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Original Article

Serum NT-ProBNP Potential Marker of Cirrhotic Cardiomyopathy

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Abstract

Introduction: Based on many previous studies, liver cirrhosis is traditionally associated with cardiac dysfunction. The main clinical features of cirrhotic cardiomyopathy include attenuated systolic contractility in response to physiologic or pharmacologic strain, diastolic dysfunction, electrical conductance abnormalities, and chronotropic incompetence. Previous studies have found that the levels of brain natriuretic peptide (BNP) and its precursor the N-terminal pro B-type natriuretic peptide (NT-proBNP) are elevated in cirrhosis with systolic as well as diastolic dysfunction.

Aim: The aim of this study was to establish the association between early changes in cardiac function in patients with liver cirrhosis and NT- proBNP plasma levels.

Materials and methods: Forty-two consecutive hospitalized patients with viral-related cirrhosis were studied. We also evaluated a control group of 20 age and sex-matched patients with arterial hypertension. All underwent abdominal ultrasound, upper GI endoscopy, ECG, and echocardiography, and their plasma levels of NT-proBNP were determined.

Results: We observed higher NT-proBNP plasma levels in cirrhotic patients than in controls. We also found that atrial volumes, ejection fraction and partially left ventricular mass and PAPs (systolic pulmonary arterial pressure) were significantly altered in comparison with the hypertensive controls. Supporting previous studies, we also found that the mean QTc interval was prolonged in 65% of women and 96% of men.

Conclusions: In conclusion, the present study shows that plasma NT-proBNP levels, LAD (left atrium diameter), the E/A ratio, EDT (end diastolic time) and E/e' ratio may be reliable indicators of the extent of cardiac abnormalities in cirrhotic patients.

Keywords

cirrhotic cardiomyopathy, diastolic dysfunction, liver cirrhosis, portal hypertension, prolonged QTc

INTRODUCTION

Cirrhotic cardiomyopathy (CCM) is a pathological condition defined as a chronic cardiac dysfunction in patients with cirrhosis.[1,2] CCM is characterized by impaired systolic or diastolic function, electrophysiological abnormalities with a prolonged ventricular repolarization (QT interval), and chronotropic incompetence.[3-5] Recent studies

have demonstrated that high serum levels of NT-proBNP are present in patients with chronic liver diseases of viral etiology.[6-8] As it seems to be related to the severity of liver disease and cardiac dysfunction, it should be a useful marker to identify cirrhotic patients with increased cardiovascular risk and therefore, a worse prognosis.

Pathogenesis of CCM

The underlying mechanisms involved in CCM are complex. CCM predominantly involves systemic multi-factorial cellular, neuronal and humoral signaling pathways. These include the impaired β-receptor and calcium signaling, altered cardiomyocyte membrane physiology, elevated sympathetic nervous tone, and increased activity of vasodilatory pathways predominantly through the actions of nitric oxide (NO), carbon monoxide, and endocannabinoids.[9,10] In addition, circulating plasma levels of inflammatory and vasoactive molecules such as endothelins, glucagone, vasoactive intestinal peptide, tumor necrosis factor (TNF)-α, prostacycline and natriuretic peptide are usually accumulated in cirrhosis due to concomitant liver insufficiency and the presence of portosystemic collaterals, and, therefore, might be implied in the CCM pathogenesis.[10,11]

Systolic dysfunction

Systolic dysfunction is mostly latent in patients with cirrhosis. Although the left ventricular systolic function (LVSF) at rest is normal in cirrhotic patients[3-5,12] when assessed by invasive and non-invasive methods, subtle alterations could be detected under conditions of stress or by using new echocardiographic techniques at rest[12]. New technique to assess cardiac function, with major focus on the left ventricle (LV) in the clinical setting is two-dimensional speckle tracking echocardiography (2D-STE).[13]

Diastolic dysfunction

Abnormalities of diastolic function are an early marker of CCM. Patients with cirrhosis show dilatation and increased LA volumes, increases in LV diameters but not volumes, increases in the thickness of the posterior wall of the LV and the interventricular septum, a prolongation of the isovolumic relaxation time (IVRT), decreased peak E velocity (early rapid filling phase), prolongation deceleration times (DT) of the E wave, and finally increased peak A velocity (atrial contraction during late diastole).[10,11,14-16] IVRT and DT may be prolonged in cirrhotic patients irrespective of the presence of ascites but a significantly reduced E/A ratio has been seen in ascitic subjects.[9,10,12,17] (The E/A ratio is the ratio of peak velocity blood flow from left ventricular relaxation in early diastole – the E wave – to peak velocity flow in late diastole caused by atrial contraction – the A wave).

Electrophysiological anomalies

Cirrhosis has been found to be associated with a number of electrophysiological anomalies such as abnormalities in the QT interval, electromechanical uncoupling, and chronotropic incompetence, the onset of which is thought to be influenced by endotoxins, severe portal hypertension, and autonomic dysfunction (sympathetic nervous system defects [SNS] and vagus injury).[18,19] The mechanisms underlying prolonged QTc interval in patients with liver disease are not clear, they are thought to be associated, at least in part, with autonomic dysfunction[12,19] and heart exposure to humoral factors (cytokines, endotoxins, and bile salts) through porto-systemic shunts[12,17-19] in the setting of decreased function of two types of potassium channels in ventricular myocytes.

Biomarkers of cardiac dysfunction in liver disease

BNP and its pro-hormone, NT-proBNP, are both secreted by heart ventricles in response to massive stretching of muscle cells or to mild cardiac damage and are capable of reducing blood pressure and cardiac hypertrophy.[6,8] Previous studies have shown that high serum levels of NT-proBNP are present in patients with chronic liver diseases of viral etiology.[6,8,20] As they seem to be related to the severity of liver disease and cardiac dysfunction, they should be useful markers to identify cirrhotic patients with increased cardiovascular risk and thus, worse prognosis.[6-8,16]

AIM

In this study, we aimed to assess in a well-characterized cohort of patients with cirrhosis of non-alcoholic etiology, before or after the development of ascites, the expression of NT-proBNP and of other parameters of cardiac dysfunction in order to determine whether the behavior of NT-proBNP is linked to the stage of liver disease or to a cardiac dysfunction secondary to cirrhosis.

MATERIALS AND METHODS

Forty-two consecutive hospitalized patients with viral-related cirrhosis were studied. We also evaluated a control group of 20 patients with arterial hypertension matched for age and sex. All underwent abdominal ultrasound, upper GI endoscopy, ECG, and echocardiography, and had the plasma levels of NT-proBNP determined **(Table 1)**.

Plasma NT-proBNP analysis

Blood was drawn from a forearm vein after at least 10 minutes of resting supine. Venous blood samples (5 ml) were collected into chilled tubes containing EDTA as anticoagu-

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Table 1. Demographic characteristics of patients with LC and controls

	Controls	Child A	Child B	Child C
Total	20	6	19	17
Men	13	4	13	16
Women	7	2	6	1
Age	52±10	56±8	54±9	57±9

lant. Blood was centrifuged as soon as possible and the plasma was then stored at −70°C for later analysis. NT-proBNP measurements were done using an ELISA.

Statistical analysis

SPSS for Windows, version 16, was used for data analysis.

RESULTS

The cirrhotic male patients were 78.6% at the median age of 62 years, and the female patients were 21.4% at the median age of 60 years. The control subjects (mean age 60.6±8.4 years, 12 men and 8 women) were comparable for arterial hypertension prevalence to the cirrhotic population. Cirrhotic patients had significantly higher NT-proBNP plasma levels compared to controls. Similarly, left atrial volume (LAV) and left ventricular ejection fraction were significantly altered in cirrhotic patients as compared to controls, and a trend was observed for left ventricular mass and systolic pulmonary arterial pressure (PAPs) **(Table 2)**.

Linear regression analysis in patients with cirrhosis revealed that NT-proBNP levels were directly related to hepatic dysfunction (lower albumin, lower INR, ascites, cirrhosis stage, and Child-Pugh score), renal impairment (higher serum creatinine levels) and with larger atrial volumes. Liver disease progression has been found to correlate with cardiac dysfunction. The observed changes in terms of E/A ratio, deceleration time, mean pulmonary pressure, TDR of LC, interventricular septal thickness (ICP), posterior wall of left ventricle (LC), size of LV and FI were in accordance with the progression of liver disease. Diastolic dysfunction was observed in all patients with varying degrees of hepatic impairment, and systolic dysfunction with decreased ejection fraction was reported in Child C **(Table 3)**.

Table 4 shows factors associated with presence of ascites. As expected cirrhotic patients with ascites had a higher impairment of both liver and kidney function compared to their counterpart without ascites. They also had higher NT-proBNP and CK-MB plasma levels and a trend to larger atrial and to a higher E/A ratio.

The values of all QT interval-related parameters were higher (p<0.001) in patients with cirrhosis than those in controls. QTc interval was prolonged in 65% of females and 96% of males, supporting the previous studies.[7] Although we found many changes in echocardiographic parameters in our population, the only echo index that showed an intermediate correlation with the QTc interval was LVEDD (r=0.41, p<0.001). In addition, prolonged QTc is associated with the stage of liver disease. Therefore, we can conclude that there is a relationship between congested heart and prolonged QTc.

Fig. 1 shows the mean levels of NT-proBNT depending on the stages of liver cirrhosis.

As seen in **Fig. 1**, the plasma levels of NT-proBNP are higher in patients with advanced liver disease.

DISCUSSION

In our study, we observed higher NT-proBNP plasma levels in cirrhotic compared to controls. We also observed that LVEDV is increased proportionally to the severity of the liver cirrhosis. We found that hypertrophy of LV, LV and LA dilatation, and diastolic and systolic dysfunction of the LV are correlated with the severity of the liver cirrhosis. The emergence of ascites is a very important moment. Its progression correlates significantly with the dilatation of the left chamber, the degree of diastolic and systolic dysfunction. In this study, we also observed that patients with ascites, compared to those without ascites, have higher plasma levels of NT-proBNP and respectively larger atrial volumes. According to some published data and our own results, we can conclude that LV hypertrophy, LA and LV dilation as well as Doppler data showing impaired relaxation are early

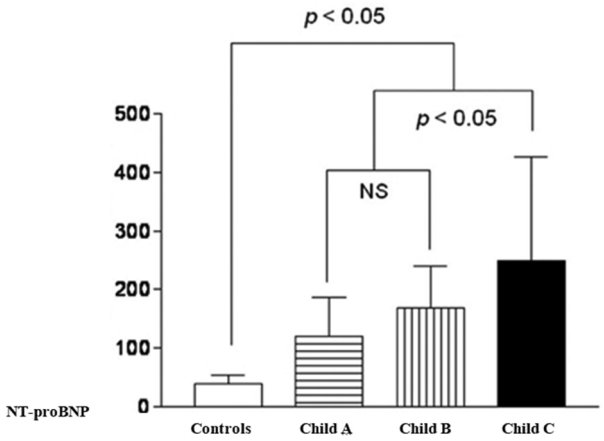

Figure 1. NT-proBNP plasma levels in controls and patients with cirrhosis based on Child-Pugh classification.

Table 2. NT-proBNP serum levels and echocardiographic features of 42 cirrhotic patients and 20 matched controls

	NT-proBNP pg/ml	CK-MB	Mean e' sept/e' lat	E Ve m/sl	E/e'	LA volume ml	E/A	LEVDV ml	EF%	PAPs mmHg	LV mass g/m^2
Patient with cirrhosis	420.2±103.2	43.8±25.6	0.10±0.03	0.77±0.24	8.2±3.1	60.8±27.3	1.07±0.40	92.3±32.3	61.7±6.7	31.4±4.8	83.3±25.0
Controls	68.8±76.6	13.8±9.6	0.11±0.07	0.69±0.18	7.2±2.5	42.5±13.1	1.04±.044	77.9±25.7	66.5±4.01	27.1±1.7	72.9±17.3
p	<0.001	<0.001	0.22	0.14	0.20	0.001	0.70	0.16	0.05	0.08	0.08

The E/e' is an index that reflects accurately the LV filling pressure, and it is a predictive factor for the development of CVDs in patients with hypertension.

Table 3. Relationship between NT-proBNP levels and clinical and echocardiographic data on linear regression analysis in cirrhotic patients

	Age	Sex	MELD	Child Pugh	ALB	BR	PLT	INR	Cr	Ascites	Mean e' sept/e' lat	E Vel	E/e'	LA volume ml	E/A	LEVDV	EF%	PAPs	LV mass
B	0.201	−0.138	0.457	0.407	−0.332	0.191	−0.194	0.420	0.339	0.485	0.059	0.009	0.100	0.316	0.171	−0.008	0.123	0.185	0. 210
S.E	0.15	111.38	9.425	22.443	87.110	17.913	0.783	150.649	180.265	88.936	1623.886	224.385	0.001	2.385	123.013	1.628	7.250	12.129	2.640
p	4.566	0.32	0.001	0.002	0.01	0.18	0.17	0.002	0.01	<0.001	0.70	0.94	0.43	0.03	0.24	0.95	0.38	0.28	0.89

MELD: model of end-stage liver disease; ALB: albumin; BR: bilirubin; Cr: creatinine

Table 4. Demographic, clinical, laboratory, and echocardiographic features of cirrhotic patients according to presence or absence of ascites

	MELD	ALB	BR	PLT	INR	CK	CK – MB	Cr mg/dl	NT pro BNP	Mean e' sept/e' lat	E Vel	E/e'	LA volume (ml)	E/A	LEVDV	EF%	PAPs	LV mass
Patients without ascites	5.7±2.9	3.6±0.5	1.0±0.5	98.2±66.6	1.2±0.1	78.9± 25.9	15±5.9	0.6±0.1	181.9±155.9	0.09±0.03	0.72±0.20	8.7±3.9	54.7±21.2	0.93±0.41	82.7±38.9	61.6±9.0	29.2±4.5	87.5±24.2
Patients with ascites	12.6±3.9	2.8±0.4	3.0±3.2	85.1±63.3	1.3±0.3	163.2±89.5	35.8.±29.5	1.0±0.2	535.2±408.1	0.10±0.02	0.81±0.26	7.8±2.2	67.2±28.8	1.13±0.45	96.3±27.3	63.6±4.3	31.5±5.1	81.2±23.8
p	<0.001	<0.001	0.005	0.46	0.002	<0.001	<0.001	0.007	<0.001	0.19	0.19	0.32	0.08	0.09	0.13	0.29	0.16	0.38

MELD: model of end-stage liver disease; ALB: albumin; BR: bilirubin; Cr: creatinine

predictive factors for the development of CCM. Concerning the investigated biomarker NT-proBNP, we found that its levels correlated with the stage of liver disease. Along this line, we also observed higher NT-proBNP plasma levels in cirrhotic compared to controls. Importantly, a significant correlation was observed between NT-proBNP and Child class, suggesting that plasma NT-proBNP levels are likely to be related to the severity of cirrhosis. Accordingly, our data confirm the hypothesis already reported by Henriksen et al.[8], that NT-proBNP levels could be a marker of cardiovascular diastolic dysfunction in patients with end stage liver disease, acting as mediator of splanchnic vasodilatation in liver cirrhosis[9,14,16]. Recent studies use speckle tracking for early diagnosis of systolic dysfunction. While conventional parameters demonstrate no alteration in systolic function, speckle-tracking analysis shows a significant increase in LV longitudinal strain throughout all cardiac layers, with significant correlation with the model of end-stage liver disease (MELD) score. In the updated criteria for diagnosis of cirrhotic cardiomyopathy by the Cirrhotic Cardiomyopathy Consortium (CCC), the evaluation of LV global longitudinal strain (GLS) in addition to left ventricular ejection fraction (LVEF) has been proposed in order to estimate systolic function.[13]

CONCLUSIONS

Our study shows that cirrhotic patients have larger atrial volumes and biochemical changes (NT-proBNP) showing cardiac dysfunction related to liver decompensation and ascites. It is clinically relevant that NT-proBNP plasma levels are increased proportionally to the severity of cirrhosis. NT-proBNP can be used as a marker of cardiac subclinical dysfunction participating to liver decompensation.

The next step in our study will be to evaluate the left ventricular and atrial myocardial deformation in patients with viral liver cirrhosis using speckle tracking technology.

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Сывороточный NT-ProBNP в качестве потенциального маркера цирротической кардиомиопатии

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Резюме

Введение: На основании многих предыдущих исследований цирроз печени традиционно ассоциируется с сердечной дисфункцией. Основные клинические признаки цирротической кардиомиопатии включают снижение систолической сократимости в ответ на физиологическую или фармакологическую нагрузку, диастолическую дисфункцию, нарушения электропроводности и хронотропную недостаточность. Предыдущие исследования показали, что уровни мозгового натрийуретического пептида (МНП) и его предшественника, N-концевого про-В-типа натрийуретического пептида (NT-proBNP), повышены при циррозе с систолической, а также диастолической дисфункцией.

Цель: Целью данного исследования было установить связь между ранними изменениями сердечной функции у пациентов с циррозом печени и уровнями NT-proBNP в плазме.

Материалы и методы: Были обследованы 42 последовательно госпитализированных пациента с вирусным циррозом печени. Мы также оценили контрольную группу из 20 пациентов с артериальной гипертонией, сопоставимых по полу и возрасту. Всем им было проведено УЗИ брюшной полости, эндоскопия верхних отделов желудочно-кишечного тракта, ЭКГ и эхокардиография, а также были определены уровни NT-proBNP в плазме.

Результаты: Мы наблюдали более высокие уровни NT-proBNP в плазме у пациентов с циррозом печени, чем в контрольной группе. Мы также обнаружили, что объёмы предсердий, фракция выброса и частично масса левого желудочка и PAPs (систолическое давление в лёгочной артерии) были значительно изменены по сравнению с контрольной группой с гипертензией. Поддерживая предыдущие исследования, мы также обнаружили, что средний интервал QTc был удлинён у 65% женщин и 96% мужчин.

Заключение: В заключение, настоящее исследование показывает, что уровни NT-proBNP в плазме, LAD (диаметр левого предсердия), отношение E/A, EDT (конечное диастолическое время) и отношение E/e› могут быть надёжными индикаторами степени сердечной недостаточности у больных циррозом.

Ключевые слова

цирротическая кардиомиопатия, диастолическая дисфункция, цирроз печени, портальная гипертензия, удлинение интервала QTc