Brain-type natriuretic peptide for detection and assessment of cardiac dysfunction in children with liver cirrhosis

Thesis

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By

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Abstract

Background: Cirrhotic cardiomiopathy is described as the presence of cardiac dysfunction in cirrhotic patients. BNP is a cardiac neurohormone released in response to increased ventricular wall tension. The level may be elevated in cirrhotic patients. **The aim of the study:** was to evaluate cardiac dysfunctions in cirrhotic patients and its relationship to BNP plasma level**.subjects and method:** we conducted a cross sectional study on fifty two cirrhotic patients following up at the hepatology clinic in Cairo University Children Hospital and fifty three healthy controls; where they were assessed by conventional echocardiography , Doppler and Tissue Doppler Imaging (TDI) for systolic and diastolic functions &BNP plasma level was measured for both groups using quantitative ELISA technique for BNP supplied by **WKEA MED SUPPLIES CORP.**

Results: We compared the echocardiographic findings of both cases & controls. The cases had significantly increased diameter of the left atrium, right ventricle, pulmonary artery& posterior wall thickness (P value =0.01, 0.02, 0.04&0.04). Using Doppler echocardiography, the E/A of both mitral & tricuspid valves inflow were significantly lower in cases (p value of 0.005 &0.0008) and also A wave velocity of tricuspid valve was significantly higher in cases (p value of 0.001).By using TDI, cirrhotic patients had significantly higher IVRT& lower IVCT of mitral valve inflow (p value of 0.008, 0.03). Patients also had significantly higher Ś wave velocity, É & Tie index & significantly lower IVCT of tricuspid valve inflow (p value of 0.01, 0.0003, 0.01 and 0.02 respectively). Also lower É & higher Ś wave velocity of the septum which was statistically significant in cases as compared to controls (p value of 0.04 & 0.001 respectively).

The BNP levels were significantly higher in cases as compared to controls (p=0.04). But it was of no statistical difference when compared between compensated & decompensated patients. In patients with cirrhosis, the only echocardiographic parameter that was significantly correlated with the BNP level was the E wave velocity on tricuspid valve (p=0.004).

Conclusion: Cirrhotic patients have a degree of cardiac dysfunction. BNP is a useful & specific marker of cardiac dysfunction in cirrhotic patients

Key words: cirrhotic cardiomyopathy, BNP, ECHO, TDI**.**

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List of abbreviations

AAT	α 1 Antitrypsin deficiency
AaO2	Alveolar arterial Oxygen
AMA	Anti mitochondrial antibody
ANA	Anti nuclear antibody
AO	Aorta
ABG	Arterial blood gases
AIH	Auto immune hepatitis
BMI	Body mass index
BSEPP	Bile salt export pump protein
CB1&2	Cannabinoid 1and 2
CM	Carbon monoxide
CNS	Central nervous system
CLD	Chronic liver disease
CPT	Child Pugh Turcotte
CT	Computed tomography
CAMP	Cyclic adenosine monophosphate
CGMP	Cyclic guanosine monophosphate
DIC	Disseminated intravascular coagulation
EF	Ejection fraction
ENOS	Endothelial nitric oxide synthase
EN	Endothelin-1
ERS/EASL	European respiratory society/ European association for study of liver
ECM	Extra cellular matrix
FS	Fractional shortening

FHVP	Free hepatic vein pressure
FDPS	Fibrin degradation products
FGF	Fibroblast growth factor
FHF	Fulminant hepatic failure
HPCS	Hepatic progenitor cells
HSC	Hepatic stellate cells
HVP	Hepatic vein pressure
HVPG	Hepatic vein pressure gradient
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HCC	Hepatocellular carcinoma
HPS	Hepatopulmonary syndrome
HRS	Hepatorenal syndrome
I NOS	Inducible nitric oxide synthase
IMV	Inferior mesenteric vein
IVC	Inferior vena cava
INR	International normalized ratio
IVS	Interventricular septum
IVCT	Isovolumetric contraction time
IVRT	Isovolumetric relaxation time
KC	Kupffer cells
LA	Left atrium
LV	left ventricle
LVPW	Left ventricular posterior wall
LVEDD	Left ventricular end diastolic diameter
LVESD	Left ventricular end systolic diameter
L MNA	N omega monomethyl L-arginine
LPS	Lipopolysaccharides
LBP	Lipopolysaccharide binding protein

LT	Liver Transplantation
MRI	Magnetic Resonance Imaging
MMPS	Matrix metalloproteinases
MELD	Model of end stage liver disease
MDRR3	Multidrug resistant 3 protein
NEP	Neutral endopeptidase
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
NAFLD	Non alcoholic fatty liver disease
NAS	Non alcoholic fatty liver disease activity score
NASH	Non alcoholic steatohepatitis
NASH CR	Non alcoholic steatohepatitis clinical research
OLT	Orthotopic liver transplantation
PaO2	Arterial partial pressure of oxygen
PAMPS	Pathogen associated molecular patterns
PRR	Pattern recognition receptors
PELD	Pediatric end stage liver disease
PAS	Periodic acid sciff
PDGF	Platelet derived growth factor
PBC	Primary biliary cirrhosis
PSC	Primary sclerosing cholangitis
PFIC	Progressive familial intrahepatic cholestasis
PH	Portal hypertension
PPH	Portopulmonary hypertension
PV	Portal vein
PVT	Portal vein thrombosis
PA	Pulmonary artery
RFvπa	Recombinant factor vπa

RAAS	Rennin aldosterone angiotensin system
RV	Right ventricle
SMA	Anti smooth muscle antibody
SVT	Splenic vein thrombosis
SPB	Spontanous bacterial peritonitis
SV	Stroke volume
TV	Tricuspid valve
TIMP 1&2	Tissue inhibitors of metalloproteinases 1&2
TLR	Toll like receptors
TIPS	Trans jugular intrahepatic portosystemic shunt
TGF b1	Transforming growth factor b1
TNF α	Tumor necrosis factor α
VEGF	Vascular endothelial growth factor
WHVP	Wedge hepatic vein pressure

INTRODUCTION

Liver cirrhosis is associated with numerous cardiovascular changes and abnormalities, including hyperdynamic circulation, portal hypertension, hepatopulmonary syndrome, and hepatorenal syndrome. The main change of cardiovascular function in cirrhotic patients is the hyperdynamic circulation, as manifested by increased cardiac output and decreased arterial blood pressure ***(Jeong et al., 2008)***.

In cirrhotic patients; cardiac output is increased at rest and it has been assumed that systolic function is normal or even supranormal, so many cirrhotic patients present with clinical manifestations that are suggestive of early cardiac dysfunction or overt heart failure ***(Baik and Lee, 2004).***

Although this cardiac dysfunction due to hepatic failure has not yet been finally classified and the mechanisms are not fully understood, early detection of this condition is crucial ***(Naschitz et al., 2000).***

Brain-type natriuretic peptide (BNP) is a peptide which has recently been used in the differential diagnosis and follow-up of patients with heart failure. It is a

neurohormone released by the ventricular myocytes and plays a key role in volume homeostasis ***(Scardovi, 2004).***

Plasma BNP level is a sensitive indicator of ventricular dysfunction both in symptomatic and asymptomatic patients and its plasma concentration increases with volume and pressure overload in patients with heart failure ***(Meune et al., 2003).***

Several studies have shown increased plasma levels of BNP and Nitrogen terminal fragment of Pro BNP(NT-proBNP) in some patients with cirrhosis, and these findings may suggest cardiac dysfunction ***(Henriksen et al., 2003).***

In addition to the left ventricular (LV) systolic dysfunction, plasma BNP levels have been suggested to be significantly associated with diastolic stage (including newer echocardiographic parameters as tissue Doppler imaging and color M-mode propagation velocity) and right ventricular (RV) functions as well ***(Yamaguchi et al.,2004).***

To the best of our knowledge no studies had been done on BNP in cirrhotic children

Aim of the study:

The present work aims to study the changes of BNP in cirrhotic children and its possible role in early detection of cardiac dysfunction in those patients and correlating it with the echocardiographic evaluation.

Chapter (1): Liver cirrhosis

ANATOMY OF THE LIVER LOBULE

The structural unit of the liver is either the lobule of Kiernan or the acinus of Rappaport. A hepatic lobule of Kiernan consists of a central venule with cords or plates of hepatocytes radiating out toward, several portal tracts, and zonal changes in the lobules are described as being centrilobular, midzonal, or periportal. A hepatic acinus of Rappaport consists of a portal tract as the axis that contains portal veins and hepatic arterioles, with blood flowing through the acinar sinusoids into several terminal hepatic venules, and the changes in the acini are described as being in zones 1, 2, and 3, corresponding to progressive decrease in tissue oxygenation; as shown in Figure 1***(Albers et al., 2006).***

In the liver there are different types of cells: hepatocytes, which constitute the hepatic parenchyma and represents 70-80% of the total cells, whereas the other 20-30% is formed by endothelial cells, cells of the bile duct, oval cells, Kupffer cells (KC), Pit cells(natural killer lymphocytes) and hepatic stellate cells(Ito or fat-storing cells) (HSC). Hepatocytes occupy 80% of the liver volume, with one or more centrally located round nuclei and are arranged in 1-cell-thick plates ***(Alexander et al., 2007).***