Frequency of cardiac complications in beta thalassemia major patients at thalassemia center, Sheikh Zayed Hospital, Rahim Yar Khan

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Abstract

Background: Heart disease is the leading cause of morbidity and mortality in patients with beta-thalassemia.
Objective: To assess the frequency of cardiac complications in Beta thalassemia major patients**.**
Methodology: Study design: Descriptive, cross-sectional study. Place and duration of study: Study was conducted in "Center for Thalassemia Care", Sheikh Zayed Hospital, Rahim Yar Khan, for a period of 6 months from 1st July to 31st December 2015. A total of 155 patients of Thalassemia major were included in this study. Data analysis was done by SPSS version 19. The outcome variables were cardiomegaly, congestive cardiac failure, cardiomyopathy, pulmonary hypertension, pericarditis and arrhythmia.
Results: Out of 155 patients of Thalassemia major, 94 (60.6%) had cardiac complication; 89 (57.4%) had Cardiomegaly, 34 (21.9%) congestive cardiac failure, 16 (10.3%) Cardiomyopathy, 10 (6.5%) pulmonary hypertension, 1 (0.6%) Pericarditis and 1 (0.6%) had arrhythmia. Frequency of cardiac complications have significant association with age, duration of transfusion and serum ferritin level, reflecting that iron overload has central role in pathophysiology of cardiac complications in thalassemia major patients.
Conclusion: This study showed that cardiac complications were present in more than half of the cases, which results in increase mortality and morbidity in thalassemia major patients.

Key Words: Thalassemia major, Iron overload, Cardiac complications.

Introduction

Inherited hemoglobin disorders are amongst the most common single gene defects in human and thalassemia is the commonest of this group.[1] Thalassemia is inherited as autosomal recessive disorder which fully manifests clinically in homozygous state called thalassemia major/Beta-thalassemia, which is characterized by defect in the synthesis of the beta chains of hemoglobin which may manifest clinically as asymptomatic to severe anemia.[2]

Thalassemia occurs with a high frequency in a broad belt extending from the Mediterranean basin through to the Middle East, Indian subcontinent, and Southeast Asia.[3] Thalassemia is a growing global health problem due to extensive population migrations. About 3% of the world population (about 200 million people) are carriers of the β-thalassemia gene.[4,5] Worldwide 15 million patients have clinically apparent thalassemic disorder. About 100,000 babies worldwide are born with severe form of thalassemia each year.[1] In Pakistan, the carrier frequency of β-thalassemia is 5% - 8% and may increase up to 62.2% in immediate family members of thalassemia patients.[6,7] There are approximately 9 million carriers of β-thalassemia in Pakistan, resulting in birth of more than 5000 thalassemia major patients every year.[8,9,10] Presently there are estimated 100,000 cases of thalassemia in Pakistan, which makes up for almost 5% of world cases.[8-10] The only curative treatment for thalassemia major is bone marrow transplantation but it is very costly not easily available and not free from hazards.[11] In Pakistan, the main treatment option is repeated blood transfusion along with iron chelation therapy. The combination of regular blood transfusion and iron chelation therapy has remarkably extended the life expectancy of thalassemic patients who can now survive up to fourth and fifth decades of life in many centers of the world.[12] On the other hand, frequent blood transfusion has also lead to iron overload with many complications. Heart disease is the primary determinant of prognosis and survival in beta thalassemia. Despite the advances in therapeutic management of thalassemia major and the resulting substantial improvement of patient survival, heart disease always represent and still remains the primary cause of mortality and a major cause of morbidity.[13,14] Heart disease is responsible for more than half of the deaths in thalassemia major patients.[15] It may manifest as heart failure,

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cardiomyopathy, pulmonary hypertension, arrhythmias, pericarditis and myocarditis.[15-18] Chronic anemia results in cardiomegaly which can lead to CCF. On the other hand repeated transfusions to correct anemia lead to iron overload. Without iron chelation therapy transfusional iron overload can affect the heart function directly. So, both chronic anemia and iron overload are responsible for cardiac complications. The objective of this study was to assess the frequency of cardiac complications in beta thalassemia major patients.

Methodology

This cross-sectional study was carried out on 155 patients of Thalassemia major with age(5-16 years) who were registered at Centre for Thalassemia Care, Sheikh Zayed Hospital, RYK over a period of 06 months from 1st July to 31st December, 2015. Informed verbal consent was obtained from parents of all the patients and approved by ethical committee. The inclusion criteria was thalassemia major patients age 5-16 years, thalassemic patients receiving blood transfusion for more than 01 year and received at least 10 transfusions since diagnosis, and serum ferritin level >1000 ng/dl. Exclusion criteria was: Thalassemic patients receiving chelation therapy.

The data was collected in the form of history, clinical examination, chest x-ray from radiology department, electrocardiography and echocardiography from Cardiology department and serum ferritin level from Pathology department, Sheikh Zayed Hospital, Rahim Yar Khan. Data was analyzed on SPSS version 19.0. All the quantitative variables (total number of transfusions, duration of transfusions and serum ferritin level) were analyzed using mean and standard deviation. All the qualitative variables (cardiomegaly, congestive cardiac failure, cardiomyopathy, arrhythmias, pulmonary hypertension, pericarditis) were analyzed by taking frequency and percentages. Overall, cardiac complications was labeled "Yes" when any one of these individual complication was present. Risk factors like age, gender, duration of transfusion and serum ferritin level were stratified by applying chi-square test taken $p \leq 0.05$ as significant.

Results

Out of 155 patients of thalassemia major, 98 (63.2%) were male while 57 (36.8%) were female. Regarding age of thalassemia major patients, mean age was 7 ± 2.59 years. Regarding age distribution 131 (84.5%) were in age group of 5 –10 years and 24 (15.5%) were in age group of 11 – 16 years. Mean number of transfusions per patient was 64.5 ± 28.05. Mean Serum ferritin level was 3411.5 ± 1768.52 ng/L. As duration of transfusion is concerned, 78 (50.3%) patients were receiving blood transfusion for < 5 years, 56 (36.8%) for 5 – 10 years and 21 (12.9%) for >10 years. Regarding serum ferritin level, 26 (16.8%) have serum ferritin level < 2000 ng/l, 56 (36.1%) have ferritin level in the range of 2001 – 3000 ng/l, 26 (16.8%) have ferritin level 3001 – 4000 ng/l and 47 (30%) have serum ferritin level > 4000 ng/l. Total Cardiac complications and different cardiac complications among thalassemia major patients is shown Figure I and Table-I. Stratification of frequency of cardiac complications with gender, age, duration of transfusion and serum ferritin level is shown in Table-II.

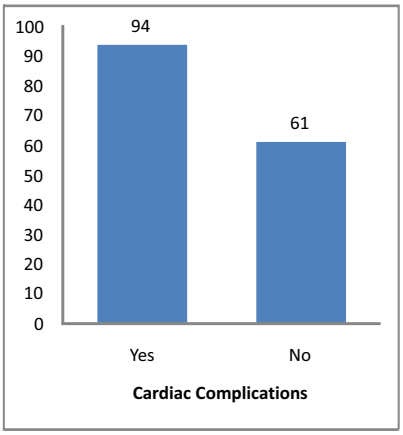
Table I: Frequency of Cardiac complications in thalassemia major patients.

Complication	Yes	No	Total
Cardiomegaly	89(94.68%)	5(5.31%)	94(100%)
Congestive Cardiac Failure	34 (36.17%)	60(63.82%)	94(100%)
Cardiomyopathy	16 (17.02%)	78(82.97%)	94(100%)
Pulmonary Hypertension	10 (10.63%)	84(89.36%)	94(100%)
Pericarditis	1 (1.06%)	93(98.93)	94(100%)
Arrhythmias	1 (1.06%)	93(98.93%)	94(100%)

Table II: Gender, Age, Duration of Transfusion & Serum Ferritin Level versus Cardiac Complications

Gender	Cardiac Complications		Total	P-Value
	Yes	No		
Male	58(59.2%)	40(40.8%)	98(100%)	0.6
Female	36(63.2%)	21(36.8%)	57(100%)	
Total	94(60.6%)	61(39.4%)	155(100%)	
Age (Years)				
5-10	73(55.7%)	58(44.3%)	131(100%)	0.003
11-16	21(87.5%)	3(12.5%)	24(100%)	
Total	94(60.6%)	61(39.4%)	155(100%)	
Duration 0f Transfusion (Years)				
<5	36(46.2%)	42(53.8%)	78(100%)	0.001
5-10	40(71.4%)	16(28.6%)	56(100%)	
>10	18(85.7%)	3 (14.3%)	21(100%)	
Total	94(60.6%)	61(39.4%)	155(100%)	
Serum Ferritin Level (ng/l)				
<2000	8(30.8%)	18(69.2%)	26(100%)	0.00
2001-3000	30(53.6%)	26(46.4%)	56(100%)	
3001-4000	20(76.9%)	6(23.1%)	26(100%)	
>4000	36(76.6%)	11(23.4%)	47(100%)	
Total	94(60.6%)	61(39.4%)	155(100%)	

Figure I: Frequency of cardiac complications in thalassemia major patients.



Discussion

Cardiac involvement is an important complication of thalassemia major, and results in increased morbidity and mortality. Disease mechanisms implicate chronic anemia due to infrequent blood transfusion and iron overload of the heart due to frequent blood transfusion. Transfusion-dependent patients receive 20 times the normal intake of iron, which leads to iron accumulation and damage in the liver, heart and endocrine organs. Although iron chelation has markedly improved outcomes, cardiac failure remains an important cause of death in thalassemia patient.[19]

In this study, total cardiac complications among thalassemia major patients were 60.6%, comparable with other studies, according to Borgne Pignatti C et al, heart dieses is responsible for more than half of the death in TM.[15]

In this study, patients in the age range of 5 – 10 years had cardiac complications in 55.7% cases as compared to patients in the age range of 11-16 years had cardiac complications in 87.5% cases. Patients who received transfusion for < 5 years, had cardiac complications in 46.2% cases, who received transfusion for 5-10 years had cardiac complications in 71.4% cases while those who received transfusion for > 10 year had cardiac complications in 85.7% cases. Patients who had serum ferritin level in the range of 3001-4000ng/l and >4000ng/l had cardiac complications in 76.9% and 76.6% cases respectively, as compared to those with serum ferritin level in the range of 2001-3000ng/l had complications in 56.3% cases, indicating that cardiac complications were mainly due to iron over load, comparable with one international study, mortality from cardiac iron overload continued to dominate the cause of death, accounting for 70% of cases.[20]

So frequency of cardiac complications (CC) increases with age, duration of transfusion and serum ferritin level with significant P- Value. Most of the patients had cardiomegaly on CXR without clinical feature of congestive cardiac failure. Out of 94 patients. 89 (94.68%) had cardiomegaly, while 34 (66.1%) had congestive cardiac failure. According to study conducted at Gomal Medical College, Dera Ismail Khan 25.5% patient of thalassemia major have Cardiomegaly on CXR, but they were not having other clinical feature of CCF.[21] Frequency of cardiomegaly increases with age, duration of transfusion and serum ferritin level. Patients in the age range of 11-16 years, 21 (87.5%) patients out of 24 had cardiomegaly. Patients who received transfusion for > 10 years, 18 (85.7%) had cardiomegaly out of 21. Patients having serum ferritin level >4000 ng/l, 36 (76.5%) had cardiomegaly out of 47 patients with significant P-value. Although frequency of cardiomegaly increases with duration of transfusion but patients who received transfusion for <5 years also had cardiomegaly in 46.2% cases, showing that along with iron overload other factors like chronic anemia has also important role.

Frequency of congestive cardiac failure also increases with age, duration of transfusion and serum ferritin level. Out of 24 patients of thalassemia major, 21 (87.5%) had cardiac complication in the age range of 11-16 years. Those patients who received transfusion for > 10 years, 18 (85%) had cardiac complications out of 21. Patients with serum ferritin level > 4000 ng/l, 36 (76%) has cardiac complications out of 47, with significant P-value.

Cardiomyopathy represents one of the most frequently found cardiac complications in thalassemia major patients. According to one international study CMP is a leading cause of morbidity and mortality (63.6-71%).[22] Frequency of cardiomyopathy increases with age, duration of transfusion and serum ferritin level. Patients in the age range of 11-16 years had cardiomyopathy in 3 (12.5%) out of 24. Patients who had received transfusion for 5-10 years, 40 (71%) had CC versus patients who had duration of transfusion >10 years had 18 (85%) patients having CC with P-value 0.001. Patients who had serum ferritin level > 4000 ng/l, CC was found in 36 (76%) patients out of 47 with

significant P-Value.

Pulmonary hypertension is a part of cardiopulmonary complication of beta-thalassemia. With improvements in the treatment of thalassemia major (TM) (regular transfusion and chelation therapy), frequency of pulmonary hypertension has been decreased in TM and considered to be primary cardiomyopathy in thalassemia intermedia (TI), but still important component of cardiac dysfunction in TM. In one international study of 110 patients, aged 32.5 ± 11.4 year, age related pulmonary hypertension was encountered in nearly 60% of cases, having caused right heart failure in 6 of them, all patients had reserved left ventricular systolic function.[23] In this study, pulmonary hypertension was found in 10 (10%) patients of thalassemia major out of 155.The association of age, duration of transfusion and serum ferritin level with frequency of pulmonary hypertension was not significant. Pericarditis is another common cardiac complication of thalassemia major. In this study pericarditis was found in only 1(0.6%) patient out of 155. Frequency of Pericarditis has been decreased now a days due to chelation therapy.[24] Although patients of TM in this study were not receiving chelation therapy but frequency for Pericarditis is less as compare to other studies.

In relation to age and duration of transfusion, pericarditis was found in 1 patient who received transfusion for >10 years, in the age range of 11-16 year with serum ferritin level >4000 ng/l, showing that frequency of pericarditis is affected by age, during of transfusion and serum ferritin level.

Arrhythmias, leading to sudden cardiac death, remains a serious concern in TM. In this study arrhythmia was found in only 1(1.06%) patient, out of 155 and had supraventricular tachycardia, comparable with one local study of Gomal Medical College at Dera Ismail Khan, in which SVT was observed in one out of 212 patients of Beta Thalassemia.[21] Similar to other cardiac complications frequency of arrhythmias is also affected by age, duration of transfusion and serum ferritin level.

Considering the gender, frequency of cardiac complications in TM patient, 58 (59.2%) male out of 98 had cardiac complications as compare to 36 (63.2%) female out of 57, same as for frequency of different cardiac complications. This shows that difference is not significant and there is no male female discrimination found.

Conclusion

Cardiac dysfunction is the main clinical problem in thalassemia major patients that may lead to early death. Both anemia and iron overload that is related to this order and its treatment can contribute to cardiac complications. In this study cardiac complications in thalassemia major patient were present in more than half of the cases and mainly iron overload due is responsible for these complications. As shown in this study frequency of cardiac complications have significant association with age, duration of transfusion and serum ferritin level. Chelation therapy can reverse iron mediated cardiac disease by removing iron from iron loaded cardiac cells as well as from circulation, contributing to heart failure.

There is a dire need to encourage chelation therapy along with regular blood transfusion to prevent complications from iron overload including cardiac complications, and also early diagnosis of cardiac involvement is crucial for a proper adjustment of therapeutic decisions in a timely manner, so that morbidity and motility from cardiac complications in thalassemia major patients can be decreased.

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