International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 15, Issue 5, 2023

Original Article

CORRELATION OF N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE (NT PRO BNP) WITH SERUM FERRITIN AND NUMBER OF BLOOD TRANSFUSIONS IN THALASSEMIA PATIENTS-A CROSS-SECTIONAL STUDY

APARNA DUTT, MALLESH KARIYAPPA, RAVICHANDRA KOTHUR RANGEGOWDA*

Department of Paediatrics, Bangalore Medical College and Research Institute, Bangalore-560002, Karnataka, India
***Corresponding author: Ravichandra Kothur Rangegowda; *Email: ravichandrakr87@gmail.com**

Received: 08 Jun 2023, Revised and Accepted: 27 Jul 2023

ABSTRACT

Objective: Thalassemia is a genetic disorder of globin chain production in which there is an imbalance between alpha globin and beta globin chain production. Thalassemia patients require frequent blood transfusions to maintain adequate tissue oxygenation, which can cause a state of iron overload. NT pro BNP is a sensitive biomarker to detect cardiac iron overload. Our objective of this study was to estimate the level of NTproBNP in beta-thalassemia patients and to find out the correlation of NT pro BNP with serum ferritin levels and the number of blood transfusions.

Methods: 50 thalassemic patients aged below 18 y with no known cardiac comorbidities were enrolled in this cross-sectional study. The correlation between the levels of NT-pro BNP with serum ferritin and number of blood transfusions and chelation therapy was measured.

Results: This study demonstrated that the levels of NT Pro BNP were elevated in thalassemia patients with a positive correlation with serum ferritin values and the number of blood transfusions which the patients received.

Conclusion: This Study also concluded that NT Pro BNP can be used as a biochemical marker used to detect early stages of cardiac failure and also to identify patients going for heart failure, especially in resource-limited settings.

Keywords: Biochemical marker, Chelation, Genetics, Heart failure

DOI: https://dx.doi.org/10.22159/ijcpr.2023v15i5.3070. Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Thalassemia is a genetic disorder of globin chain production in which there is an imbalance between alpha globin and beta globin chain production [1]. Thalassemia is a considerable health problem in India. There are studies which show the overall prevalence of β-thalassemia, the most common form of thalassemia account to 3–4 % with an average of about 8,000 to 10,000 new births with major disease each year [2, 3]. Patients with this disease have repeated episodes of hemolysis due to the abnormal hemoglobin chain. Due to ongoing hemolysis, β-thalassemia patients require frequent and regular blood transfusions to maintain adequate tissue oxygenation and thus give rise to an increased risk of iron overload [4].

Iron overload attributes to most of the complications of the disease with heart, liver and various endocrine glands are being the most commonly affected organs. Clinically they may not be evident initially and hence, investigations are required for early detection and should be done in all thalassemia children from time to time and treat them appropriately.

The most serious and frequent fatal consequence of iron overload in thalassaemia major is cardiac failure or dysrhythmia due to iron deposition in the myocardium and conduction system. This is well recognized and documented in the literature for transfusion dependant thalassaemia (Aldouri, *et al.* 1990, Davis and Porter 2000) [5, 6]. Cardiac complications leads to 70% of deaths in beta-thalassemia. Excess iron gets deposited in the heart especially in ventricular walls and the conduction system.

Iron overload cardiomyopathy is characterized by early diastolic dysfunction, which precedes systolic dysfunction. The early diagnosis of myocardial involvement is crucial for a proper adjustment of therapeutic decisions in a timely manner [7]. Imaging techniques such as doppler echocardiography are useful in revealing the progressively failing myocardial contractility but are unable to identify the "preclinical" state of diastolic dysfunction on an individual basis.

It has been shown recently that amino-terminal pro-B-type natriuretic peptide (NT PRO BNP) may be used as an early index of diastolic left ventricular dysfunction in patients with thalassemia major [8]. Indeed, NT PRO BNP was found to be increased in a group of 52 patients with thalassemia major with preserved left ventricular systolic function, compared with normal controls, and that increase was evident before the conventional Doppler indices of diastolic left ventricular function became abnormal [8]. In comparison with B-type natriuretic peptide, NT PRO BNP circulates at higher concentrations and has a longer half-life, properties that might confer improved accuracy for detection of early left ventricular diastolic dysfunction [9].

Serum ferritin level, which is widely used in the evaluation of thalassemia patient's iron load status, is not a reliable indicator of cardiac iron [10]. Cardiac magnetic resonance imaging T2-star (MRI T2) is an easy and highly reproducible measurement technique which correlates better with cardiac iron concentration [11]. However, it is relatively expensive and it is not widely available in developing countries. Doppler echocardiography and tissue Doppler imaging can detect early cardiac dysfunction, but their clinical use is limited due to high operator dependence and poor correlation with cardiac iron [12].

Brain natriuretic peptide (BNP) and amino-terminal pro-BNP (NT-proBNP) are released after increased cardiac stress and volume overload. The increase of NT-proBNP is detected early in the course of the disease and is a reliable indicator for the early detection of cardiac hemosiderosis in adult β-thalassemia patients. Elevated NT-proBNP levels in thalassemia patients were associated with cardiac iron deposition.

In our study, we aim to estimate NT pro BNP level and its correlation to serum ferritin levels and the number of blood transfusions.

MATERIALS AND METHODS

Source of data**:** Thalassemia patients registered in the department of Paediatrics.

Study design: cross-sectional study

After obtaining approval and clearance from the institutional ethics committee, the children fulfilling the inclusion criteria were enrolled for the study. A detailed history, along with the necessary demographic details was collected from the patients. Clinical evaluation and detailed history of patients to look for signs of cardiac failure was done. Patients having known cardiac disease by 2D Echocardiogram were excluded from the study. Hemoglobin, serum ferritin values, NT PRO BNP values were measured prior to transfusion. To avoid the diurnal variations of NT PRO BNP, all the samples were collected at the same time (10:00 to 11:00 a. m.). In those patients in whom NT PRO BNP was elevated, duration of illness number of transfusions given was noted. The correlation between the level of NT-pro BNP, serum ferritin levels and number of blood transfusions was measured.

Inclusion criteria

1. Age below 18 y

2. Thalassemia patients who have received blood transfusion

3. No signs of heart failure

Exclusion Criteria:

1. Known Cardiac dysfunction

2. Structural heart diseases

3. Patients with renal or hepatic dysfunction

Statistical methods

The Statistical analysis was performed by STATA 11.2 (College Station TX USA). Data was entered in the excel spreadsheet. Student-independent sample t-test was used to find the significance of difference between the NT PRO BNP with serum ferritin levels. Pearson Correlation coefficient was used to find the relationship between number of blood transfusions with NT PRO BNP and its expressed correlation coefficient r with a scatter plot. P<0.05 was considered as statistically significant association.

RESULTS

A total of 50 children were included in the present study after calculating the sample size. Among them 58% were females and 42% of the study subjects were male. In this study the number of blood transfusions per year varied between 2 per year to more than 12 per year, mean number of transfusion being 9.98 per year with a standard deviation of 2.98. The mean pretransfusion hemoglobin was 7.31 mg/dl with a standard deviation of 1.31 while the post-transfusion hemoglobin was 9.94 mg/dl with a standard deviation of 1.28 (p value<0.001).

In our study population, 54% (27 cases) had serum ferritin value of>/=2000 µg/l while 46% had<2000 µg/l. The mean value of NT PRO BNP in our study population was 154.96 pg/dl, with a minimum value of 32 pg/dl, maximum value of 339pg/dl and the standard deviation was 89.72 pg/dl.

The mean value of NT PRO BNP was 219.82 pg/dl in patients whose serum ferritin value was>2000 µg/l with a standard deviation of 63.83 while in those patients whose serum ferritin was<2000 µg/l. The mean value of NT pro BNP was 78.82pg/dl. This shows a significant correlation between NT pro BNP and serum ferritin values with p value of<0.001.

In our study it was shown that the value of NT pro BNP increases with the number of blood transfusions and also with duration of chelation. It was also proven in our study that the value of NT pro BNP increases with age of the patients and is more elevated in the 2nd decade of life. The mean value of NT pro BNP was elevated in splenectomised patients compared to non splenectomised patients and the p value being<0.001.

DISCUSSION

Beta-thalassaemia is a genetic disease with different clinical aspects, which can lead to heart failure with a multifactorial mechanism. Cardiac complications are the main cause of mortality and one of the most significant causes of morbidity in patients with beta-thalassemia.

Natriuretic peptides are gaining increased recognition as diagnostic markers in heart failure. Brain natriuretic peptide (BNP) and its amino-terminal portion NT PRO BNP, which may have advantages because of its greater stability has proved especially promising. Over the last years, growing interest has been reported for biomarkers that may help in the diagnosis, staging and prognosis of heart disease at an early stage, in patients with beta-thalassemia [13].

In thalassemia patients, the level of serum ferritin is elevated due to iron overload secondary to repeated episodes of blood transfusions. In our study, 54% (27 cases) had serum ferritin value of>2000 µg/l while 46% had<2000 µg/l. Hahalis *et al.* in a prospective 12 y study of 36 β-TM patients, showed that median ferritin concentrations of ≥2800 ng/mg and resting left ventricular ejection fraction<60% were independent factors of cardiac mortality [14]. Olivieri *et al.* showed that patients with thalassemia major and frequent blood transfusions without cardiac disease had a very good prognosis for survival, if ferritin levels were <2500 µg/l with iron chelation treatment [15].

NT PRO BNP levels and thalassemia

BNP and/or NT PRO BNP plasma levels are mainly used in the diagnosis of heart failure. Plasma concentrations of BNP<35 pg/ml and/or NT-proBNP<125 pg/ml make Heart Failure diagnosis unlikely [16].

However, there are several other conditions that may lead to high BNP/NT-pro-BNP levels either cardiac such as acute coronary syndromes, pulmonary embolism, tachyarrhythmias, cardioversion or non-cardiac such as renal failure, liver failure, ischeamic stroke, subarrachnoid hemorrhage and anaemia [17]. In conclusion, although natriuretic peptides have a cornerstone position in the diagnosis of Heart Failure, there are supportive studies of their use in the field of thalassaemia, their diagnostic and prognostic role in the latter group of patients.

In our study, it was shown that NT PRO BNP levels were elevated in thalassemia patients; mean NT PRO BNP value in our study population was 154.96 pg/dl with the minimum value of 32 pg/dl and maximum value being 339 pg/dl and the standard deviation was 89.72 pg/dl. It can be used as a strong predictor for detection of early diastolic dysfunction, especially in resource-limited settings.

NT PRO BNP and serum ferritin levels

In our study, a positive correlation was found between NT PRO BNP levels and mean serum ferritin levels with a p value of<0.001.

Balkan c *et al.*, in a cross-sectional study concluded that NT PRO BNP secretion begins in the early phase of the disease before the increase in diastolic pressure becomes overt and there was a strong correlation between the plasma NT PRO BNP levels and iron overload p value<0.01 [18].

Noori *et al.*, in their study found that there was a strong correlation between plasma NT PRO BNP and iron overload. An increased level of ferritin and NT PRO BNP can be used as a marker for the intensification of iron chelation therapy, which reverses iron-induced cardiomyopathy [19].

In study done by Alizadeh *et al.* who recruited 50 patients with thalassemia in a cross-sectional study, where the BNP level was correlated with the diastolic dysfunction. There was no statistical significance between the BNP level in all groups. There was also no statistical significance between BNP level and serum ferritin and type of iron chelators used [20]. This was in contrast to our study where a statistical significance between BNP level and serum ferritin levels were found.

Correlation of NT PRO BNP with age and number of blood transfusions

In our study it was also proven study that the value of NT PRO BNP increases with age of the patients and is more elevated in the 2nd decade of life. This is in accordance with the study conducted by

Kremastinos which showed that an increase of NT pro BNP levels in patients with beta-thalassemia major was related to age and diastolic dysfunction (E/E' ratio>15) and the highest decade in the study [17]. Similar study done by Raymond I *et al.* concluded that the plasma concentration of NT-proBNP almost doubled per age decade in the present study, regardless of sex or normality status and this was in lieu with our study findings [21]. In the study done by Noori *et al.* titled Diagnostic Value of NT-pro BNP Biomarker and Echocardiography in Cardiac Involvements in Beta-thalassemia Patients confirmed that NT-pro BNP increases in thalassemia patients and is related to age and LV diastolic dysfunction [19].

Our study showed a positive correlation between value of NT pro BNP and the number of blood transfusions, with higher NT pro-BNP values upon an increase in the number of transfusion among study subjects. However Mehrzad V *et al.* in their study did not find any correlation between NT-proBNP levels and the number of transfusion sessions or total amount transfused in the year prior to study entry (p=0.383 and p=0.243, respectively) [22].

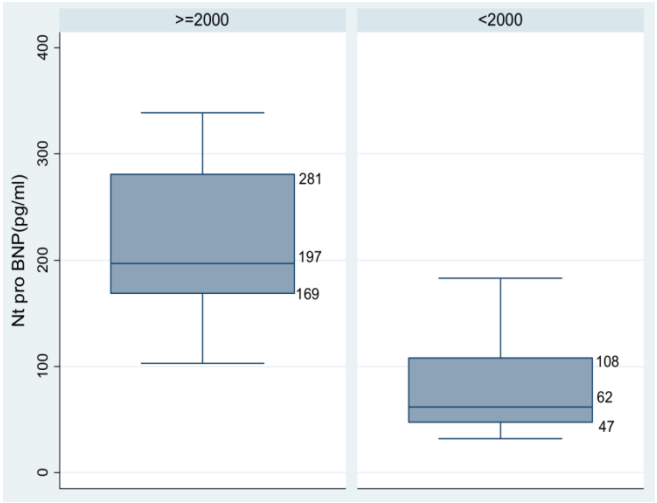

Fig. 1: Box diagram showing correlation of NT BNP with serum ferritin

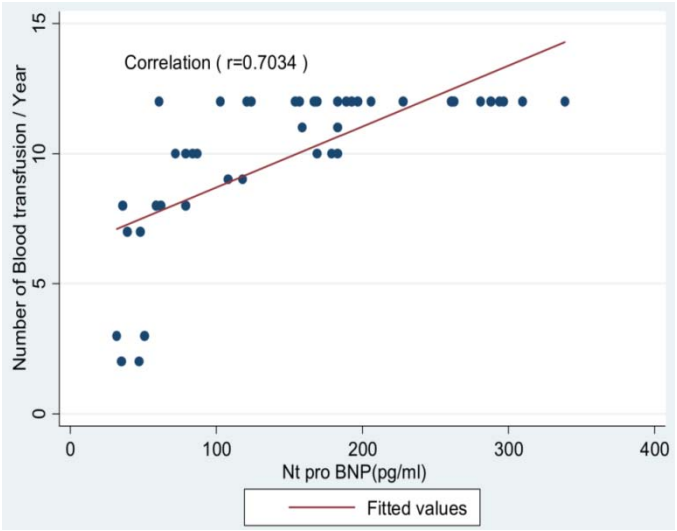

Fig. 2: Correlation of NT BNP with number of blood transfusion

CONCLUSION

In thalasseima, due to repeated amount of blood transfusions, iron overload is bound to occur and as a result cardiomyopathy is a well-known complication of thalassemia. In response to this, cardiac myocytes secrete BNP which can be used as an early marker for estimating the cardiac dysfunction. As the amount of blood transfusions increases, the ferritin values and BNP values also increases.

In conclusion, the findings of this study have demonstrated that the level of NT Pro BNP is elevated in thalassemia patients. It shows a positive correlation with serum ferritin values; as the ferritin value increase NT PRO BNP value also increases. NT PRO BNP was also found to be increased with increasing age of the patients and the value of NT PRO BNP was also found to have a positive correlation with the number of blood transfusions which the patients received.

Studies have proved that NT PRO BNP is a biochemical marker used to detect early stages of cardiac failure and this can be used for early identification of patients going for cardiac failure in resource-limited settings where Echocardiography and cardiac MRI are not available.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Aparna Dutt-Intervention and Data collection, Mallesh Kariyappa–Conception and planning, Ravichandra Kothur Rangegowda-

Manuscript preparation, Data interpretation and review.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. DeBaun RM, Feri Jones JM, Vichinsky P. Hemoglobinopathies. In: Nelson textbook of paediatrics.20th ed. Vol. 2. Amsterdam: Elsevier; 2016. p. 2349.
2. Madan N, Sharma S, Sood SK, Colah R, Bhatia LH. Frequency of β-thalassemia trait and other hemoglobinopathies in northern and western India. Indian J Hum Genet. 2010;16(1):16-25. doi: 10.4103/0971-6866.64941, PMID 20838487.
3. Balgir R. Genetic heterogeneity of population structure in 15 major scheduled tribes in central-eastern India: a study of immuno-hematological disorders. Indian J Hum Genet. 2006;12(2):86. doi: 10.4103/0971-6866.27792.
4. Hershko C. Iron loading and its clinical implications. Am J Hematol. 2007;82(12) Suppl:1147-8. doi: 10.1002/ajh.21070, PMID 17963253.
5. Aldouri MA, Wonke B, Hoffbrand AV, Flynn DM, Ward SE, Agnew JE. High incidence of cardiomyopathy in beta-thalassaemia patients receiving regular transfusion and iron chelation: reversal by intensified chelation. Acta Haematol. 1990;84(3):113-7. doi: 10.1159/000205046, PMID 2123060.
6. Fitchett DH, Coltart DJ, Littler WA, Leyland MJ, Trueman T, Gozzard DI. Cardiac involvement in secondary haemochromatosis: a catheter biopsy study and analysis of myocardium. Cardiovasc Res. 1980;14(12):719-24. doi: 10.1093/cvr/14.12.719, PMID 7260965.
7. Spirito P, Lupi G, Melevendi C, Vecchio C. Restrictive diastolic abnormalities identified by doppler echocardiography in patients with thalassemia major. Circulation. 1990;82(1):88-94. doi: 10.1161/01.cir.82.1.88, PMID 2364528.
8. Kremastinos DT, Tsiapras DP, Kostopoulou AG, Hamodraka ES, Chaidaroglou AS, Kapsali ED. NT-proBNP levels and diastolic dysfunction in beta-thalassaemia major patients. Eur J Heart Fail. 2007;9(5):531-6. doi: 10.1016/j.ejheart.2006.11.004, PMID 17317307.
9. Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. Eur Heart J. 2005;26(21):2277-84. doi: 10.1093/eurheartj/ehi406, PMID 16014646.
10. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J. 2001;22(23):2171-9. doi: 10.1053/euhj.2001.2822, PMID 11913479.
11. Carpenter JP, He T, Kirk P, Roughton M, Anderson LJ, de Noronha SV. On T2* magnetic resonance and cardiac iron. Circulation. 2011;123(14):1519-28. doi: 10.1161/circulationaha.110.007641, PMID 21444881.
12. Leonardi B, Margossian R, Colan SD, Powell AJ. Relationship of magnetic resonance imaging estimation of myocardial iron to left ventricular systolic and diastolic function in thalassemia. JACC Cardiovasc Imaging. 2008;1(5):572-8. doi: 10.1016/j.jcmg.2008.04.005, PMID 19356483.
13. Vlachou M, Kamperidis V, Giannakoulas G, Karamitsos T, Vlachaki E, Karvounis H. Biochemical and imaging markers in patients with thalassaemia. Hellenic J Cardiol. 2021;62(1):4-12. doi: 10.1016/j.hjc.2020.04.012, PMID 32387594.
14. Hahalis G, Kourakli A, Gerasimidou I, Kalogeropoulos AP, Sitafidis G, Papageorgiou U. Cardiac mortality in β-thalassemia major: resting but not dobutamine stress echocardiography predicts mortality among initially cardiac disease-free patients in a prospective 12 y study. Eur J Heart Fail. 2009;11(12):1178-81. doi: 10.1093/eurjhf/hfp152, PMID 19889689.
15. Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A. Survival in medically treated patients with homozygous β-thalassemia. N Engl J Med. 1994;331(9):574-8. doi: 10.1056/NEJM199409013310903, PMID 8047081.
16. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. doi: 10.1093/eurheartj/ehw128, PMID 27206819.
17. Kremastinos DT, Hamodraka E, Parissis J, Tsiapras D, Dima K, Maisel A. Predictive value of B-type natriuretic peptides in detecting latent left ventricular diastolic dysfunction in beta-thalassemia major. Am Heart J. 2010;159:68–74
18. Balkan C, Tuluce SY, Basol G, Tuluce K, Ay Y, Karapinar DY. Relation between NT-proBNP levels, iron overload, and early stage of myocardial dysfunction in β-thalassemia major patients. Echocardiography. 2012 Mar;29(3):318-25. doi: 10.1111/j.1540-8175.2011.01584.x, PMID 22066516.
19. Noori NM, Teimouri A, Nakhaey Moghaddam M. Diagnostic value of NT-pro BNP biomarker and echocardiography in cardiac involvements in beta-thalassemia patients. Int J Pediatr. 2017;5(11):6077-94.
20. Alizadeh B, Badiee Z, Mahmoudi M, Mohajery M. Evaluating the correlation between serum NT-proBNP level and diastolic dysfunction severity in beta-thalassemia major patients. J Tehran Heart Cent. 2016;11(2):68-72. PMID 27928257.
21. Raymond I, Groenning BA, Hildebrandt PR, Nilsson JC, Baumann M, Trawinski J. The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. Heart. 2003;89(7):745-51. doi: 10.1136/heart.89.7.745, PMID 12807847.
22. Mehrzad V, Khajouei AS, Fahami E. Correlation of N-terminal pro-B-type natriuretic peptide levels and cardiac magnetic resonance imaging T2* in patients with β-thalassaemia major. Blood Transfus. 2016;14(6):516-20. doi: 10.2450/2016.0120-15, PMID 27136436.