A Comparison Between MRIT2 and NT-ProBNP in Early Detection of Heart Diseases in Thalassemia Major Patients: A Cross-Sectional Study

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Abstract One of the most common causes of mortality in major thalassemia is cardiac complications. Despite existence of several methods for diagnosis of cardiac complications in thalassemia, this sequel persists as a major problem in these patients. The aim of this study is to compare the level of serum NT-ProBNP and cardiac MRI T2* in early detection and treatment of cardiac disorders in beta thalassemia major patients. 35 major thalassemic patients on regular transfusion were selected in our center from 2013 to 2014. All of the patients were at least 8 years old. NT-ProBNP and MRIT2* analyses were carried out for these patients, and consequently the findings were compared together and analyzed. There is a strong correlation between NT-ProBNP and MRIT2* (p value < 0.001) in early detection of cardiac disorders. NT-ProBNP is an important marker for diagnosis of cardiac complications before emergence of heart failure in thalassemic patients. Given the findings of this study, it is recommended that this marker be used on a regular basis for thalassemic patients on regular transfusion.

Keywords Major thalassemia · NT-ProBNP · Heart failure · Iron overload · T2* MRI

Introduction

Beta thalassemia major is an inherited genetic disorder of beta chain hemoglobin synthesis. The disease leads to a significant increase of erythropoiesis. However, more than 95% of increased erythropoiesis can be ineffective. Severe and progressive anemia appears in second 6 month after birth and regular blood transfusion is necessary to prevent fatigue and heart failure due to anemia [1]. The most fundamental necessity in continuous treatment of thalassemic patients is frequent blood transfusion which has major side effects including iron overload. This condition causes impaired function of endocrine system, liver and heart [2]. Cardiac complications are the main leading causes of mortality and have a significant effect on thalassemic patient's morbidity. Cardiac involvement generally appears as the left ventricular heart failure. Although there are diverse reasons for heart failure in thalassemic patients, iron overload remains the main cause. Arrhythmia and cardiomyopathy are the other cardiac complications that can be cured if diagnosed early [3]. There are different methods to diagnose heart failure; such as measuring the level of serum ferritin, electrocardiography and chest X-ray. Unfortunately, these methods can only diagnose high risk patients at the end stages of the disease [4]. Cardiovascular magnetic resonant (CMR) is a non-invasive method for measuring the level of cardiac iron deposition that can be performed either as spin echo (T2) or gradient echo (T2*). Currently, MRI T2* is regarded as a suitable non-invasive method for early diagnosis of heart failure which is relatively an expensive method [5]. Whereas more recently, natriuretic peptides are used as the markers of cardiac dysfunction. The most sensitive form of natriuretic peptides is type B natriuretic peptide (BNP) having an amine terminal, N-Terminal prohormone of brain natriuretic peptide (NT-ProBNP). This

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hormone is produced by cardiac myocytes as a reaction to cardiac muscles traction. Studies have shown increased level of NT-ProBNP in thalassemia major patients is associated with cardiac dysfunction [6–8].

This study is a comparison between the level of serum NT-ProBNP and cardiac MRI T2* findings in children with thalassemia major admitted to thalassemia clinic of Mofid hospital, Tehran, Iran. The results can be used as a prevention and early treatment of cardiac disorders in beta thalassemia major patients in order to increase their life expectancy.

Materials and Methods

This cross-sectional comparative study was carried out from 2013 to 2014 on 35 children who were diagnosed with beta thalassemia major using hemoglobin electrophoresis. Patients were visited frequently at the thalassemia clinic of Mofid Pediatric Hospital. Required data were gathered with informed consent of all individual participants parents included in the study. Diagnosed thalassemia major patients with informed consent for performed test, imaging, and functional analysis were included in the study. On the other hand, Patients with hypertension, ischemic heart disease or cardiac hypertrophy diagnosed by echocardiography, renal failure and body mass index (BMI) more than 95% of their age and sex were excluded from the study. Echocardiography by an expert cardiology physician using *Philips CX50* device was performed for all patients and Ejection fraction, left and right atrial dimensions, left and right ventricular diameters and pulmonary arterial pressure were determined. Patients were evaluated for heart failure using echocardiography findings specifically on the basis of ejection fraction. MRI T2* using *Philips MRI device 1.5 Tesla* on T2 weighted method was performed as a basic test to determine cardiac disorders in these patients. Later on, 3 cc of non-fasting venous blood was sampled to measure the level of serum NT-ProBNP using sample kits *Elecyss 2012* made by *Roche*. Eventually, the correlation between the results of MRI T2* and NT-ProBNP were evaluated.

For statistical analysis, the comparison between the average values was performed using Mann-Whitney U test. The relation of continuous data was evaluated by correlation tests. $p < 0.05$ was considered statistically significant and statistical calculations were performed using SPSS 16.

Results

We enrolled 35 patients (16 males, 19 females, mean age of 17.1 ± 5.3) in the study. The patients average BMI was $20 \pm 2 \text{ kg/m}^2$. mean NT-ProBNP level, MRI T2 index and

level of serum ferritin were $111 \pm 57 \text{ pg/ml}$, $14 \pm 6 \text{ ms}$, $2203 \pm 2265 \text{ ng/ml}$ respectively which did not follow the normal distribution curve. Echocardiography results revealed 2 patients (5.7%) with heart failure and 33 patients (94.3%) without evidences of cardiac dysfunction.

As stated in MRI cardiac results, 9 patients (25.7%) were normal and 6 patients (17.1%) with mild failure, 10 patients (28.6%) with moderate failure and 10 patients (28.6%) with severe failure were reported. Comparing NT-ProBNP level and MRI T2, there was a significant negative correlation between NT-ProBNP and MRI T2 (p value < 0.001 , spearman's correlation co-efficient = -0.780) (Fig. 1). The average of discussed factors in patients with and without heart failure according to echocardiography is shown in Table 1 which demonstrates a significant difference between the average of NT-ProBNP and MRI T2 in these patients. On the other hand, only two patients were detected with heart failure using echocardiography while 26 patients (74.3%) detected with heart failure using MRI T2*, so it reduces the reliability of Table 1 findings. Echocardiography can evaluate cardiac failure considering ejection fraction and ventricular function. Therefore, Cardiac complications are unrecognized until the late stages. The mean NT-ProBNP level in

Fig. 1 The correlation between NT-PROBNP and MRI T2

Table 1 The average indices in patients with heart failure and patients without heart failure (based on echocardiography)

Variable	Heart failure	Normal echocardiography	p value*
NT-ProBNP	258.5 ± 12.1	102.1 ± 45.3	0.003
MRI T2	6.5 ± 0.7	14.9 ± 6.5	0.003
Ferritin	3348 ± 2307	2133 ± 2316	0.272

* Mann-Whitney U

Fig. 2 The comparison of NT-ProBNP average based on MRI T2

patients with Normal, mild moderate and severe MRI T2 was 39 ± 19 , 121 ± 28 , 108 ± 18 and 171 ± 46 pg/ml respectively which demonstrates a significant difference ($p < 0.001$). (Figure 2) Although NT-ProBNP level in patients with heart failure has significant difference compared to the normal group, however the use of NT-ProBNP does not seem appropriate to differentiate between cases of mild, moderate and severe heart failure.

There were no difference in MRI T2 findings and NT-ProBNP levels between genders. In addition there were no differences in our findings between different age groups. In evaluation of gender, age, BMI, NT-ProBNP and ferritin level, our findings showed a significant independent relation between MRI T2 and NT-ProBNP ($p < 0.001$) and no significant relation between other variables and MRI T2.

Discussion and Conclusion

Congestive heart failure and other cardiac complications are the leading causes of mortality in beta thalassemia major patients. Iron overload and chronic anemia can lead to cardiac dysfunctions which include about 60% of patient's complaints.

In a study by Atiq et al. 75 patients with average age of 13 ± 5 were studied. Echocardiography, electrocardiography and chest X-ray were performed. 44 patients suffered from left ventricular Systolic dysfunction, 17 patients had Diastolic dysfunction, 22 patients had pericardial effusion and 12 patients suffered from pulmonary hypertension. The results demonstrated cardiac dysfunctions as prevalent complaints in Beta thalassemia patients ($p = 0.025$, $r = 0.35$) [9]. This issue shows the importance of early diagnosis of cardiac complications in these patients, which requires accessible, affordable, less expensive and non-

invasive methods. Performing laboratory analyses can provide acceptable data regarding this issue.

In our study, Echocardiography findings showed cardiac dysfunction in approximately 6% of patients. Since echocardiography shows heart failure by ejection fraction and ventricular function, myocardial status must lead to dysfunction to be diagnosed by echocardiography. Whereas according to cardiac MRI T2 findings, 9 patients (25.7%) were normal and 26 patients (74.3%) were abnormal; including 6 patients (17.1%) with mild, 10 patients (28.6%) with moderate and 10 patients (28.6%) with severe cardiac dysfunction. This issue demonstrates that MRI T2* has a higher diagnostic value in the early stages. For this reason the relation between NT-ProBNP and MRI T2 can possess a high diagnostic value. Our findings indicate a significant invert correlation between these two variables so that as MRI T2* decreases, the level of NT-ProBNP increases. In other words, as the severity of heart failure increases in MRI T2*, cardiac dysfunction showed by NT-ProBNP also increases equally.

Previous studies revealed similar trends. Kremastinson, et al. studied 52 beta thalassemia major patients with the average age of 27 ± 12 and 52 healthy control group with similar age. The results indicated the increased level of NT-ProBNP in beta thalassemia major patients with impaired cardiac function, which is the diagnosis of left ventricular diastolic dysfunction ($r = 0.35$, $p = 0.014$) [7]. Akpinar et al. also demonstrated that although thalassemia can lead to both systolic and diastolic dysfunction, systolic dysfunction appears in earlier stages. Using NT-ProBNP as an early detection marker can be diagnostically helpful ($r = 0.32$, $p = 0.027$) [8]. A study by Bayraktaroglu et al. indicated that cardiac involvement in MRI T2* ($20 \text{ ms} > \text{T2}^*$) associates with decreasing ejection fraction in echocardiography. ($r = 0.31$, $p = 0.037$) [10]. Kremastinson et al. reported that NT-ProBNP level increases significantly in left ventricular diastolic dysfunction ($r = 0.31$, $p = 0.037$) [11].

Our findings show that MRI T2* in patients with heart failure diagnosed by echocardiography is lower than MRI T2* in patients with normal echocardiography. However there was no significant association between heart failure and ferritin level. These findings are similar to Bayraktaroglu S. study which showed increasing MRI T2* associates with ejection fraction reduction in echocardiography [10]. These findings demonstrate that MRI T2* and NT-ProBNP can be used in both genders and in all ages for assessing cardiac function in beta thalassemia major patients particularly in early stages.

Compliance with Ethical Standards

Conflict of interest This article does not include any conflict of interests or financial supports.

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of Shahid Beheshti University of Medical Science research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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