

The role of adrenomedullin and brain natriuretic peptide levels in acute rheumatic fever in adults

Erişkin akut romatizmal ateşli hastalarda adrenomedüllin ve beyin natriüretik peptidin rolü

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ABSTRACT

Objective: Rheumatic fever, a multisystem disease following infection with group A beta-hemolytic streptococcus, is common among young (5-15 years) but can occur in adults as well. Recently, brain natriuretic peptide (BNP) has been validated as a marker of cardiac function and prognosis. Plasma adrenomedullin (ADM) levels are elevated in various pathological states including cardiovascular and inflammatory diseases. We aim to assess the relationship between ADM and BNP levels in adult patients with acute and convalescent rheumatic fever (ARF).

Methods: This case -controlled prospective study included 45 patients with ARF (mean age 21.04±1.91 years) and 30 age/gender-matched control subjects. Brain natriuretic peptide and adrenomedullin levels were studied in the acute and convalescent phase of ARF. Adrenomedullin was detected by enzyme immunoassay kit of peptides, while brain natriuretic peptide was measured by a commercially available instrument. The study was carried out between May 2006 and October 2006 in Atatürk University Medical Faculty Hospital. Statistical analysis was performed using Shapiro-Wilk, Mann Whitney U, Wilcoxon signed rank, Chi-square tests and Pearson correlation analysis.

Results: Plasma ADM and plasma BNP levels were significantly higher ($p<0.05$) in adults with ARF, regardless of whether they were in acute or convalescent phase of disease. Plasma ADM levels were 74.43±3.4 pmol/mL in acute phases, 59.35±1.45 pmol/mL in the convalescent phase, and 44.79±13.12 pmol/mL in control group. Plasma BNP levels were 197.51±47.41 pg/mL in the acute phase, 145.25±51.25 pg/mL in the convalescent phase, and 33.45±10.42 pg/mL in control group. The differences were statistically significant for all ($p<0.05$). Plasma ADM and BNP levels in the acute phase of disease showed significant negative correlation with the left ventricular ejection fraction ($r=-0.56$, $p<0.05$ and $r=-0.61$, $p<0.05$, respectively).

Conclusion: In patients with acute and convalescent rheumatic fever, BNP and ADM levels were high compared to those of healthy subjects and this could be used as a complementary tool in the treatment and prognosis of ARF. (*Anadolu Kardiyol Derg 2008; 8: 188-91*)

Key words: Acute rheumatic fever, adrenomedullin, brain natriuretic peptide

ÖZET

Amaç: Akut romatizmal ateş A grubu beta hemolitik streptokok enfeksiyonunu takiben oluşan multisistem bir hastalıktır. Gençlerde (5-15 yaş) yaygın olmasına rağmen erişkin yaş gurubunda da görülmektedir. Yapılan son çalışmalarda beyin natriüretik peptidin (BNP) kardiyak fonksiyon ve prognoz tayininde önemli bir belirteç olduğu görülmüştür. Plazma adrenomedüllin (ADM) seviyesi de kardiyovasküler ve inflamatuvar patolojiler gibi birçok durumda yükselmektedir. Bu çalışmada romatizmal ateşin akut ve iyileşme döneminde, erişkin hasta gurubunda ADM ve BNP seviyeleri araştırıldı.

Yöntemler: Vaka kontrollü ve prospektif bu çalışmaya akut romatizmal ateşli 45 hasta (ortalama yaş 21.04±1.91 yıl) ve yaş/cinsiyet karşılaştırmalı 30 sağlıklı olgu alındı. Beyin natriüretik peptid ve adrenomedüllin düzeyleri akut romatizmal ateşin akut ve konvelascent fazında çalışıldı. Adrenomedüllin düzeyleri enzim radyoimmunoassay, BNP düzeyi ise piyasada mevcut olan ticari kitlerle ölçüldü. Mayıs 2006 ve Ekim 2006 tarihleri arasında Atatürk Üniversitesinde akut romatizmal ateş ile başvuran 45 erkek hastada BNP ve ADM seviyeleri çalışıldı. İstatistiksel analiz Shapiro-Wilk, Mann Whitney U, Wilcoxon signed rank, Ki-kare testleri ve Pearson korelasyon analiz ile yapıldı.

Bulgular: Plazma ADM ve BNP seviyeleri, akut romatizmal ateşli erişkin hasta gurubunda hastalığın hem akut, hem de iyileşme fazında belirgin derecede ($p<0.05$) yüksek tespit edildi. Adrenomedüllin seviyesi akut fazda 74.43±3.4 pmol/mL, iyileşme fazında 59.35±1.45 pmol/mL, kontrol gurubunda ise 44.79±13.12 pmol/mL. Beyin natriüretik peptid seviyesi ise akut fazda 197.51±47.41 pg/mL, iyileşme fazında 145.25±51.25 pg/mL, kontrol gurubunda ise 33.45±10.42 pg/mL olarak tespit edildi. Fark tüm değerler için istatistiksel olarak anlamlıydı ($p<0.05$). Plazma ADM and BNP değerleri ile sol ventrikül ejeksiyon fraksiyonu arasında anlamlı negatif ilişki saptandı (sırası ile $r=-0.56$, $p<0.05$ ve $r=-0.61$, $p<0.05$).

Sonuç: Hem akut, hem de iyileşme fazında romatizmal ateşte kontrol gurubu ile karşılaştırılınca BNP ve ADM seviyeleri belirgin olarak yüksek bulundu. Bu yüksekliğin akut romatizmal ateşin tedavisinde ve takibinde tamamlayıcı bir yöntem olarak kullanılabileceği kanaatindeyiz.

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Anahtar kelimeler: Akut romatizmal ateş, adrenomedüllin, beyin natriüretik peptid

Introduction

Rheumatic fever (RF), a complication following an episode of group A streptococcal pharyngitis, is an acute, immunologically mediated, multisystem inflammatory disorder. Rheumatic fever is generally classified as a connective tissue disorder involving multiple organs (1). The diagnostic criteria established in 1944 for RF was revised and updated by American Heart Association in 1992 (2). RF occurs mostly in the young (5-15 yr) (3) but can occur in adults as well (4). Rheumatic fever and rheumatic heart disease are still important causes for heart failure in developing countries. Recently, the pathogenic role of inflammatory cytokines, such as IL-8, IL-6, and alpha tumor necrosis (TNF- α) has been recognized (5). Adrenomedullin (ADM), a hypotensive peptide (6) has also been identified as a potent vasodilator. Indeed, ADM appears to play a pivotal role in both reprioritizing the biological needs of tissues and organs during the three phases of inflammatory response as well as a role in restoring homeostatic equilibrium to the body (7). Previous studies showed that AM may have a role in the immunoinflammatory process of acute rheumatic fever (ARF) (7, 8).

Human brain natriuretic peptide (BNP), secreted from the ventricular myocardium has diuretic, natriuretic, and vasodilator activities (9). Plasma BNP levels increase following overload, such as left ventricular hypertrophy or left ventricular failure (10, 11) and in patients with normal left ventricular (LV) systolic function and abnormal LV diastolic function on echocardiography (12). In addition, BNP levels increase with severity of organic mitral or aortic regurgitation with normal LV systolic function (13). That BNP is increased in patients with rheumatic valve diseases, has been shown by several studies (14-16), however there are no studies on the possible role(s) of ADM and BNP in adult ARF.

The aim of the study was to assess whether there are differences in adrenomedullin and BNP values in adult patients with acute rheumatic fever as compared with healthy subjects, as well as to investigate the dynamics of ADM and BNP values during acute and convalescent phases of acute rheumatic fever.

Methods

Forty-five adults with ARF (age range 19-24 years; mean 21.04 ± 1.91 years, 19 women and 26 men) and 30 healthy age and sex matched control subjects were included into the study. The study was carried out between May 2006 and October 2006 in the Department of Biochemistry of Atatürk University Medical Faculty Hospital. Acute rheumatic fever was defined by two major, or one major and two minor manifestations accompanied with supporting evidence of antecedent group A streptococcal infection as a positive throat culture, or elevated or rising antistreptolysin (ASO) titer and echocardiographic findings (17). Patients were studied in acute and convalescent phases of the disease. A new murmur of aortic or mitral regurgitation was considered as clinical evidence of carditis. This was confirmed by echocardiographic guidelines to define pathological mitral and aortic insufficiency (18). All of our patients had carditis, 38 of them also had polyarthritis and 9 had erythema marginatum. None had subcutaneous nodules and chorea. All patients had

signs of inflammation in acute phase, clinically and laboratory such as tachycardia, fever, pallor, anorexia and elevated ASO titer, erythrocyte sedimentation rate (ESR). They were treated with bed-rest, acetylsalicylic acid as an analgesic and antipyretic for arthritis, penicillin, and corticosteroid for patients with severe carditis and the treatment continued until acute inflammation was subsided (19). Patients with hypertension, abnormal creatinine level, the presence of moderate or severe respiratory diseases, previous congenital cardiac surgery were excluded, because they could affect plasma levels of ADM and/or BNP (20). All subjects gave written informed consent before enrollment.

Study design

The study, case-controlled and prospective, comprised 45 patients with ARF (mean age 21.04 ± 1.91 yr) and 30 age/gender-matched control subjects. Brain natriuretic peptide and adrenomedullin levels were studied in the acute and convalescent phase of ARF.

All control subjects had normal physical examination and normal echocardiographic findings and ASO, ESR levels were within normal limits at the time of study. The blood samples for the acute phase were obtained within the first 24-48 h of diagnosis. The samples for the convalescent phase were obtained on the third post discharge visit (within 90 days), when all symptoms had completely disappeared. Only one blood sample was taken from each control subject. The samples were kept at -80°C until the study day.

Blood samples were collected in tubes with 2mg/ml of ethylenediaminetetraacetic acid (EDTA)-2Na and 500 KIU/ml aprotinin. After collection, samples were promptly centrifuged at $1600 \times g$ for 15 minutes at 4°C . Total plasma ADM was measured by using enzyme immunoassay kit (EIA) (Human Adrenomedullin (1-52), Phoenix Pharmaceuticals Inc. California, USA). The concentrations of plasma ADM (pmol/mL) were calculated from the standard curve for the known concentration of ADM.

Blood samples were collected by venipuncture into tubes containing potassium EDTA. They were analyzed within half an hour after the draw time, each tube was turned upside down several times to ensure homogeneity. Brain natriuretic peptide was measured using the Triage B-Type Natriuretic Peptide test (Biosite Diagnosis). The test is self-processing and produces a result within 15 min. The detection range of the BNP level is 5-1300 pg/mL (21, 22).

Statistical analysis

Values are given as Mean \pm Standard Deviation, Median (Range) and proportions/percentage. Normality was tested by Shapiro-Wilk method. Data were analyzed with Mann-Whitney U test, Wilcoxon signed rank test and Chi-square test based on statistical assumptions using Statistical Package for the Social Sciences for Windows (SPSS, version 10.0, Chicago, IL, USA). Pearson correlation was used to identify the relationship between the variables. All p values < 0.05 were considered statistically significant.

Results

Table 1 presents the patients and control subjects clinical characteristics. There were no differences in age between patients with RF and control subjects ($p > 0.05$). Mean LV ejection

fraction (EF) value for convalescent phase was significantly higher than that for acute phase ($p < 0.001$). There were significant differences for NYHA classes (I-IV) between convalescent and acute phases ($p < 0.001$).

The plasma ADM and BNP levels were significantly higher in patients with RF (acute or convalescent phase) compared to control subjects ($p < 0.001$) (Table 2). Plasma ADM levels were higher in the acute phase as compared with the convalescent phase ($p < 0.0001$) (Table 1). Similarly, plasma BNP levels were significantly ($p < 0.0001$) in the acute phase when compared with the convalescent phase (Table 2).

Plasma ADM and BNP levels in the acute phase of disease showed significant negative correlation with the EF ($r = -0.56$, $p < 0.05$ and $r = -0.61$, $p < 0.05$, respectively). No significant correlation was found between plasma ADM, BNP levels and other clinical and laboratory findings ($r = 0.231$, $p > 0.05$).

Discussion

We found the plasma ADM and BNP levels to be significantly higher in adult with ARF in the acute and convalescent phases compared with control subjects.

Endogenous ADM may play an important role as a counter-regulatory hormone in states where there is pathological inflammatory reactions. Thus, increased levels of plasma ADM may also be compensatory against inflammatory reactions in ARF.

Elevated BNP levels are known to correlate with LV systolic and diastolic dysfunction (23, 24). In addition, previous studies have shown that BNP levels correlate with LV filling pressure (24). Majority of patients with rheumatic carditis have normal LV systolic function. Congestive heart failure was more common in patients with a recurrence of carditis. All patients with congestive heart failure had hemodynamically significant valvular lesions, and majority had normal left ventricular systolic function. Patients with a reduced fractional shortening had significant valvular lesions. These observations are in agreement with recent reports (25, 26). Suggesting that valvular disease, as opposed to myocardial dysfunction, is the mechanism of congestive heart failure in rheumatic carditis, it may represent the combined effects of elevated ventricular afterload, left ventricular enlargement and right ventricular volume overload. In this study, the plasma levels of BNP in patients with ARF in the acute and convalescent phases were found to be higher compared to healthy subjects. The elevated afterload and/or left ventricular enlargement seems to be the principal stimulus for BNP secretion in ARF patients.

Table 1. Clinical characteristics

Variable	Acute Phase (n = 45)	Convalescent Phase (n = 45)	Control, (n = 30)
Age, years*	21.04±1.91 21 (18-23)	21.04±1.91 21 (18-23)	19.24±1.15 20 (18-22)
LVEF, %**	36.91±6.138 37 (27-45)	52.98±7.509 53 (43-63)	-
NYHA class, n (%)***			
I	22.2 (10)	44.4 (20)	
II	57.8 (26)	48.9 (22)	-
III	13.3 (6)	6.7 (3)	
IV	6.7 (3)		

Values are given as Mean ± Standard Deviation, Median (Minimum-Maximum) values or proportion/percentage
 * $p > 0.05$ - differences between patients and control groups are nonsignificant, Mann Whitney U test
 ** $p < 0.001$ - difference between acute and convalescent phases, Wilcoxon signed rank test
 *** - $p < 0.001$ - difference between acute and convalescent phases, Chi Square Test
 LVEF - left ventricular ejection fraction, NYHA -New York Heart Association class

Table 2. Plasma adrenomedullin and brain natriuretic peptide levels in adults with acute rheumatic fever

	Plasma ADM, pmol/mL	Plasma BNP, pg/mL
Acute phase, (n = 45) ^a	74.43±3.4 74.9 (68.25-81.40)	197.51±47.41 198.3 (132.30-285.45)
Convalescent Phase, (n = 45) ^b	59.35±1.45 58.7 (46.30-62.15)	145.25±51.25 146.1 (83.50-211.44)
Control, (n =30) ^c	44.79±13.12 45 (27.20-62.95)	33.45±10.42 34.2 (18.20-51.60)
a-b	$p < 0.0001$ - Wilcoxon signed-ranks test	$p < 0.0001$ - Wilcoxon signed-ranks test
a-c	$p < 0.001$ - Mann Whitney U test	$p < 0.001$ - Mann Whitney U test
b-c	$p < 0.0001$ - Mann Whitney U test	$p < 0.001$ - Mann Whitney U test

Values are given as Mean ± Standard Deviation and Median (Minimum-Maximum) values
 ADM - adrenomedullin, BNP - brain natriuretic peptide

Adrenomedullin and brain natriuretic peptide are elevated in heart failure (27). The negative correlation between ADM, BNP levels and EF in acute phase of disease suggests that such increased levels may be because of asymptomatic LV dysfunction. However, ADM and BNP levels were still higher than those of control subjects in the convalescent phase of disease (8). Although we obtained the convalescent phase samples within 3 months after the diagnosis, most of patients (79.8%) had carditis and valvular lesions. Moreover, most of these patients may have sub-clinical inflammation in the convalescent phase of disease. Therefore, increased ADM levels in the convalescent phase may be related to possible lasting effect of sub-clinical inflammation. Increased BNP levels in this phase may also be related to persistence of LV dysfunction.

Study limitations

Further prospective studies including the importance of ADM and BNP levels in the follow up and management of patients with ARF are needed. Although BNP and ADM levels were higher in the acute and convalescent phase of the disease, whether these parameters may be used as follow-up markers like C-reactive protein and erythrocyte sedimentation rate in acute rheumatic fever should be investigated.

Conclusion

The plasma ADM and BNP levels were significantly higher in patients with RF compared to control subjects especially in the acute phase of the disease. Adrenomedullin and brain natriuretic peptide levels may be used as complementary tools for the clinical diagnosis and follow up of the patients with ARF.

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