Evaluation of Brain Natriuretic Peptides in Early Diagnosis of Cardiac Involvement Comparing to Echocardiographic Findings in Major Thalassemia Patients

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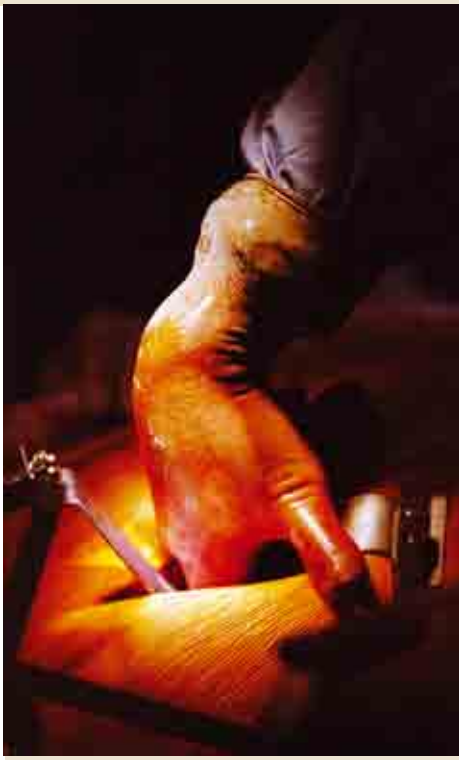

Abstract:

Background: Heart disease is one of the leading causes of disability in major thalassemia patients. Timely diagnosis and effective treatment in these patients are essential. The aim of this study is to evaluate the diagnostic value of BNP in the diagnosis of heart involvement compared with echocardiographic findings in patients with major thalassemia.

Methods: This case-control study was carried out in patients with major thalassemia aged 9-25 years old admitted to Aliasghar hospital from October 2010 to November 2011. Patients with no obvious cardiac abnormalities were included. 80 major thalassemia patients with 80 healthy children matched by age and sex were entered and for both, echocardiography was performed by a pediatric cardiologist. The serum level of Brain Natriuretic Peptides (BNP) was also evaluated. The data were analyzed by SPSS17.

Results: The groups studied were matched well regarding age and gender (P =0.1346, 0.429). Regarding the echocardiographic results, some of the parameters of the left heart in case group were significantly higher than control group as well as some of the parameters of right heart. The mean value of BNP in case group was higher significantly. There was a significant correlation between BNP and right heart MPI (r = 0.229, P = 0.041) and age (r = 0.237, P = 0.035).

Conclusion: Based on the results, systolic and diastolic function in patients with major beta thalassemia were impaired. Therefore, measurement of BNP level in addition to serial echocardiography is recommended to early diagnose heart involvement in patients with major beta thalassemia without clinical symptoms.

Key words: major thalassemia, echocardiography, BNP and children

Introduction

Precursor NT PRO BNP, BNP, is a prehormone with 134 amino acids that formed in moist and changed to BNP with 108 amino acid. This pre hormone is released by stress. Natriuretic peptides are cleared by kidneys. Hypovolemia, decreased blood pressure and renal failure lead to increase secretion of BNP, especially "NT PRO BNP in the patients (1). NT Pro BNP and BNP biomarkers are commercially available and these biomarkers are widely used in the diagnosis of heart failure. BNP measurement appears to be beneficial in order to diagnose and classify the patients with chronic heart failure. This provides a better predic-

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tion of death than plasma norepinephrine or endothelinone (1). Increase in plasma BNP has been observed in the first days of life and its rapid decline occurs during the first week. The reason for increasing level of BNP immediately after birth is unknown. Increased preoperative BNP was not due to chronic heart disease but is due to congenital heart disease that is assumed that stretching the muscle cell walls is the primary stimulus for BNP secretion (2). Voskaridou and colleagues demonstrated that the occurrence of pulmonary hypertension in patients with β/S thalassemia was similar to patients with sickle cell disease (SCD) and the serum amount of NT Pro BNP was a strong indicator for patients with β/S thalassemia with pulmonary hypertension and in addition to the findings of echocardiography, it may be used for diagnosis of pulmonary hypertension (3). Kremastinous and colleagues showed that in patients with major thalassemia plasma level of BNP and NT pro BNP significantly increased when diastolic left ventricular dysfunction occurred. NT Pro BNP marker seemed to have better predictive value than BNP in detecting abnormalities of left ventricular diastolic function in patients with major thalassemia (4). Garadah and colleagues indicated that patients with major thalassemia had high serum NT Pro BNP in relation with levels of E / Em in Doppler tissue imaging (DTI) (5). Marwick and colleagues have indicated that activity can increase BNP biomarker in patients with diastolic dysfunction confirmed evidently by Doppler tissue imaging (DTI) echocardiography (6). Berger has concluded that multidisciplinary care and BNP measurement, improved clinical outcomes in patients with heart failure after hospitalization (7). Since studies of the diagnostic value of BNP in determination of heart dysfunction in patients with beta major thalassemia are limited and early diagnosis of cardiac involvement in these patients reduces the incidence of mortality, this study was conducted with the purpose of early diagnosis of cardiac involvement in patients with major thalassemia compared to the findings of echocardiography.

Methods and materials

This study was carried out in all asymptomatic major thalassemia patients who referred to the center for patients with special diseases of Aliasghar hospital from 2010-2011. These patients were examined for chest radiography and electrocardiogram. Patients with no important clinical symptoms of disease entered the study and those with hypertension, endocrine disease, heart failure and valve involvement were excluded from the study. Patients underwent echocardiography 48-72 hours after receiving blood transfusions. Physical examination and echocardiography were performed by one pediatric cardiologist in the same place using challenge 7000(made in Italy). There were eighty individuals aged 9-25 years old in each group matched by sex and age. Following parameters were measured: MPI: myocardial performance index, LVMI: Left ventricular mass index, PEP: pre-ejection period, ET: ejection time, PEP/ET: pre-ejection period/ejection time ratio, IVSD: interventricular septal dimension in diastole, LVPWD: left ventricular posterior wall dimension in diastole , IVSS: interventricular septal dimension in systole, LVPWS: left ventricular posterior wall dimension in systole, LVEDD :left ventricular end – diastolic dimension, LVESD: left ventricular end- systolic dimension, LVEDV: left ventricular end-diastolic volume, EF: ejection fraction, FS: fractional shortening, AO: Aorta diameter, LA: left atrium diameter, LA/AO: left atrium, aorta ratio, ICT: isovolumic contraction time, IRT: Isovolumic relaxation time, AT: acceleration time, DT :deceleration time, E/A ratio peak E/Peak A velocity in both groups. Three cardiac cycles were measured by Doppler echo M-Mode 2D and the mean value of each parameter was considered. This method was performed in the supine position (supine) while breathing. M-Mode in the tip mitral valve in position of Para sternal view was obtained. The thickness of the wall between ventricular in systole and diastole, the wall thickness of posterior left ventricle in diastole and systole, the end diastolic and systolic left ventricular ejection fraction (EF), fraction shortening were obtained using M-Mode.

The pulsed Doppler method was used to determine the velocity of blood in the heart valves through E-velocity, A-velocity, ejection time, pre ejection time, E/A, PEP/ET. After 3 or 4 days of transfusion, 5 cc blood was taken and the level of BNP was measured using ELISA kit BNP. Patients remained at rest for 30 minutes before blood sampling. All samples were centrifuged in around 3000 rps for 10 minutes at 4 centigrade degree and plasma was kept in minus 80□c.

The specificity and sensitivity of BNP laboratory testing compared to the results of echo were calculated. To analyze data, T-test, the Kappa coefficient of agreement, Mc-Namar Test and correlation coefficients were used.

Consent form was obtained from patients and they were enrolled if they were satisfied.

Results:

In case and control groups, 80 individuals matched by age and sex were entered.

There were 42 males and 38 females in the case group and 36 males and 44 females in the control group (P=0.429) but the mean value of weight, height, hemoglobin, systolic and diastolic blood pressure in case group were lower than the control group (Table 1). The mean values of PEP, ET, PEP / ET, LVEDD, LVEDV, LVMI, LA, LA / AO, MPI, IRT, ICT, DT, peak E, A and E / A of the left heart in the case group were higher than control group (Table 2). The mean values of PEP, ET, PEP / ET, MPI, IRT, ICT, and Peak A of the right heart were higher in the case group compared to the control group. Furthermore, the mean value of BNP was higher in case group (Table 3).

Table.1-Demographic and Characteristic of case and control groups

Variable	Mean ± SD (patients)	Mean ± SD (control)	P value
Age(year)	18.21±5.14	16.95±5.49	0.136
Weight(Kg)	38.21±8.82	50.2±15.9	0.0001
Height(Cm)	145.83±12.3	158.47±15.47	0.0001
Hemoglobin(g/dl)	10.37±0.34	14.32±1.09	0.0001
Systolic BP(mmHg)	90.31±7.80	100.58±23.16	0.0001
Diastolic Bp(mmHg)	64.31±5.72	70.18±6.58	0.0001

BP; Blood Pressure

Table.2- Left-heart echocardiographic parameters in case and control groups

Variable	Mean ± SD(patients)	Mean ±SD (control)	P value
PEP(ms)	92.93±10.37	86.35±9.26	0.0001
ET(ms)	255.57±22.17	271.01±22.83	0.0001
PEP/ET	0.36±0.05	0.31±0.03	0.0001
IVSD (mm)	8.26±1.51	8.12±1.27	0.520
LVPWD(mm)	4.6±0.74	4.73±0.86	0.317
IVSS(mm)	11.28±1.84	11.11±1.64	0.536
LVPWS(mm	5.31±0.89	5.57±0.83	0.058
LVEDD(mm)	48.47±4.91	46.83±5.47	0.048
LVDS(mm)	30.04±4.11	28.95±5.11	0.141
LVEDV	75.64±21.11	63.31±18.16	0.0001
LVMI	84.35±23.63	66.06±17.05	0.0001
EF(%)	67.73±6.07	69.16±5.99	0.137
FS(%)	38.07±6.25	38.81±5.22	0.420
Diameter of LA(mm)	28.03±4.17	25.26±3.79	0.0001
Diameter of Aorta(mm)	24.19±3.11	24.92±3.75	0.180
LA/ Aorta	1.17±0.18	1.01±0.12	0.0001
MPI	0.61±0.1	0.42±0.05	0.0001
ICT(ms)	43.77±21.22	23.33±16.28	0.0001
IRT(ms)	112.16±18.04	94.8±14.54	0.0001
AT(ms)	61.26±16.16	59.75±8.92	0.465
DT(ms)	137.91±18.71	149.81±23.67	0.001
E(cm/s)	94.61±17.56	89.95±16.89	0.039
A(cm/s)	50.08±10.38	51.73±12.92	0.375
E/A	1.95±0.49	1.77±0.40	0.015

MPI: myocardial performance index, LVMI: Left ventricular mass index, PEP: pre-ejection period, ET: ejection time, PEP/ET: pre-ejection period/ejection time ratio, IVSD: interventricular septal dimension in diastole, LVPWD: left ventricular posterior wall dimension in diastole , IVSS: interventricular septal dimension in systole, LVPWS: left ventricular posterior wall dimension in systole, LVEDD :left ventricular end – diastolic dimension, LVESD: left ventricular end- systolic dimension, LVEDV: left ventricular end-diastolic volume, EF: ejection fraction, FS: fractional shortening, AO: Aorta, LA: left atrium, LA/AO: left atrium, aorta ratio, ICT: isovolumic contraction time, IRT: Isovolumic relaxation time, AT: acceleration time, DT :deceleration time, E/A ratio peak E/Peak A velocity

Table.3- Right-heart echocardiographic parameters in case and control groups

Variable	Mean – SD(patients)	Mean- SD (control)	P value
PEP(ms)	93.12±10.82	85.48±9.14	0.0001
ET(ms)	255.2±23.32	268.23±21.26	0.0001
PEP/ET	0.36±0.04	0.31±0.03	0.0001
ICT(ms)	45.43±21.62	31.3±17.99	0.0001
MPI	0.69±0.12	0.41±0.05	0.0001
IRT(ms)	128.41±19.99	98.81±16.85	0.0001
AT(ms)	66.6±18.77	62.66±12.87	0.124
SD(ms)	136.81±18.72	130.11±30.40	0.096
DT(ms)	138.41±16.32	144.80±24.48	0.054
E(cm/s)	61.2±13.94	57.80±12.92	0.112
A(cm/s)	45.90±10.75	42.51±9.31	0.035
E/A	1.36±0.3	1.38±0.31	0.684
BNP	7.53±26.04	5.08±6.23	0.043

MPI: myocardial performance index, PEP: pre-ejection period, ET: ejection time, PEP/ET: pre-ejection period/ejection time ratio, ICT: isovolumic contraction time, IRT: Isovolumic relaxation time, AT: acceleration time, DT : deceleration time, E/A ratio peak E/Peak A velocity, BNP: Brain Natriuretic Peptides

Sensitivity and specificity of BNP with a cut of point 8, were 6.3% and 72.5% but with the cut of point 2, they were 68.8% and 74% respectively. There was a significant correlation between BNP and right heart MPI ($R=0.229, P=0.041$) and age ($R=0.237, P=0.035$).

Discussion:

Most studies have been concentrated on plasma BNP measurement which is more specific for myocardial failure. BNP is a neurohormone similar to atria natriuretic peptide (ANP) that firstly identified in brain and now in heart especially in ventricles. Plasma concentration of BNP is less than 20% of ANP in normal subjects. It can be equal or greater than ANP in patients with heart failure (8). Ventricular cells are able to secrete ANP and BNP in response to increased high ventricular filling pressures. Increased serum level of BNP can confirm CHF that is related to diastolic dysfunction and systolic dysfunction, although this does not have value to differ of systolic and diastolic dysfunctions. In our study the presence of significant relationship between BNP and right ventricular MPI confirmed the systolic and diastolic dysfunction this is similar other studies (8).

Kremastinos and colleagues demonstrated that increased NT-Pro BNP in patients with major beta thalassemia compared with the control group was associated with age and left ventricular diastolic dysfunction.

It would appear that NT-Pro BNP in thalassemia patients may act as a biomarker for early left ventricular dysfunction compared with conventional Doppler echocardiographic indices (9). In our study, the significant relation between the level of BNP and age was similar to Kremastino study.

Hamodraka and colleagues, have shown that levels of both BNP and NT Pro BNP in patients with major thalassemia with diastolic and systolic dysfunction, increased but NT Pro BNP was a better biomarker to identify the patients with diastolic and systolic dysfunction (10). In our study we did not use NT-Pro BNP, but the level of BNP increased in major thalassemia patients with diastolic and systolic dysfunction. In the study of Kremastinous and colleagues, the level of BNP and NT pro BNP in thalassemia patients significantly increased when diastolic left ventricular dysfunction occurred. It seemed that the NT Pro BNP was

a better predictive marker than BNP in order to detect left ventricle diastolic dysfunction in thalassemia patients who have no significant signs of the diseases (4). In our study, there was no correlation between BNP and left ventricular markers, since we studied patients with major thalassemia without clinical symptoms of diseases with younger age.

In the study of Aessopos and colleagues, cardiac complications in major thalassemia were the causes of mortality in these patients and the main characteristic of disease was left ventricular dysfunction that was due to consume iron consumption.

Levels of BNP in patients with impaired regional or global function and left ventricular diastolic dysfunction will arise and appear after increased wall stretch of left ventricle that is associated with the severity of symptoms and the prognosis of disease therefore the measurement of serum level of BNP in this cases can be important (11). In our study, patients who had symptoms of heart failure were excluded from the study and as a result, this study does not conform to our research.

Krematinos and colleagues indicated that NT Pro BNP in patients with major thalassemia is related to aging and left ventricular diastolic dysfunction. NT Pro BNP biomarker appeared to be a marker of early left ventricular diastolic dysfunction compared with conventional Doppler echocardiography index (9). In this study BNP was only available for research and because our patients were asymptomatic without clinical signs of dysfunction.

Meloni and colleagues indicated in their study that in patients with major thalassemia, NT Pro BNP was associated significantly with diastolic right ventricular dysfunction and the presence of myocardial fibrosis. (12). The present study demonstrated that there was a direct relationship between increasing right ventricular MPI and BNP.

Aessopos and colleagues showed that BNP was useful in predicting the risk of developing heart disease. BNP only increased in patients with obvious and significant dysfunction in heart disease and BNP levels did not reflect the severity of heart failure in these patients. In our study that was conducted on patients without significant symptom of the disease, BNP had direct correlation with increased right ventricular MPI since right ventricular involvement is earlier than left ventricle (13). Wahl and his colleague indicated that NT Pro BNP levels had correlation with increased severity of pulmonary artery pressure and right ventricular dysfunction in patients with primary pulmonary artery pressure (14). This study has been performed in symptomatic patients whereas in our study patients were clinically asymptomatic. Thus the findings of two studies are different. Lim (15) and Galasko (16) studied the development of screening programs for the treatment of left ventricular systemic dysfunction. This study showed that ECG, Echo, BNP and NT Pro BNP are all cost effective for screening. All of the above studies were used for screening of left ventricular dysfunction, therefore this study like our study were conducted to prevent the occurrence of heart failure.

Bursi and colleagues indicated that more than 1/ 2 of patients with heart failure diastolic dysfunction occurred in 40% of isolated patients. EF and diastolic dysfunction was independently related to the level of BNP (17). Maisel had shown that mid regional Pro BNP as BNP were useful in diagnosis of heart failure with dyspnea (18). This research is consistent with our study since our patients were thalassemia without clinical symptoms.

Conclusions:

Based on the findings of this study, the patients with beta thalassemia, systolic and diastolic function of left and right heart were damaged. Therefore, it is recommended that in patients with major beta thalassemia without clear symptoms and signs of heart involvement, the measurement of plasma level of BNP is necessary in addition to serial echocardiography in order to diagnose the early involvement of heart.

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