A Study on N-terminal-pro Brain-type Natriuretic Peptide in Cirrhosis of Liver

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Abstract

Background: Plasma N-terminal-pro brain-type natriuretic peptide (NT-proBNP) is a standard test for detection of heart failure. There is a conjecture that progressive heart failure occurs in cirrhosis of liver. This study is undertaken to investigate the plasma concentrations of NT-proBNP in a case of cirrhosis of liver.

Methods: 35 patients with pre-diagnosed cirrhosis of liver were divided into three groups according to the Child-Pugh classification: Grade A (n=11, 32%), B (n=12, 34%), and C (n=12, 34%). Blood pressure, electrocardiogram, and echocardiography were done in all these patients. Plasma NT-proBNP levels were determined in all these patients using an electrochemiluminescence sandwich immunoassay technique.

Results: The presence of heart failure (diagnosed clinically, left ventricular ejection fraction <50% and higher serum NT-proBNP level, with a cutoff value of >101 pg/mL) was correlated with degrees of severity of cirrhosis of liver according to Child-Pugh scoring (sensitivity, 87.60% and specificity, 72.73%; P < 0.001).

Conclusions: NT-proBNP which is a marker of the presence of heart failure was significantly correlated with progression of liver cirrhosis. In cirrhotic patients, high NT-proBNP value >101 pg/mL was shown to be a valuable non-invasive parameter in predicting the presence of heart failure. Therefore, serial measurements of NT-proBNP can be used in cirrhosis of liver for early detection of heart failure.

Key words: Cirrhosis of liver, Heart failure, N-terminal-pro brain-type natriuretic peptide

INTRODUCTION

The common clinical features associated with cirrhosis of liver patients are characterized by hyperdynamic circulation (increased cardiac output, heart rate, and plasma volume), normal or low arterial blood pressure (BP), and lowered peripheral resistance.¹³ These pathophysiological changes occur due to interactions between systemic hemodynamic factors and neurohormones.⁴⁻⁹

In response to cardiac wall distension and stretching in heart failure, there is secretion of pro-brain-type natriuretic peptide (proBNP1-108), a 108-amino acid prohormone from the cardiomyocytes. This is due to neurohormonal activation in response to ventricular volume and pressure overload.¹⁰ The BNP and atrial natriuretic peptide (ANP) may be deemed as counterregulatory hormones acting against the sympathetic and renin-angiotensin-aldosterone systems (RAAS). Secretion of BNP and ANP cause natriuresis, vasodilation activation with a concomitant inhibition of the RAAS and adrenergic activity, inhibition of cardiomyocyte hypertrophy, angiogenesis promotion, and delay in the activation of cardiac fibroblasts, all of which give rise to improved myocardial relaxation.¹¹⁻¹² However, in heart failure with cirrhosis, elevated levels of N-terminal proBNP (NT-proBNP),were more confirmatory than elevated plasma levels of BNP as the latter correlated best with diastolic dysfunction mainly.¹³⁻¹⁶ However, there was no significant relation of NT-proBNP levels to other measures of hyperdynamic circulation, such as cardiac output or systemic vascular resistance.¹⁵ A study that evaluated the severity of disease compared to plasma levels of BNP in non-alcoholic cirrhotic patients found no significant BNP...
level difference. Therefore, in this study NT-proBNP is used as a tool for diagnosis and detection of severity of heart failure in cirrhosis of liver.

The aim of this study is to investigate the association between plasma concentrations of NT-proBNP and severity of cirrhosis. The severity of liver disease was estimated by Child-Pugh score as well as by clinical means.

**MATERIALS AND METHODS**

The study included 35 adult male and female patients diagnosed with cirrhosis of liver from urban to suburban areas and attending. Age range of eligible patients was 30-70 years. The diagnosis of liver cirrhosis included a complex set of typical clinical findings including relevant medical history, presenting symptoms, decreased prothrombin time, hypoalbuminemia with albumin-globulin inversion, hypergammaglobulinemia, advanced diffuse chronic hepatic lesion on abdominal ultrasound examination, and liver biopsy, whenever feasible.

Patients with liver cirrhosis with suspected malignant comorbidity, prior known cardiac ailment, advanced multiorgan disorders or infections, acute gastrointestinal bleeding, cardiac arrhythmias, ischemic or valvular heart disease, renal failure, along with those treated with pharmacological agents that potentially affect systemic circulation, such as beta-adrenergic blockers or nitrates were not included in the study. Patients treated with diuretics were included in the study. All patients signed an informed consent before the inclusion according to the approval of the ethics committee and following good clinical practice criteria.

The patients were asked to fast overnight and then, lie down for approximately 2 h before having blood samples taken and system hemodynamic parameters measured. The blood samples were used to measure liver function tests and NT-proBNP concentrations. BP measurement, electrocardiogram, and echocardiography were done in all patients. NT-pro BNP in plasma was determined using an electrochemiluminescence sandwich immunoassay method (Elecsys proBNP, Roche Diagnostics, Meylan, France).

**Statistical Analyses**

Appropriate parametric tests were used in the analyses, namely, Student \( t \)-test, ANOVA, and Pearson correlation. \( P < 0.05 \) was considered significant. IBM SPSS, version 19.0.0.1 (SPSS Inc., Chicago, IL, USA) was used.

**RESULTS**

This study included 35 patients with an age range from 3 to 70 years. Patients were divided into three groups according to the Child-Pugh classification: Grade A (\( n=11, 32\% \), B (\( n=12, 34\% \)), and C (\( n=12, 34\% \)).

Patients with Grade A cirrhosis of liver had a significantly higher serum NT-proBNP level (mean value 338.63 pg/mL), compared to Grade B cirrhotics (mean value 196.45 pg/mL), and Grade C cirrhotics (mean value 107.72 pg/mL). Tests on non-cirrhotic healthy persons (Control) showed the serum level of NT-proBNP was between 5 and 45 pg/mL. 100 pg/mL was taken as the cutoff value for the presence of heart failure in patients with liver cirrhosis (\( P < 0.001 \)), with a sensitivity of 87.60% and specificity of 72.73%.

**DISCUSSION**

Our study showed an association between NT-proBNP and hepatic dysfunction as revealed by Child-Pugh gradation. With increasing disease stage, plasma NT-proBNP levels were greater and left ventricular ejection fraction was lower. This correlates with the hyperdynamic circulation theory based on a central hypovolemia and systolic dysfunction. Thus, NT-proBNP was shown as a possible marker of disease progression, with a massive increase in its level observed in advanced stages of liver disease, showing a positive association of NT-proBNP with cirrhosis of liver. In advanced cirrhosis with pronounced vasodilatation, central hypovolemia, and arterial hypotension, RAAS and sympathetic system are highly activated causing hyperdynamic circulation. Low mean arterial BP (MABP) found in cirrhosis of liver is said to be a result of reduced vascular reactivity to adrenaline and angiotensin-II because of increased release of nitric oxide.

Cirrhosis of the liver is a generic disease characterized by progressively increasing diffuse fibrosis of the liver concomitantly associated with nodular regeneration of the liver. Chronic alcoholism is by far the most common etiology of cirrhosis of the liver. However, in developing and tropical countries chronic malnutrition is supposed to be another big cause of this disease. Other important causes which are increasingly coming into picture are infections with Hepatitis A, B, and C. Previously, there were no known treatment for these conditions. However, in recent years, treatment of hepatitis A, B (including delta antigen), and C with the relevant antiviral compounds for a prolonged period not only cures the patients off the viral load but also in many cases totally reverses...
the fibronodular degeneration of the liver leading to a non-cirrhotic state of the liver, cured from the disease in question. For, alcoholic cirrhosis, complete stoppage of alcoholic drinks, preferably life-long, together with intake of hepatoregenerative drugs for a long period is the sheet anchor of treatment. For cirrhosis due to malnutrition, good and nutritious diet for a prolonged period might help. Sometimes, cirrhosis of liver might be due to toxicity, usually the common toxic agents are carbon tetrachloride, chloroform, arsenic, and so on; detoxication might help, but proper cure with disease-free state is very difficult to achieve. At the beginning, cirrhosis of liver is almost a symptom-free disease and is very difficult to diagnose clinically. However, as portal hypertension, the foremost complication of cirrhosis of liver gradually sets in, the symptoms begin to manifest. These include ascites, edema mostly affecting the lower limbs, caput medusae, palmar erythema, and occasional jaundice. Among, the other symptoms, the most common are anorexia, loss of weight, pallor, and extreme weakness.

It has been demonstrated that patients with cirrhosis of the liver have a lower cardiac index and systolic volume, higher values of peripheral vascular resistance, and MABP.\(^3\) In cirrhotic patients, portal hypertension evolves due to increased portal venous resistance together with increased blood flow within the portal venous system. Both are the consequence of splanchnic arterial vasodilation caused by endotoxemia, through the opening of portosystemic collaterals, which leads to reduced activity of RAAS and intestinal disturbance resulting in increased synthesis of vasodilators. As cirrhosis progresses, effective hypovolemia, and arterial hypotension progress and RAAS induces low renal perfusion, glomerular filtration rate, and subsequently sodium and water retention, which together aggravate systolic and diastolic dysfunction, leading to increased production of NT-proBNP.

Patients with cirrhosis and ascites present with lower BP, lower peripheral vascular resistance, and increased stroke volume.\(^22\) The association between NT-proBNP and ascites is currently deemed controversial. Woo et al. did not find differences in plasma NT-proBNP level between pre-ascitic and ascitic patients.\(^19\) However, Yildiz et al. found higher plasma NT-proBNP level in ascitic patients.\(^15\) Our study did not find any difference in plasma NT-proBNP level between patients with and without ascites. Probably, these results could be explained by high sodium intake and concomitant use of diuretic therapy, which lower BNP concentration.\(^23\)

A major limitation of our study is the small number of patients and further larger prospective studies are needed to confirm our results and establish the eventual use of this parameter in clinical practice.

**CONCLUSION**

In our study, it has been found that plasma levels of NT-proBNP were significantly correlated with severity or grades of cirrhosis of liver. Therefore, NT-proBNP measurement can be used as a marker of cardiac dysfunction commonly associated with cirrhosis of liver. This can be used for the purpose of early detection of heart failure in liver cirrhosis. However, a comparatively low number of patients is a limitation of this study.

**REFERENCES**


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