ORIGINAL ARTICLE

Left Ventricular Dysfunction in chronically transfused Patients with Thalassemia Major

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ABSTRACT

Background: Thalassemia is one of the most common single gene disorders effecting the population of Pakistan. It has been found to be one of major health problem in our country leading to morbidity as well as mortality. One of the major causes for both morbidity as well as mortality is due to the effect of the deposition of iron within the myocardium, which predominantly leads to heart failure. This can be either systolic or diastolic heart failure and may involve either the left or the right ventricle. Echocardiography helps to recognize ventricular dysfunction.

Aim: To determine the frequency of left ventricular dysfunction in chronically transfused children with thalassemia major having iron overload.

Methods: The descriptive cross-sectional survey was conducted at Children Hospital & Institute of Child Health, Lahore from 10-12-2012 to 10-06-2013. Two hundred and sixty diagnosed cases of thalassemia major, aged up to 18years were included in the study by purposive non-probability sampling. Children with history of acquired or congenital heart disease, concomitant infective process (aided by chest x-ray and echocardiography) and with previous history of cardiac surgery were excluded. Transfusional iron overload was defined as serum ferritin >1000ng/dl and left ventricular dysfunction in terms of ejection fraction (EF) (<30%).

Results: Two hundred and sixty patients with mean age 9.3 years±3.93 and mean weight 27.5 kg±11.1 were studied. Mean serum Ferritin came out 3067±1276 ng/dl while mean EF was 44.7±12.1%.10% patients were <30% EF while 90% had EF >30%. Serum Ferritin was negatively correlated with EF in Thalassemia patients.

Conclusion: Early left ventricular dysfunction is common in cases of thalassemia major with iron overload in chronically transfused children. There is need of timely and periodic screening of left ventricular dysfunction by echocardiography

Keywords: Left ventricular dysfunction, Iron overload, Thalassemia major, Echocardiography

INTRODUCTION

The normal adult haemoglobin molecule is made of two alpha and beta globin chains. The fetal haemoglobin contains two alpha and two gamma chains. The fetal haemoglobin is replaced by adult type haemoglobin within the first few months of life. The normal formation of the haemoglobin molecule allows the red blood cell to carry oxygen optimally to the tissues.

The thalassemias are a group of the haemoglobin disorders which arise from defective synthesis of either the alpha or the beta chains of haemoglobin molecule. It is basically a quantitative defect of normal haemoglobin production. It is one of the most common single gene disorders. In Pakistan it is thought that around 5000-9000 children are born every year with β-thalassemia. It is estimated that the carrier rate is 5-7%, with 9.8 million carriers in the total population[1]. Much improvement has taken place in regards to the management of this disease with better understanding of the need for blood transfusions, availability of centres providing the facility, as well as proper chelation in order to reduce the iron overload presented by the large quantity of transfusions given. This in turn has served to improve the quality of life as well as longevity of the patients. This has thus converted Thalassemia from a rapidly fatal disease to a chronic disease[2].

Chronic hemolytic anaemia that needs frequent blood transfusions unfortunately carry the adverse effect of iron overload. Iron gets deposited in multiple areas i.e., liver, heart, joints, reticulo-endothelial system and the endocrine glands. When there is deposition of iron within the heart it leads to cardiac dysfunction. There is free radical mediated cardiac

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tissue injury. Out of these complications; cardiomyopathy is the major cause of morbidity and mortality (respectively 63.6% to 71%). The predominant cardiac problem is congestive cardiac failure and fatal cardiac tachyarrhythmia that may result in sudden cardiac death. Echocardiography is major tool to recognize preclinical left ventricular dysfunction[3.4].

If the iron chelation therapy is ineffective this results in iron-induced myocardial damage. Monitoring the iron load in the body is an essential part of the management of transfusion dependent thallasaemics to reduce the risk of cardiac sysfuncton and liver cirrhosis.[1] Cardiac complications are the leading cause of death in thalassemia patients all over the world. Improved management protocols including regular chelation therapy and introduction of new chelators have reduced deaths due to cardiac complications of iron overload. Cardiac imaging provides the cornerstone of management of these patients in early recognition of cardiac dysfunction, but the process is complex and analytical methods need to be time adjusted in order to better predict the mortality risk[6,7,8].

A very high percentage of thalassemia patients have LV dysfunction that is due to a number of causes i.e., chronic anaemia, poor compliance with chelation therapy and lack of proper cardiac monitoring. Watchful monitoring of cardiac function may be of great help to reduce mortality and will also be helpful to reduce the morbidity of these patients[2]. Various modalities are being used for the determination of cardiac iron overload. These include Echocardiography, Radioisotope studies, Cardiac Magnetic Resonance Imaging[9]. Out of these, in our country where resources are limited; Echocardiography is the mainstay of diagnosis. It is less expensive and easier to perform. The main drawback is that it is operator dependent. A large number of measurements can be obtained from echocardiography. These can provide immediate and valuable data on the cardiac status and can also be compared to the clinical progress, as long as they are obtained by a skilled echocardiographer who is following internationally standardised protocols. On each visit the minimum data that should be measured include right and left heart dimensions, estimated intra-cardiac pressures (pulmonary artery pressure, systolic and mean) biventricular function (left ventricular fractional shortening and ejection fraction), and Doppler analysis of intra-cardiac flows. LV restrictive filling pattern is an ominous echocardiographic finding in thalassemia major (TM)[10]. In a study done by Arshad et al[2] found that 38% children had LV dysfunction. This indicates that the heart is getting stiff and is unable to dilate and fill properly during diastole. This is usually due to the deposition of iron within the myocardium.

Duration and frequency of transfusions give us an idea about iron overload and cardiac status of the patient but serum ferritin is best indicator of iron overload.[5] Various chelation regimens are being currently used, all having variable compliance. Poor compliance to chelation therapy due to non-availability or non-affordability in our country contributes a great deal to the morbidity and mortality. In a developing country like ours, where monetary constraints pose huge problems, the best modality of study of cardiac iron overload is 2 D echocardiography. This provides a great deal of information about the cardiac status and response to treatment. Regular monitoring of cardiac function by echocardiography may be of great help in significant reduction of morbidity and mortality and will improve the quality of life and wellbeing of these patients.[2] Early detection of cardiac dysfunction may help in preventing further cardiac damage by introducing early treatment with chelation therapy thereby reducing iron overload. Cardiac dysfunction has been studied in many adult patients and there are few studies in children especially in patients younger than 10 years.[11] Children are not young adults. Their physiology differs according to age. Thalassemia patients in our population usually die before reaching adult age mostly due to cardiac complications.

SUBJECTS AND METHODS

The descriptive cross-sectional survey was conducted at Children Hospital & Institute of Child Health, Lahore from 10-12-2012 to 10-06-2013. Two hundred and sixty cases of thalassemia major, who had been diagnosed on basis of Hb electrophoresis, aged up to 18 years were included. Children with history of acquired or congenital heart disease, concomitant infective process (aided by chest X-ray and echocardiography), and with a history of cardiac surgery were excluded. The left ventricular dysfunction was assessed by using echocardiography. Ejection fraction was noted and subsequently categorized into two groups i.e. below and above 30% ejection fraction. Transfusional iron overload was defined as serum ferritin >1000ng/dl and left ventricular dysfunction in terms of ejection fraction (EF) (<30%). Data was entered and analyzed by using SPSS-19.

RESULTS

There were 260 patients, out of which 145 (56%) patients were males and 115 (44%) were females, mean age was 9.3±3.93. Mean serum ferritin came out 3067±1276 ng/dl. Patients were divided into two

groups i.e. <2000 and >2000. 28% patients had serum ferritin <2000 ng/dl while 72% had Serum ferritin >2000 ng/dl. The ejection fraction found 10.4% patients were <30% EF while 89.6% had EF >30% with mean 44.7±12.1% (Table I). Age showed a modifying effect on ejection fraction (EF) of beta-thalassemia patients and found significant relation (p=0.0001) [Table 2]. But there was no effect of gender on EF and found non-significant relation (p = 0.7) [Table 3]. Ejection fraction and serum ferritin was significantly associated with one another (Table 4).

Table 1: Demographic information of the patients

Variable	No.	%
Gender		
Male	145	55.8
Female	115	44.2
Age (years)		
< 10	156	60.0
>10	104	40.0
Ejection Fraction (%)		
< 30	27	10.4
> 30	233	89.6
Serum Ferritin (ng/dl)		
<2000	73	28.0
>2000	187	72.0

Table 2: Comparison of ejection fraction with age

Ejection fraction (%)	Age (years)		Total
	Below 10	Above 10	
Below 30	3	24	27
Above 30%	153	80	233
Fisher's Exact Test = 0.0001			

Table 3: Comparison of ejection fraction with gender

Ejection fraction (%)	Gender		Total
	Male	Female	
Below 30	16	11	27
Above 30%	129	104	233
Fisher's Exact Test = 0.700			

Table 4: Comparison of ejection fraction with serum ferritin

Ejection fraction	Serum ferritin		Total
	Below 2000	Above 2000	
Below 30	1	129	130
Above 30%	72	58	130
Fisher's Exact Test = 0.000			

DISCUSSION

In individuals with thalassemia major there is a complete absence of beta globin chains production leading to suppression of normal haemoglobin production. This is a major public health problem in our country. The development of regular transfusions and iron chelation therapy has significantly improved the quality of life and transformed thalassemia from a rapidly fatal disease to a chronic disease compatible with prolonged survival.

Chronic anaemia requiring repeated transfusions carry the adverse effect of iron overload in these patients. There is extravascular haemolysis and also an increased intestinal absorption of iron that results in systemic iron overload.

Due to in-effective iron chelation therapy, many patients sustain iron induced myocardial injury. The monitoring and treatment of iron overload with proper chelation therapy in transfusion dependent thalassemia patients is essential to prevent fatal complications

Myocardial iron deposition damages the cardiac myocytes. It leads to hypertrophy, degeneration and dilatation of the heart muscle. This is usually in the form of patchy involvement of the ventricles. The injury to myocytes also causes conductive disturbances and tachyarrhythmia. The regular assessment of cardiac status can help in identifying the early stages of cardiac dysfunction and allows early intervention[13]. The multidisciplinary team management would involve the regular advice by cardiologist to establish the best treatment protocols.

Various modalities are being used for the determination of cardiac complications related to iron overload. These include ECG, Echocardiography, Radioisotope studies; Cardiac Magnetic Resonance Imaging[12]. Echocardiography is relatively easily available.

Echocardiography is easy to use, reproducible and non-invasive way of recording early cardiac dysfunction in thalassemia major patients. It serves as a tool to monitor the cardiac status and in the assessment of the effectiveness of the chelation therapy. In this study, we found LV systolic dysfunction in 10% of patients if EF is taken less than 30% but came 50% if dysfunction is defined below 40%. Age was confounding factor in determination of EF. Similarly serum ferritin has high correlation with EF. Our study did not match with previous Pakistani study done by Arshad et al[2], which concluded that 38% children had LV dysfunction.

Mean age was 9.3 years so we divided the subjects group into two groups above and below 10 years. Severe LV dysfunction was defined as ejection fraction below 30% there were only 27 patients (10.4%). To comply with the definition criteria to detect early changes in ejection fraction we redefined early LV dysfunction as EF below 40%. This definition screened maximum number of the patients. We found 130 patients (50%) have ejection fraction below 40%. When we compared our results with the already done Pakistani study by Arshad et al[2], there were contradictory results. They had concluded that 38% people suffer from LV dysfunction. The definition

of LV dysfunction was same as 30%. Although the study showed the mean age same as ours but it was a very small study, only 50 patients were included and there is no stratification on the basis of serum ferritin.

CONCLUSION

Early left ventricular dysfunction is common in cases of thalassemia major with iron overload in chronically transfused children. There is need of timely and periodic screening of left ventricular dysfunction by echocardiography.

REFERENCES

1. Ansari SH. Molecular epidemiology of β-thalassemia in Pakistan: far reaching implications. Int J Mol Epidemiol Genet 2011;2(4): 403–8.
2. Arshad MS, Haider SN. Evidence of abnormal left ventricular function in patients with thalassaemia major: an echocardiography based study.J Ayub Med Coll Abbottabad 2009;21(2):37-41.
3. de Gregorio C, Piraino B, Morabito G, Salpietro CD, Coglitore S. On the use of conventional and tissue Doppler echocardiography in patients with β-Thalassemia major and myocardial iron-overload: Preliminary data by a single centre study. Int J Cardiol 201; 145(3): 490-92.
4. Malcolm Walker, J. and Nair, S. Detection of the cardiovascular complications of thalassemia by echocardiography. Ann NY Acad Sci 2010:1202: 165–72.
5. Kell DB. Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. BMC Med Genomics 2009;2:2.
6. Chouliaras G, Yiannoutsos CT, Berdoukas V, Ladis V. Cardiac related death in thalassaemia major: time trend and risk factors in a large Greek Unit.Eur J Haematol 2009;82(5):381-7.\
7. Maggio A, Vitrano A, Capra M. Improving survival with deferiprone treatment in patients with thalassemia major: a prospective multicenter randomised clinical trial Under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies. Blood Cells Mol Dis 2009;42:247–51.
8. Tanner MA, Galanello R, Dessi C. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. J Cardiovasc Magn Reson 2008;10:12.
9. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel MB. Cardiac T2* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major. Circulation 2009; 120: 1961-8.
10. Efthimiadis GK, Giannakoulas G, Hassapopoulou HP, Karvounis HI, Tsikaderis DD, Styliadis IH, Parcharidis GE. Prognostic significance of right ventricular diastolic function in thalassaemia major. Swiss Med Wkly 2008; 138(3-4): 52-4.
11. Noori NM, Mehralizadeh S. Echocardiographic evaluation of systolic and diastolic heart function in patients suffering from beta-thalassemia major aged 5-10 years. Anadolu Kardiyol Derg 2010; 10(2): 150-3.
12. Thalassemia International Federation: Guidelines for the clinical management of thalassemia 2nd edition. 2008 [http://www.thalassemia.org.cy].
13. Aessopos A, Farmakis D, Loukopoulos D: Elastic tissue abnormalities resembling pseudoxanthomaelasticum in beta thalassemia and the sickling syndromes. Blood 2002, 99:30-35.