 1.7	13.7 ± 1.1	>0.05
Hematocrit (40-51 %)	39.3 ± 5	39.6 ± 3.2	>0.05
ESR (0-20 mm/h)	25 (3-80)	23 (6-75)	>0.05
D-dimer (< 250 ng/ml)	417 ± 344.4	256.2 ± 125.9	**0.013**

Data were expressed as mean ± standard deviation, median (interquartile range).

P value was calculated by T test or Mann–Whitney U test.

FBG: Fasting blood glucose, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein cholesterol, LDL: Low-density lipoprotein, LDH: Lactate dehydrogenase, ESR: Erythrocyte Sedimentation Rate.

DISCUSSION

Atrial fibrillation is an arrhythmia that is becoming increasingly common, with its frequency doubling every decade, causing significant morbidity and mortality, and is responsible for one-fifth of all ischemic strokes (3,6). Apart from major thromboembolism, cerebral infarcts due to microembolism have been described in AF patients (4,5). As is known, the pituitary gland is an organ with a high blood supply and is very sensitive to ischemia. Susceptibility of cells to ischemia, in order from most to least: somatotrophs, gonadotrophs, corticotrophs, thyrotrophs and lactotrophs. Busch et al. (7) reveal a quantitatively lower IGF-1 levels and IGF-1/IGFBP-3 ratios in individuals with AF than individuals without AF in a large population-based study. Duron et al. (8) reported similar results as low IGF-I and IGFBP-3 serum levels were independently associated with AF in an elderly population. However, the exact underlying mechanisms of a decreased level of IGF-1 and the presence of AF could not be elucidated by the authors (7,8). In our study, serum IGF-1 level in AF patients was significantly lower than in the control group. There was no liver dysfunction in our patients and no statistical difference in the liver function tests between the groups. Therefore, it was thought that the low IGF-1 may be due to pituitary origin rather than liver dysfunction.

Larsson et al. (9) encouraged AF monitoring in patients with Cushing syndrome due to hypercortisolemia as a potential risk of AF. Nevertheless, there has been no published study on the cause of low levels of cortisol and ACTH in patients with AF so far. In our study, ACTH and cortisol levels were low in the patient group. Because the secretion pulses are uncertain and have a short half-life, significant changes occur in the ACTH level during the day, so random ACTH measurements are not recommended. Similarly, cortisol exhibits a diurnal rhythm, with levels being highest in the early morning hours and lowest in the late afternoon and evening. The gold standard is insulin tolerance test (ITT) to detect growth hormone (GH) deficiency and ACTH reserve, however, ITT is contraindicated in AF patients due to a high risk of cardiovascular or cerebrovascular events. For this reason, ITT could not be performed on our patients yet, hormone levels were studied in the morning serum samples in order to minimize diurnal impact.

Some previous studies have shown that there is a hypercoagulant environment and cerebral microembolism occurs in patients with atrial fibrillation (10-12). Nevertheless, since there is no study on pituitary microembolism in patients with AF in the literature, we could not compare our findings with another study. In a prospective study by Boehncke et al. (13), in the follow-up of patients after ischemic stroke, variable degrees of pituitary dysfunction were detected in 82% of the patients. It was shown that GH insufficiency (79.5%) and secondary adrenal insufficiency (14.6%) developed predominantly. Secondary gonadal failure was detected in 4.3% of the patients. Additionally, pituitary dysfunction was found to be independent of post-stroke time, stroke type, and gender (13). As a result of this study, it was shown that pituitary ischemia and associated pituitary dysfunction may develop as a complication of ischemic stroke, and therefore pituitary function tests were recommended to be performed in patients with stroke (13). Similarly, in our study, mainly IGF-1, ACTH and cortisol levels were lower in the patient group, and this might be the result of growth hormone and ACTH deficiency due to pituitary microvascular ischemia.

Most of the testosterone and estrogen in the bloodstream are bound to SHBG, a very small part of the total sex hormone concentration (1% - 5%) is free, and biological activity is created by the free fractions. Therefore, SHBG levels may directly alter sex hormone bioavailability. Three recent large-scale population-based studies have shown that male sex hormones may be modulators of cardiac endocrine functions (14-16). These studies showed that circulating BNP and N-terminal proBNP levels were inversely proportional to free and total testosterone in both genders. There was a positive relationship between SHBG, BNP and N-terminal proBNP levels in adolescents and adults of both genders. No significant relationship was detected with estrogen. According to these results, it has been suggested that androgens suppress N-terminal proBNP and this situation can be explained by the changes in free testosterone levels due to sex hormone-related differences in natriuretic peptides (14-16). In our study, there was no significant difference in age and

BMI between both groups and SHBG levels were significantly higher in patients with AF compared to the control group and were correlated with increased BNP levels. High SHBG levels suggest that circulating free androgen levels in patients with AF may be lower than in the control group. BNP and C-peptide levels were also significantly higher in the group of patients with AF in our study. It has been declared that a high plasma BNP and C-peptide levels might be the risk factor for atrial fibrillation (17,18).

There was no significant difference in FT4 and TSH levels between the patient and control groups, and the FT3 level was lower in the patient group than in the control group. However, it was not detected within the limits of hypothyroidism. It was thought that this clinical picture, called 'euthyroid patient syndrome', developed as a result of the mechanisms proposed in its pathogenesis such as insufficiency of peripheral metabolism in extrathyroidal tissues and inhibition the 'type 1 deiodinase' enzyme that converts T4 to T3 in the periphery by inflammatory cytokines released during the emergence of chronic systemic diseases (19).

There are some limitations of this study. Given the cross-sectional nature of the study, we were not able to reveal the exact cause-effect relationship of lower levels of pituitary hormones in AF patients compared to the control group. The sample size was relatively small, however, in both groups, the number of individuals, mean age and gender ratios were similar. Additionally, as mentioned above, some dynamic tests could not be performed to detect hormone deficiency in patients with AF due to contraindications. Despite these limitations, this study is the first in the literature in order to draw attention to the fact that silent microembolism in AF patients may lead to pituitary ischemia.

CONCLUSION

These findings support that silent cerebral ischemia may lead to pituitary dysfunction in patients with AF and no history of cerebrovascular accident. The pathogenesis of the relationship between cerebral ischemia and pituitary dysfunction is still unclear. Individuals with hypopituitarism have a higher risk of morbidity and mortality than healthy individuals. Even if no obvious stroke occurs, pituitary dysfunction should be investigated in suspected cases in patients with AF.

Ethical approval

This study has been approved by the Keçiören Training and Research Hospital Clinical Research Ethics Committee (approval date 11/04/2012, number B.10.4.İSM.4.06.68.49/2012). Written informed consent was obtained from the participants.

Author contribution

Concept: DTE; Design: BY; Data Collection or Processing: RKC; Analysis or Interpretation: RKC, BY; Literature Search: RKC, EB; Writing: RKC. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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