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Original Article

Alterations of serum brain type natriuretic peptide (BNP) in patients with Crimean-Congo hemorrhagic fever

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Abstract: Background: Crimean-Congo hemorrhagic fever (CCHF) is known to be associated with cardiac damage. Brain type natriuretic peptide (BNP) is secreted from stressed myocardium. Objectives: This study investigated that BNP levels in CCHF and its association with clinical course of disease. Methods: Consecutive CCHF diagnosis confirmed patients were enrolled to the study. Results of patients were compared with age-sex-matched healthy volunteers. Blood samples for BNP levels were collected from the patients during emergency room applications. Mortality, hospitalization duration and other disease severity predictors (thrombocyte count, hemoglobin, white blood cell count, alanine aminotransferase, aspartate aminotransferase, prothrombin time, lactate dehydrogenase, international normalized ratio, activated partial thromboplastin time) were recorded. These parameters' correlations with BNP levels were analyzed. Result: Forty-three CCHF patients and 28 control subjects recruited to the study. Groups were similar for age and gender. There was no mortality. Levels of BNP were found to be significantly higher in patients than control subjects (100.4±45.4 vs. 78.0±40.4, P=0.033). But BNP levels were not correlated with duration of hospitalization and disease severity predictors (P > 0.05). Conclusions: This study showed that BNP levels are modestly increased in CCHF but this increase does not correlated with disease severity predictors.

Keywords: Crimean-Congo hemorrhagic fever, brain type natriuretic peptide, cardiac damage

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a thick-borne viral disease. Multiple organs such as endothelium, hepatic cells and blood cells are involved by CCHF viruses [1, 2]. Novel studies demonstrated that CCHF involves cardiac tissues and to be associated with cardiac damage [3, 4]. Electrocardiographic or echocardiographic demonstration of cardiac involvement associated with poor prognosis in patients with CCHF [4, 5].

Mortality rate is high and establishment of high risk patients is important in CCHF management. Brain type natriuretic peptide (BNP) is a neurohormone secreted mainly from the cardiac ventricles in response to volume expansion and pressure overload. BNP is proved as a prognostic factor and guide to treatment of heart failure [6-8]. Measurement of BNP from serum is simple and rapid in emergency room (ER) settings. In patients diagnosed or suspected with CCHF an advantageous marker like BNP may help to discriminate high risk patients. Otherwise, there is no data about BNP levels and CCHF in the literature.

We investigated the BNP levels in CCHF during the ER application and its correlates with clinical course of the disease.

Materials and methods

Consecutive patients were reviewed for the study which is applicants to our ER with symptoms and findings related to CCHF between the April and October 2012. Only patients with confirmed CCHF diagnosis enrolled to the study. The healthy control (HC) group consisted of age and gender matched consecutive healthy volunteer adults free of any cardiac damage or disease. Demographic data and basic laboratory findings blood count, blood glucose, creatinine

Table 1. Clinical and laboratory findings of groups

	Control group n=28	CCHF group n=43
Brain natriuretic peptide (ng/ml)	78.0±40.4	100.44±45.4*
Age (years)	36.5±10	39.9±19
Male/female	17/11	27/16
Duration of symptoms (days)	-	9.1±2
BUN (mg/dl)	15.9±6.6	16.6±7.2
Creatinine (mg/dl)	0.8±0.1	0.9±0.2
ALT (IU/l)	24.3±8.4	83.4±66.1*
AST (IU/l)	29.6±11.2	250.5±231.5*
LDH (IU/l)	53.6±12.4	727.7±489.6*
aPTT (s)	25.6±4.6	53.7±17.4*
INR	0.8±0.1	1.2±0.2
WBC ($\times 10^9$ cells/l)	8.6±2.7	3.0±1.2*
Hemoglobin (g/dl)	14.0±1.2	14.1±1.0
Thrombocyte count ($\times 10^9$ cells/l)	120.6±43.5	58.9±35.3*

*P-Value < 0.05. Results are mean ± standard deviation. BUN, blood urea nitrogen; INR, international normalized ratio.

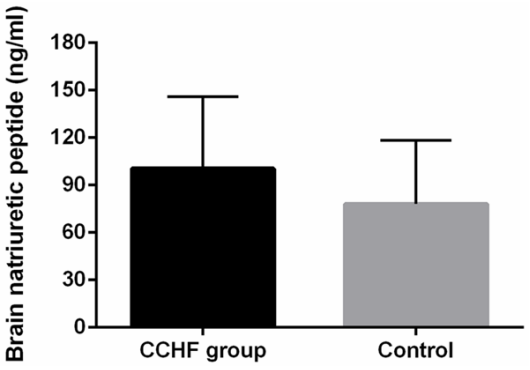

Figure 1. Comparing of BNP levels of groups.

levels etc. were recorded. Patients with known cardiac or other disorders affecting BNP levels were excluded. Blood samples were collected from all patients when applicant to ER as soon as possible via venous line which placed to the antecubital vein. Blood samples were centrifuged and the serum was stored below -80°C. Serum BNP levels were measured by enzyme immunoassay (EIA) kit, based on standards and which ELISA technology (Biomedica Medizinprodukte GmbH, Wien, Divischgasse). The study was approved by the local ethics committee and informed consent was obtained from all subjects.

The diagnosis was confirmed by ELISA test (anti-CCHF IgM and IgG antibodies) and/or of genomic segments of the CCHF virus by reverse transcription-polymerase chain reaction (RT-PCR) either in the acute and/or convalescent phase of the disease. These analyses were done by the Virology Laboratory of the Refik Saydam National Hygiene Center which is the reference laboratory of the Turkish Ministry of Health.

All patients were hospitalized. Primary endpoints of the study were mortality and duration of hospitalization. Other clinical and laboratory signs which showed priory as risk factor, were also recorded [9-12]. They are included thrombocyte count (PLT), hemoglobin, white blood cell count (WBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), lactate dehydrogenase (LDH), international normalized ratio (INR), activated partial thromboplastin time (aPTT).

Statistical analysis

Continuous variables were expressed as the mean ± Standard deviation when they were suitable for normal distribution. Categorical variables expressed as count and percentages (%). Comparisons of BNP levels between the groups, normally distributed as confirmed by KS test, were performed using student t test. Categorical variables were analyzed using the Chi-square test. We used Pearson test to quantify the correlation of variables with the mortality and the duration of hospitalization SPSS 14.0 (SPSS, Inc., Chicago, IL, USA) was used to perform the statistical procedures. A *P*-value of less than 0.05 was considered as statistically significant.

Results

Forty-three (mean age 39.9±19 years, 27 males) CCHF diagnosis confirmed patients were enrolled to the study. Patients results compared with the 28 healthy subjects' (36.5±10 years, 11 males) results. Groups were similar for age and gender. When the data of the patient and the control groups were compared, AST, ALT, LDH and aPTT values were significantly higher ($P < 0.05$) and PLT and WBC levels

Table 2. Correlates of hospitalization duration

	CCHF group	
Continuous variables	Correlation Coefficient[a]	*P*
Age	-0.395	0.017*
BNP	-0.081	0.637
AST	-0.165	0.336
ALT	-0.215	0.209
LDH	-0.256	0.132
PT	0.436	0.008*
aPTT	0.371	0.074
INR	0.708	0.001*
WBC	0.358	0.032*
Hemoglobin	0.074	0.731
Thrombocyte count	0.029	0.865

*Statistically significant. [a]Pearson's correlation or Spearman's correlation between variables following Gaussian or non-Gaussian distribution, respectively.

were significantly lower in the CCHF group ($P < 0.05$). However, there was no significant difference in terms of blood urea nitrogen (BUN) and creatinine levels, hemoglobin, and INR ($P > 0.05$). Demographic data and laboratory parameters of patients and controls are showed at **Table 1**. Levels of BNP were found to be significantly higher in CCHF patients comparing to the control subjects (100.4±45.4 vs. 78.0±40.4, P=0.033) (**Figure 1**).

There was no mortality during the study period. Duration of hospitalization of patients were mean 9.1±2.0 days. Levels of BNP were not significantly correlated with duration of hospitalization (r=-0.08, P=0.63). Age, WBC and PT were significantly associated with hospitalization duration. There was no correlation among clinical and laboratory parameters other than these parameters. The BNP levels were also not correlated with these parameters. These results shown in **Table 2**.

Discussion

This study showed that BNP levels are modestly elevated in CCHF disease, but BNP levels measured at ER don't predict clinical course of the disease. Hospitalization duration was correlated with younger age, higher WBC and longer PT. The BNP levels were not correlated with these parameters.

CCHF is a contagious thick-borne disease and induced by CCHF virus which is member of hemorrhagic fever viruses family. Rate of mortality in CCHF patients varies between 3% and 30% [13]. The rate is reported to be around 5.2% in Turkey [13, 14], however in this study no mortality was seen. Early admission because of raising vigilance in our region for the disease and accumulated experience of our center may be explaining this favorable result.

The specific mechanisms underlying the pathogenesis of the disease is not well defined. Mononuclear phagocytes, hepatocytes, and endothelial cells are major targets for the CCHF virus [15]. Patients with fatal prognosis develop terminal multiple organ failure, including cerebral, liver, and kidney failure and cardiac and pulmonary insufficiency [16]. C-type natriuretic peptide released by vascular endothelial cells played a crucial role in the organization of vascular tone and was associated with the severity of CCHF by Turkdogan et al. reported [17]. Prior two studies from our center were found that clinical cardiac pathologies herald bad prognosis [3, 4]. BNP is natriuretic peptide and released from myocardium and blood levels are increased when myocardial stressed or overloaded. So, the cardiac failure is the most frequent and well described cause of increased BNP levels. The role of BNP was demonstrated in patients with cardiac failure [18]. Other situations than cardiac failure causing BNP elevation are volume loading, atrial fibrillation, pulmonary embolism, chronic renal failure etc. [19, 20]. The elevation of BNP in CCHF as our finding could not be well explained, but subclinical cardiac involvement may be the reason. Previous studies supported this hypothesis which was showed cardiac involvement [4, 21, 22]. Also limited increase in BNP levels are compatible with there was not severe patients in the study group. We have not data in the literature but might be excessively increased BNP levels in mortal cases associated with heart failure.

Some of previously proposed prognostic factors for CCHF are thrombocytopenia, AST, ALT, and LDH elevation, aPTT and PT prolongation, INR elevation [10, 12]. Concordantly, we found that longer PT is associated with longer duration of hospitalization. As oppositely, WBC showed positive correlation with duration of hospitalization this was not reported. Age is negatively associated with longer duration of hospitalization, this finding conditional with previous reports [4]. Also considering lack of mortality and these data, it may be concluded that the

study population was not severely diseased. This aspect also support just modestly increase in BNP levels.

The most important limitation of the study is there was no mortality. So study could not tested between the CCHF mortality and BNP levels. Absent of patients' echocardiographic data is another important limitation.

Conclusions

In CCHF, BNP levels are increased modestly, but this change has not correlation with severity of the disease. Small sample size of study and absent of mortality may be masked correlations. So, prospective studies with large patient populations may be more clearly explain the role of BNP in CCHF disease.

Implications

Crimean-Congo hemorrhagic disease (CCHF) is a highly mortal disease and associated with cardiac damage. This study found that brain type natriuretic peptide (BNP) levels which is secreted from stressed myocardium are mildly increased in CCHF. Importance of BNP levels in CCHF should be investigated in large sample sized prospective studies.

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Disclosure of conflict of interest

None.

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