Relationship of increased serum brain natriuretic peptide levels with hepatic failure, portal hypertension and treatment in patients with cirrhosis

Sirozlu hastalarda karaciğer yetmezliği, portal hipertansiyon ve tedavi ile artmış B tipi natriüretik peptid arasındaki ilişki

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Background/aims: *Brain natriuretic peptide is a cardiac neurohormone secreted from ventricles in response to end diastolic pressure and increased volume. It has diuretic, natriuretic and vasodilator effects. In cirrhosis, a hyperdynamic circulation occurs because of hemodynamic and hemostatic alterations. The increase in brain natriuretic peptide concentration shows parallelism with the stage of cirrhosis. The aim of this study is to investigate the relation of increased brain natriuretic peptide level with the pathophysiologic components of cirrhosis and treatment.* ***Methods:*** *Ninety-five cirrhotic patients in different stages (Child-A: 33; Child-B: 25; Child-C:37) and age and sex matched 86 healthy indivudials were recruited for the study. Brain natriuretic peptide concentration was measured with brain natriuretic peptide-Triage test device using fluoresan immun assay method.* ***Results:*** *Brain natriuretic peptide levels of patients with hepatic cirrhosis were significantly higher compared to control group (288,5±329,2 / 60,2± 29,5 / p=0.000, respectively). Serum brain natriuretic peptide levels were positively correlated with Child score (Child A-B-C; 201,2±266 / 258,7±233,6 / 386,5±407,7, respectively). A negative correlation was observed between brain natriuretic peptide and albumin levels (p=0.002). Brain natriuretic peptide concentration was significantly correlated with the grade of esophagus varices, and presence of ascites and collateral circulation (p=0,006; p=0,001; p=0,002; respectively). Patients receiving with beta-blocker and diuretic treatments had significantly higher brain natriuretic peptide levels.* ***Conclusions:*** *High brain natriuretic peptide levels in patients with cirrhosis may be due to hepatocelluler insufficiency or portal hypertension, but a cardiomyopathy developing insiduously should not be regarded.*

Key words: Cirrhosis, brain natriuretic peptide, Child-Pugh Classification

Amaç: *Beyin natriüretik peptid artmış diyastol sonu basınç ve volüme bağlı olarak ventrikülden salgılanan bir kardiyak nörohormondur. Diüretik, natriüretik ve vazodilatör etkileri vardır. Sirozda hemodinamik ve hemostatik değişiklikler nedeniyle hiperdinamik bir dolaşım olmaktadır. Beyin natriüretik peptid konsantrasyonundaki artış sirozun evresiyle paralellik göstermektedir. Çalışmamızın amacı artmış beyin natriüretik peptid düzeyi ile sirozun patofizyolojik komponentleri ve tedavisi arasındaki ilişkiyi araştırmaktır.* ***Yöntem:*** *Çalışmaya sirozun farklı evrelerinde bulunan 95 hasta (Child-A: 33; Child-B: 25; Child-C:37) ve yaş ve cinsiyet dağılımı açısından benzer 86 sağlıklı gönüllü alındı. Beyin natriüretik peptid konsantrasyonu flöresan immün assay yöntemi ve beyin natriüretik peptid-Triage test cihazı kullanılarak ölçüldü.* ***Bulgular:*** *Karaciğer sirozlu hastaların serum beyin natriüretik peptid düzeyleri kontrol grubundan anlamlı derecece yüksek bulundu (p: 0,000). Child-Pugh sınıflamasına göre de hastalar arasında anlamlı düzeyde farklılıklar vardı (p=0.045). Serum albumin ve beyin natriüretik peptid düzeyleri arasında negative korelasyon olduğu görüldü (p=0.002). Beyin natriüretik peptid konsantrasyonu ile özofagus varislerinin derecesi, asit varlığı ve kollateral dolaşım arasında anlamlı korelasyon vardı (sırayla p=0,006; p=0,001; p=0,002). Beta bloker ve diuretic tedavisi alan hastalardaki serum beyin natriüretik peptid düzeyi almayanlara göre anlamlı derecede daha yüksek bulundu.* ***Sonuç:*** *Sirozlu hastalardaki artmış serum beyin natriüretik peptid düzeyleri portal hipertansiyon veya hepatosellüler yetmezliğe bağlı olabilir, ancak sinsi gelişen kardiyomyopatinin de etkisinin olabileceği unutulmamalıdır.*

Anahtar kelimeler: Siroz, B-tipi natriüretik peptid, Child-Pugh sınıflaması

INTRODUCTION

Brain natriuretic peptide (BNP) is a cardiac neurohormone secreted from ventricles in response to end-diastolic pressure, related to volume load. BNP has diuretic, natriuretic and vasodilator ef-

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Manuscript received: 10.04.2009 **Accepted:** 05.11.2009

doi: 10.4318/tjg.2010.0124

fects. Increased serum BNP levels are correlated with the severity and functional capacity of chronic heart failure. BNP is useful in distinguishing cardiac dyspnea from non-cardiac causes. It is also useful in screening patients with coronary heart disease, hypertension, diabetes, cirrhosis, and other vascular diseases who are at risk for left heart failure (1-4). BNP increases before the symptoms of heart failure appear, which allows early diagnosis (5). BNP increases in both systolic and diastolic dysfunction, but the increase is more pronounced when both are present (6-8).

BNP level has shown to be increased in patients with liver cirrhosis. In cirrhosis, intestinal flora disorder, the transition of intestinal flora to mesenteric lymph nodes, bacterial translocation, and decreased hepatic clearance of endotoxins cause an endotoxemic medium. Consequently, various mediators (nitric oxide, von Willebrand factor (VWF), etc.) are released from endothelial cells and a hyperdynamic circulation occurs (9,10). These changes result in functional and structural cardiac disorders in patients with liver cirrhosis. Thickness of the left ventricular wall, diastolic dysfunction and stress-induced systolic dysfunction are indicative of cirrhotic cardiomyopathy (11). BNP increases in correlation with the severity of this pathology.

As aforementioned, hyperdynamic circulation (also volume overload) and structural cardiac changes may be related to the increased BNP levels in patients with liver cirrhosis. The aim of this study was to determine the association of BNP levels with the clinical severity of cirrhosis.

Table 1. The different etiologies of cirrhosis

Etiology	Number of patients	Etiology	Number of patients
HBV	30	Cryptogenic	20
HCV	16	Alcohol	13
HBV+HCV	3	Budd-Chiari	2
HBV+HDV	4	Autoimmune	3
HCV+ALCOHOL	1	Other	3

MATERIALS AND METHODS

This randomized prospective case controlled study was conducted in the Gastroenterology Department of a university hospital between April-December 2005. Patients with liver cirrhosis consecutively admitted to the outpatient gastroenterology clinic and healthy controls composed the study population. Patients who had factors affecting BNP levels such as hypertension, diabetes, coronary heart disease, and oral contraceptive use were excluded from the study.

The demographic features of patients, medications, etiological factors, and BNP levels were recorded onto the study form.

The diagnosis of liver cirrhosis was made by clinical, laboratory and imaging methods in 90 patients and with liver biopsy in five patients. The stage of cirrhosis was classified according to the Child-Pugh classification, which reflects the severity of the disease. Moreover, Model for End-Stage Liver Disease (MELD) scores were calculated and their correlations with serum BNP levels were determined. Other possible causes of BNP increases were diagnosed from the patient history, physical examination, electrocardiography, chest X-ray, and laboratory assays.

Esophageal varices were detected by endoscopic examination and graded with Paget classification (12). Portal-splenic vein diameter and spleen dimensions were measured using an ALT-HDI 3500 Doppler-ultrasonography device. The measurement of left ventricle posterior wall thickness was performed with an ALT HDI 3500 echocardiography device.

Biochemical analysis was done with Olympus AU 600 analyzer using nephelometry method. Complete blood count was performed using a spectrophotometer with Beckman Coulter STKS analyzer. Prothrombin time measurement was conducted with STA Compact brand device by clotting method.

BNP concentrations were determined with a Triage-BNP device. Blood samples taken into EDTA-

Table 2. Number of patients with different signs of hepatocellular failure and portal hypertension

Group	N	Group	N
Encephalopathy	65 (68%)	Esophageal varices grade 1-2-3	42-22-10
Ascites	60 (68%)	Collateral	24 (25%)
PT ≤14 sn / >14 sn	20 (21%)	Portal vein diameter ≤11 mm / >11 mm	44/51
Bilirubin ≤1.9 / 2-2.99 / ≥3	51/21/23	Splenic vein diameter ≤10 mm / >10 mm	52/43
Albumin ≤2.8 / 2.81-3.5 / ≥3.5	31/31/33		

N: Number of patients. PT: Prothrombin time. Sn: Second.

containing tubes were added to the test device and the device was placed in a Triage Meter using fluorescent immunoassay (13, 14).

Statistical Analysis

All statistical analysis was performed by SPSS 11.0 (Statistical Package for the Social Sciences) for Windows. Continuous variables were expressed as mean ± standard deviation. Frequent variables were expressed as percentage. Student-t test was used in the comparison of two groups normally distributed. Chi-square test was used for dichotomous variables. We used ANOVA for the comparison of three or more groups normally distributed, and chi-square test was used for categorical variables. Kruskal-Wallis test was used for the comparison of three or more groups if the assumptions for ANOVA and chi-square were not fulfilled. In the post-hoc analyses of normally distributed variables, Turkey-HSD was used. A two-sided P value <0.05 was considered significant.

RESULTS

A total of 95 patients with hepatic cirrhosis and 86 healthy controls were included into the study. The mean age of the study population was 45.1±12.3 years, and 58% (105) of them were male. According to Child-Pugh classification, 33 patients were Child A, 25 were Child B and 37 were Child C. The different etiologies of cirrhosis are shown in Table 1. Details of hepatocellular failure and portal hypertension in cirrhotic patients are displayed in Table 2. Table 3 shows the number of patients on different medications and their stages.

BNP levels of patients with hepatic cirrhosis were significantly higher compared to the control group (288.5±329.2 vs 60.2± 29.5; p=0.000). There was also a significant difference among the cirrhotic patients after classifying them according to the Child-Pugh classification (p=0.045) (Table 4). In the post hoc analyses, the BNP levels between Child A and C groups were found to be significantly different (p=0.014). Although BNP levels of the Child C group were higher than in the Child B group, the difference was not statistically significant. The BNP levels of the control group and cirrhotic group and the results of cirrhotic patients with different stages classified according to Child-Pugh are shown in Table 4.

When patients were evaluated according to MELD scores, Child A was 9.8±2.3, Child B 11.3±1.8 and Child C 18.8±4.3. There was no significant association with serum BNP levels (p=0.72).

The BNP levels of patients with alcoholic cirrhosis (n=13) did not differ from those of other cirrhotic patients (p=0.298).

Serum BNP levels were significantly higher in patients with a left ventricle posterior wall thickness ≥11 mm compared to patients with a wall thickness <11 mm (206.4±267 vs 379.7±368, respectively; p: 0.001). There was no significant association between QT intervals and serum BNP levels (p=0.109).

There was no statistical difference between BNP levels of patients with and without a history of hepatic encephalopathy during the previous three months (p=0.278). Although patients with prothrombin time >14 seconds had a higher mean BNP level, this elevation did reach a statistical significance (312.5 vs 198.5, respectively; p=0.097). The relation between bilirubin levels and BNP was also not significant (p=0.205). Lower albumin levels, an indicator of both hepatocellular failure and portal hypertension, were related to higher BNP levels according to the results of this study (p=0.002) (Table 5).

Table 3. Number of patients on different medications and their stages

Drug	Stage	n	n
Beta-blocker			
(Propranolol 40-80 mg) /day	Child A	15	18
	Child B	12	13
	Child C	15	22
Diuretic			
Spironolactone 100-300 mg/	Child A	3	30
day or Furosemide	Child B	4	21
40-80 mg/day or both	Child C	16	21

n: Number of patients.

Table 4. BNP levels of control and cirrhotic groups

Group	n	Mean BNP levels (min-max)		p
Control	86	60.2±29.5	(14-169)	P: 0.000
Cirrhosis (total)	95	288.5±329.2	(7.4-1594)	
Child A	33 (35%)	201.2±266	(15.8-1555)	
Child B	25 (26%)	258.7±233.6	(25-1006)	P: 0.045
Child C	37 (39%)	386.5±407.7	(7.4-1594)	

Min: Minimum. Max: Maximum. n: Number of patients.

Table 5. Relation between albumin and BNP levels

Albumin	n	Mean BNP levels		p value
<2.8	31 (33%)	400.8±433.8	(7.4-1594)	0.02
2.8-3.5	31 (33%)	280±229.2	(46-970)	
>3.5	33 (34%)	181±265.6	(15.8-1555)	

n: Number of patients.

BNP levels were higher in patients with ascites than in patients without ascites (347.8 vs 186.8, respectively; p=0.001). There was no difference between the BNP levels of patients with and without splenomegaly (306.2 vs 244.1, respectively; p=0.804). The Child scores of these two groups were also not statistically different (p=0.247).

The presence of collateral circulation diagnosed with physical examination or Doppler ultrasonography was also related to high BNP levels (367.2 vs 261.9, p=0.002). Patients with esophageal varices had significantly higher BNP levels than patients without esophageal varices (310.8±310.7 vs 210±385.7, respectively; p=0.006). Although BNP levels increased with higher grades of esophageal varices, the difference was not significant in post-hoc analyses. BNP levels of patients with varices are shown in Table 6.

Patients were classified as having a portal vein diameter of >11 mm or not (283±3236.3 vs 294±339.3, respectively; p=0.740) and splenic vein diameter of >10 mm or not (344.9±420.4 vs 241±222, respectively; p=0.455) as an indicator of portal hypertension; however, there was no difference between the groups.

Patients using beta-blockers (propranolol 40-80 mg) had significantly higher BNP levels than other patients (364.4±377.7 vs 228.4±274, respectively; p=0.005). The Child-Pugh classifications of these two groups were also similar (p=0.832). There was no significant difference regarding mean MELD scores in patients treated with β-blockers (n=42) and other patients (13±4.4 vs 14.2±5.7, respectively; p: 0.484). Furthermore, patients receiving diuretics also had significantly higher BNP levels (411.7±354.7 vs 249.1±313; p=0.001). Table 7 shows the BNP levels of patients using beta-blocker and diuretic.

Table 6. BNP levels of patients with and without varices

Varices	n	Mean BNP levels	p
No varices	21 (22%)	210±385.7 (7.4-1594)	0.006
Patients with varices	74 (78%)		
Grade-1	42	274.7±253.3 (17-1366)	
Grade-2	22	347±350.2 (41-1594)	
Grade-3	10	382±435.2 (108-1555)	

n: Number of patients.

Table 7. Comparison of patients receiving or not receiving beta-blocker and diuretic according to their BNP levels

Beta blocker (+)	n	Mean BNP levels	p
Child A	15	293.2±366.8	0.005
Child B	12	316.3±171.1	
Child C	15	474±489.8	
Total	42	364.4±377.7	
Beta blocker (-)			
Child A	18	124.5±93.2	
Child B	13	205.6±275.5	
Child C	22	326.8±340.3	
Total	53	228.4±274	
Diuretic			
Diuretic (+)	23	411.7±354.7	0.001
Diuretic (-)	72	249.1±313	

n: Number of patients.

DISCUSSION

Our study showed a significant correlation of serum BNP levels with stage of cirrhosis according to Child-Pugh classification, evidences of hepatocellular failure, and findings of portal hypertension and portal hypertension-lowering therapies.

There is little data about the relationship between BNP levels and the clinical course of hepatic cirrhosis. Previous studies showed that two pathological conditions, a hyperdynamic circulation secondary to the hemostatic and hemodynamic alterations in cirrhosis and cardiomyopathy, may be related to higher BNP levels in cirrhotic patients (15-18). Furthermore, higher BNP level is an indicator of both diastolic and systolic dysfunction (15).

The BNP levels of healthy and cirrhotic patients were found to be different, and even the Child A group had higher BNP levels than the control group in the present study. This finding indicates that BNP may be an early indicator of cirrhosis in patients with hepatocellular diseases. Furthermore, BNP levels increase with higher grades of Child-Pugh classification, indicating that BNP levels are related to the severity of cirrhosis.

Lower albumin levels and prolonged prothrombin time are indicators of hepatocellular failure. In the present study, lower albumin levels and prolonged prothrombin time, with lack of statistical significance, were related to higher BNP levels. This association may be a result of hemodynamic alterations seen secondary to the liver cirrhosis that are also correlated with the albumin levels and prothrombin time. Existence of ascites, collateral circulation and esophageal varices were related to increased BNP levels according to the results of this study. Although there was a lack of statistical significance, higher variceal grades tended to be present together with higher BNP levels. These findings are indicators of high portal vein

pressure, and cirrhotic patients with portal hypertension had significantly higher BNP levels than the patients without portal hypertension according to the results of this study. All three of these states are related to volume overload and increased preload causing myocardial wall tension, which may result in BNP release. These findings indicate that BNP may be a prediction tool to follow the clinical progress of cirrhotic patients. BNP may also be used for pursuing the responses to the treatment given to these patients. However, further studies are needed in order to reveal the relationship between BNP and treatment modalities in cirrhotic patients.

Cirrhotic cardiomyopathy is an asymptomatic situation differing from alcoholic cardiomyopathy. It can cause clinical findings with the occurrence of hyperdynamic circulation (19,20). Alcoholic cardiomyopathy is characterized by a decrease in left ventricular function regardless of the presence of hepatic cirrhosis (21,22). These two clinical situations should be distinguished. There is a decrease in the left ventricular function in alcoholic cirrhosis, while beta adrenergic receptor and plasma membrane dysfunction and increase in intracardiac volume are seen in cirrhotic cardiomyopathy (16). Henriksen et al. (23) and Wong et al. (15) found a significant correlation between alcohol use and BNP concentration in patients with cirrhosis, and thus alcohol may have an independent effect on cardiac involvement in cirrhotic patients. There was no statistically significant difference between the BNP levels of patients with and without alcoholic cirrhosis in our study. This may result from the low number of patients with alcoholic cirrhosis, or it may suggest that serum BNP levels are independent of the toxic effects of alcohol on myocytes and the etiology of cirrhosis (31).

We also evaluated the effects of beta-blocker and diuretic treatments on BNP levels. Beta-blocker and diuretics decrease BNP levels by improving cardiac function and diuresis; however, patients on these treatments had higher BNP levels than other patients. Except in cirrhotic cardiomyopathy, diuretics and beta-blockers decrease intracardiac pressure and BNP levels in patients with decompensated heart failure (24). Diuretic treatment alone causes moderate decreases in BNP levels (25). Beta-blockers reduce BNP levels by improving hemodynamic parameters and left ventricle functions (26). Although the Child-Pugh scores did not differentiate between the patients receiving and not receiving beta-blockers, patients on diuretic treatment had higher Child-Pugh scores than the others. Thus, many factors may be associated with the higher BNP levels in patients receiving these drugs. The probable underlying cause of increased levels of BNP in patients using beta-blocker and diuretics may be that these patients were more likely to suffer from volume overload, because these medications are usually given in these patients. Thus, these findings may be a result of a selection bias.

A study by Radvan et al. (32) reported a significant correlation between serum BNP levels and MELD scores. That study included decompensated cirrhotic patients with hypervolemia and ascites. In our study, there was no significant association between serum BNP levels and MELD scores. Sixty-eight percent of our patients had ascites. The different results of the two studies may be due to different patient populations included in the studies and may suggest that MELD scores can be more important in decompensated cirrhotic patients with hypervolemia.

In conclusion, serum BNP level is correlated significantly with the stage of cirrhosis, hepatocellular failure, and findings of portal hypertension and portal hypertension-lowering therapies. Therefore, serum BNP level can be used as a valuable parameter in predicting the prognosis and monitoring the response to therapy.

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