

Association of Biochemical Markers with Cardiovascular Status in Sickle Cell Disease

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ABSTRACT

Background: Sickle-cell disease is a group of blood disorders caused by single nucleotide polymorphism at the 6th codon of HBB gene. It is well known fact that in sickle cell disease patients many cardiac abnormalities found. So aim of this study is to find out whether these biochemical markers are associated with cardiac diseases in sickle cell patients or not.

Materials And Methods: This cross sectional study enrolled 60 subjects positive for sickle cell disease. Serum IRON, LDH, TIBC was measured using I lab 650. Serum FERRITIN, NT-proBNP, was measured by chemiluminescence. Cardiac status of all the patients was assessed by echocardiography.

Results: Serum LDH was found to be increase in all the study subjects (mean=938.21). So there is no correlation between high serum LDH and cardiac disease of sickle cell patients. Significant difference was observed between normal and abnormal ECHO findings for iron ($p=0.55$). Serum NT Pro BNP was found to be significantly higher in subjects with abnormal ECHO findings ($P<0.0001$). Significant difference was observed in ECHO findings for different age groups in study subjects indicating that Normal ECHO findings were significantly frequent in lower age group ($p=0.186$).

Conclusion: 13 patients out of 70 who were having abnormal echo findings and also they have abnormal serum NT pro BNP level. Most common echo finding was left ventricular hypertrophy, tricuspid regurgitation. Ldh was higher in all the study subjects.

Keywords: Sickle Cell Disease, Biochemical Markers, Cardiovascular Status, Blood Disorders

INTRODUCTION

Sickle hemoglobin (HbS) is the first molecular disease known to human. The mutation causing sickle cell anemia is a single nucleotide substitution (A to T) in the codon for amino acid at 6th position. This change converts a glutamic acid codon (GAG) to valine codon (GTG). [1]

Sickle cell is caused by a single point mutation in the hemoglobin gene, which is called as hemoglobin S. Hb S leads to polymerization of deoxygenated hemoglobin. So the red blood cells of a person with sickle cell anemia tend to be fragile and less flexible or rigid, stiff in nature than normal RBC. [2]

When the red blood cells become fragile this leads to cardiac complications in SCD and are known to be an important cause of the morbidity and mortality. [3]

To assess the function of heart in sickle cell patients a peptide hormone called Brain natriuretic peptide (BNP) is estimated. The human BNP gene is located on chromosome 1 and encodes the prohormone proBNP. The biologically active BNP and the remaining part of the prohormone, NT-pro BNP (76 amino acids) can be measured by immunoassay in human blood. Cardiac myocytes constitute the major source of BNP related peptides. The main stimulus for peptide synthesis and secretion is myocyte stretch. [4]

Pulmonary hypertension and diastolic dysfunction has been identified as a predictor of death in the adult SCD population. [5]

The severity of cardiac dysfunction depends on the amount of iron deposited in the myocardium and the overall body iron burden, hepatic iron content (HIC) persistently greater than 15 mg Fe/g of dry weight liver is associated with cardiac morbidity.^[6]

Left ventricular systolic dysfunction (decreased ejection fraction) is a late finding of heart disease from iron accumulation, since cardiac iron deposition is associated with the duration of blood transfusions.^[7]

MATERIALS AND METHODS

This hospital based, observational case control study was conducted in the Department of Biochemistry, Pt. J.N.M. Medical College and DR. B.R.A.M. Hospital, Raipur, C.G. among patients who attended the Sickle Cell OPD, Department of Biochemistry, Pt. J.N.M. Medical College and Inpatients of the medicine Ward and was approved by the ethical committee.

70 patients with Sickle Cell Disease (SCD) who fulfilled inclusion and exclusion criteria were studied. History taking, general and systemic examination of patients of all the patients was conducted according to the proforma. The study design was presented before the Ethical Committee of Pt. J.N.M. Medical College, Raipur and necessary clearance were taken.

About 5 ml venous blood samples were collected with all usual precautions. Remaining blood sample was allowed to clot in plain vial and then spun in a centrifuge at 1500 rpm for 10 minutes. The supernatant serum was used for estimation of iron parameters. Samples were kept at 2-8°C for a maximum period of 5 days when required.

Serum Iron and TIBC was measured by Ferrozine/Magnesium Carbonate method using fully automated biochemistry I-Lab 650i auto analyzer.

Serum Ferritin, NT pro BNP was measured by Electrochemiluminiscence (Roche cobas e411).

Serum lactate dehydrogenase by DGCA method (deutsche gesellschaft fur klinische chime).

Statistical analysis was done using Microsoft Excel and IBM software SPSS v16.0. The analysis of the results was done by Chi-square test, ANOVA. A 'p' value of <0.05 was considered significant.

For the assessment of cardiac function we have done Echocardiography in all the study subjects.

RESULTS

The study group consisted of total 70 subjects. All the patients were sickle cell disease positive. In this study 91.4% were from younger age group from 16 to 30 yrs of age and 8.6% patients were from older age group >30 yrs of age. Gender distribution in study subjects was noted. Out of 70 subjects in total 36 (51.4%) were males and 34 (48.6%) were females.

Clinical findings in study subjects were noted. Iron was found to be normal in 40 (57.1%) subjects followed by low levels in 22 (31.4%) and high levels in 8 (11.4%) subjects. Ferritin was found to be normal in 40 (57.1%) subjects and in 27 (38.6%) subjects it was found to be high and low in 3 (4.3%) subjects. TIBC was observed to be low in maximum 55 (78.6%) subjects while normal in 8 (11.4%) subjects and high in 7 (10.0%) subjects. All the subjects were observed to have high LDH.

Comparison of ECHO findings with various parameters was assessed using unpaired t test. NT Pro BNP was found to be significantly higher in subjects with abnormal ECHO findings ($P < 0.0001$) while, No significant difference was observed between normal and abnormal ECHO findings for iron ($p = 0.55$).

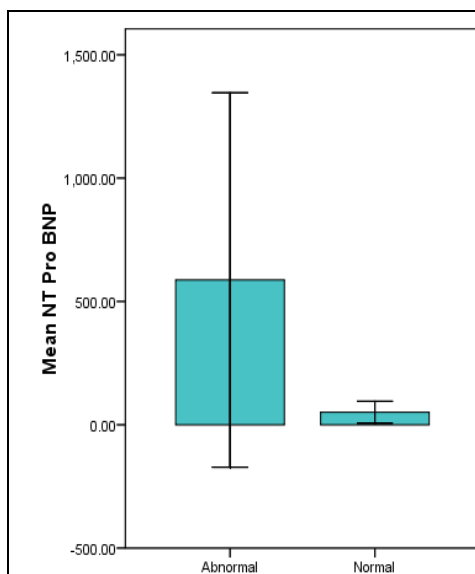


Figure no.1:- Comparison of NT Pro BNP with ECHO findings.

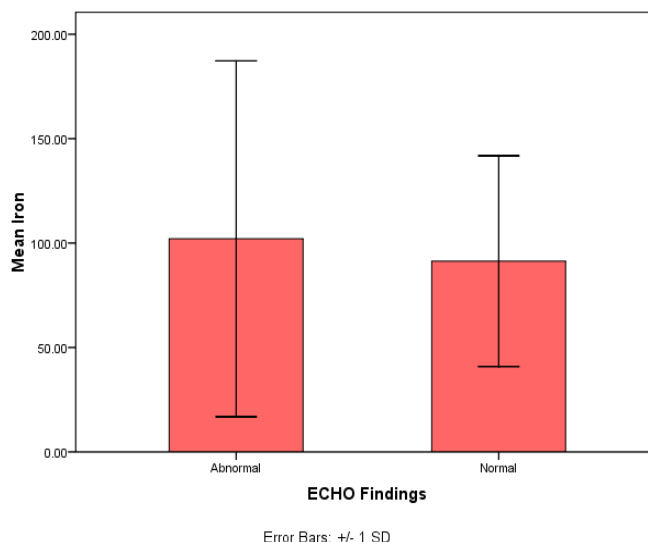


Figure no.2:- Comparison of IRON with ECHO findings.

	ECHO Findings	N	Mean	S.D.	S.E. Mean	T	P value
NT Pro BNP	Normal	57	50.88	44.95	5.95	-5.429	<0.0001
	Abnormal	13	587.29	759.07	210.53		
Iron	Normal	57	91.33	50.46	6.68	-0.601	0.55
	Abnormal	13	102.08	85.23	23.64		

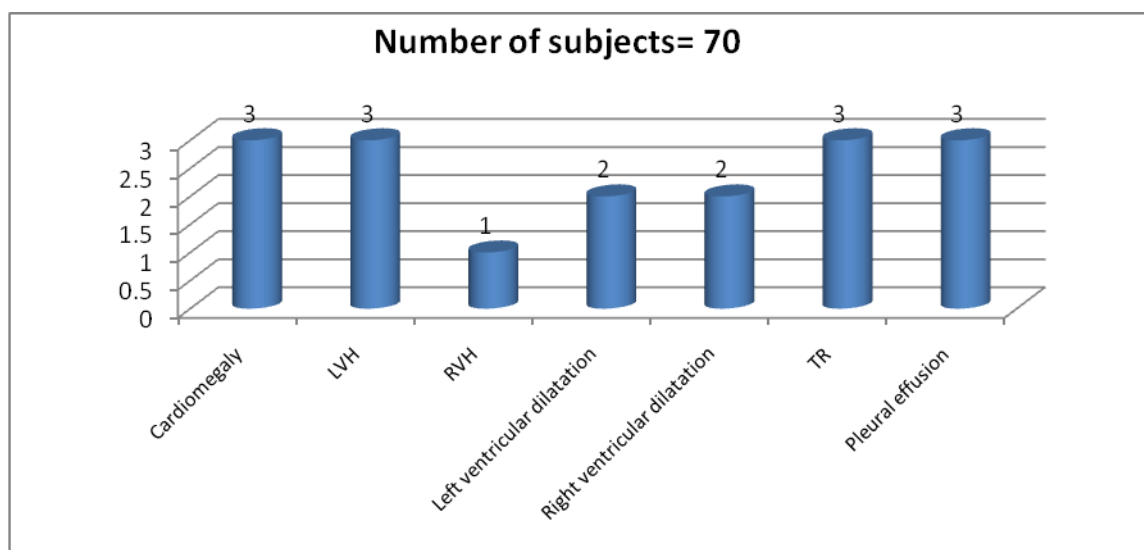


Figure no.4:- Frequency of various abnormalities detected on ECHO

DISCUSSION

It has been estimated that about 50% of the total world population of SCD patients resides in India especially in the central zone. Chhattisgarh is a newly created state of central India and most of the people of this region either belong to the tribal or backward classes. Occurrence of SCD is found to be very high in this state. [8]

This study was done to look for any association between serum Iron, TIBC, serum Ferritin, serum LDH and cardiac

dysfunction in sickle cell disease patient. Seventy patients of sickle cell disease were enrolled in this study according to predetermined exclusion and inclusion criteria. All the patients were subjected to echocardiography and estimation of serum NT-proBNP to determine the functional status of heart. S.Iron, TIBC, S.Ferritin, S.LDH were also measured in all study subjects.

It is well known fact that pulmonary artery hypertension (PAH) is the main cause

of development of cardiac abnormality in sickle cell patients. Because in these patients there is increase cardiac overload which causes increase in NT pro BNP level in blood and in echocardiographic findings we found various cardiac abnormality.

Our study shows frequency of various abnormalities detected on ECHO.

Total 70 sickle cell disease patient were enrolled for echocardiography and we found that 13 patient had abnormal echocardiography findings. In which 3(4.29%) had cardiomegaly, LVH 3(4.29%), TR=3(4.29%), pleural effusion 3(4.29%) and RVH in 1(1.43%), LV dilation 2(2.86%), RV dilation 2 (2.86%).

Study	Total patients	No. of Positive finding	% of positive finding	Echocardiographic finding
Raja Marouf et al (2014) [9]	57	14	24.5%	Tricuspid regurgitation
Barsaoui S et al (1991) [8]	41	30	73%	Cardiomegaly
Guedeny P et al (2018) [10]	60	27	45%	Left ventricle hypertrophy
Ricardo Beditrian et al (2018) [11]	60	30	50%	Left atrial hypertrophy Left ventricle hypertrophy

In present study correlation analysis of various parameters with NT Pro BNP was done. In which Mild positive correlation was detected between NT proBNP with AGE (0.003) and TIBC (0.004) which was found to be statistically significant.

In present study Association of LDH and Ferritin levels in 70 study subjects done. In which we found increase in LDH level in all the study subjects with high ferritin in 27(38.6%), low in 3(4.3%) and normal in 40(57.1%). So LDH is not the marker for the development of heart disease in sickle cell patients.

CONCLUSION

The study was conducted with an aim to find any association between serum biochemical markers and cardiovascular status in sickle cell disease patients. Serum LDH, ferritin, total iron and TIBC were estimated in all the patients. Echocardiography and serum NT- proBNP was done to assess the cardiovascular status.

Thirteen patients (18.57%) among the total enrolled 70 sickle cell study subjects were found to have some abnormality in Echocardiography who also had a significantly high serum NT-proBNP than the rest of the participants. Left ventricular hypertrophy and tricuspid regurgitation were the most common abnormality detected.

All the patients were having a high serum LDH level than the population

average. None of the parameters except serum TIBC had any significant co-relation with serum NT-pro BNP level or echocardiographic findings.

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