Heart Failure in Children having Thalassemia Major

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Abstract: Background- Thalassemia is a hereditary chronic hemolytic anemia that typically requires life-long blood transfusion therapy. Cardiac complication is the major cause of morbidity and mortality in those patients. Cardiac involvement is mainly expressed by cardiomyopathy secondary to iron over-load that progressively leads to heart failure and death. Objective- This study was undertaken to determine the type and immediate outcome of heart failure among children having thalassemia major. Methods- This prospective study conducted over 3 years in Dhaka Shishu (Children) Hospital. All children (2-16 year of age) having thalassaemia major were included when the diagnosis of heart failure was established. All children underwent a full clinical examination with X-ray chest, ECG, Color Doppler Echocardiography and serum ferritin level. The Chi-square test and un-paired t-test were used for statistical analysis. P value <0.05 was considered as statistically significant. Result- Among total 32 children, 25 (78.13%) had left sided heart failure (LHF) and 6 (18.75%) had right sided heart failure (RHF) and only one children presented with anemic heart failure. Overall mortality was 43.75% but individually, 66.66% (4/6) death occurred in RHF. Conclusions- Occurrence of LHF was significantly high in children having thalassemia major but mortality was relatively higher in RHF who had normal EF% with restrictive cardiomyopathy, however the difference was not statistically significant.

Keywords: Heart failure, Children, Thalassemia

1. Introduction

Thalassemia is an inherited disorder characterized by chronic hemolytic anemia which is caused by impaired production of one or more of the globin chain that make up the hemoglobin (Hb) tetramers [1]. Worldwide, it is one of the most common genetic disorders [2-3]. This hereditary hemolytic anemia typically requires life-long blood transfusion therapy for patient’s survival [4]. Regular blood transfusion prevents many complications in thalassemic patient which are introduced by ineffective erythropoiesis but on the other hand, can produce toxic iron accumulation in heart, endocrine glands and other organs [5]. Although, the heart is not the first target organ for iron deposition, cardiac iron overload is regarded as the most serious condition [6]. Iron is stored inside cardiomyocytes in three different forms- ferritin, hemosiderin and labile cellular iron, among which there is a constant flux [7]. In cardiomyocytes labile iron, the most toxic form, is quickly bound to ferritin and degraded to hemosiderin. This buffering mechanism creates clinically silent condition in spite of having increased storage of cardiac iron [8]. But this intracardiac iron buffering mechanism fail eventually in thalassemic patient with the increase of iron storage in the heart and ultimately high labile iron in cardiomyocyte produces oxidative damage to membranes, iron transporters and DNA, triggering cardiac dysfunction [9]. Heart injuries in iron overload include dilatation of atria and ventricles, arrhythmia, valvular dysfunction, pericarditis, cardiomyopathy and finally heart failure [10]. Cardiac failure is the main cause of death in thalassemic patient [11]. In 1964, Engle et al reported that 64% of their studied 41 thalassemic patients developed congestive heart failure and died mostly within a year from the onset of symptoms [12]. To manage this deleterious effects of transfusion iron overload, in mid 1970s parenteral deferoxamine was introduced. But in 1989, in spite of deferoxamine therapy, Zurlo et al showed that 64% of death rates were due to heart disease in a cohort of 1087 thalassemic patients [13]. The recent introduction of oral chelating agents including deferiprone and deferasirox as monotherapy or in combination with parenteral deferoxamine has enhanced the efficacy of iron chelation therapy significantly [14]. But despite of advances in therapeutic management of thalassemia major by intensification of iron chelation therapy, heart failure still remains the primary cause of
mortality and a major cause of morbidity [13,15]. According to Borgna-Pignatti et al the prevalence of heart failure in thalassemic patient born later than 1970 is 7% [16]. And Aessopos et al showed a prevalence of heart failure of 2.5% in a series of 202 well treated patients having thalassemia major [17]. Actually pathophysiology of cardiac dysfunction, as well as heart failure in thalassemia major is still poorly understood and multifactorial in etiology [18]. Although iron overload is still considered as the central role, immune-inflammatory and inherited components are considered as significant contributing factors [19-20]. Kremastinos DT et al studied 43 patients with thalassemic children in Bangladesh. They showed that the estimated prevalence of overt heart failure is 2.5% in a population with clinical evidence of myocarditis, documented mainly by myocardial biopsy [22]. Heart failure in thalassemia major patient is mainly expressed as two different phenotypes: a dilated cardiomyopathy phenotype, characterized by left ventricular dilatation and reduced contractility, leading to congestive heart failure and a restrictive cardiomyopathy phenotype, characterized by restrictive left ventricular filling with subsequent pulmonary hypertension, right ventricular dilatation and heart failure [23]. In these patients, clinical presentations of heart failure are variable. Classic left heart failure features are dyspnea on exertion, crackles of rales and orthopnea are a late finding; right heart failure symptoms including neck vein distension, hepatomegaly and peripheral edema are often the first clinical signs [24]. Whatever the causes or pathophysiology, heart failure is the primary cause of morbidity as well as mortality in thalassemia major patients [25].

Bangladesh is a developing country. It is presumed that approximately 6000 thalassemic children are born each year in Bangladesh [26]. Khan et al estimated that existing thalassemic patient in Bangladesh is about 1 lac [27]. But, yet there is very few published data regarding cardiac complications as well as heart failure in thalassemic children in Bangladesh.

The aim of this study was to determine the type and immediate outcome of heart failure among children having thalassemia major.

2. Methods

It was a prospective study conducted in Dhaka Shishu (Children) Hospital from January 2014 to December 2016. All children from 2 years to 16 year of age having thalassemia major were included in the study when the diagnosis of heart failure was established. Diagnosis of Thalassemia was confirmed by Hemoglobin Electrophoresis test. After enrolment, meticulous history regarding previous blood transfusion, chelation therapy, follow up status were taken in every case and all data were noted in a preformed datasheet with structured questionnaire. All children underwent a full clinical examination with X-ray chest, ECG, Color Doppler Echocardiography and serum ferritin level. All patients were treated by standard treatment regimen. Consideration was given to total number of cases, age at presentation, sex distribution, types of Heart failure, status of blood transfusion, iron chelation therapy, serum ferritin level and immediate outcome of the patient. Data entered and analyzed for frequency, percentages and means on SPSS version 12. The Chi-square test (for number of patients and mortality rate) and un-paired t-test (for serum ferritin level and EF%) was used for statistical analysis. P value less than 0.05 was considered as statistically significant.

4. Results

During the study period total 32 children were diagnosed as Thalassemia with HF in Dhaka Shishu (Children) Hospital. Among them 8 were diagnosed during the year of 2014. Eleven and 13 Thalassemic children developed HF during the year of 2015 and 2016 respectively. Among them male were 22(68.7%) and female were 10(31.3%) with a male female ratio of 2.2:1. Amongst the total children, 25 (78.13%) children had LHF and 6 (18.75%) developed RHF and only one (3%) child presented with anemic heart failure (Figure 1).
Out of total 32 children, 31 were previously diagnosed case of Thalassemia major and took blood transfusion (BT) at different interval of time. Among them 3 children were on irregular BT at local primary health care centers without any iron chelation therapy. Remaining 28 thalassemic children were on regular BT at 3-4 weeks interval. But out of them only 1 child was on regular oral iron chelation therapy, total 12 children took oral iron chelation drug irregularly and remaining 15 children did not take any iron chelation therapy. None of the child in this series took parenteral iron chelation drug. Only one child developed anemic HF. She was the youngest child (four years old girl) in the series, was an undiagnosed case of thalassemia major before admission. She admitted in hospital with severe pallor with HF. The status of blood transfusion and iron chelation therapy in all of the enrolled children of the current study are shown in Figure 2.

The age distribution of patients, serum ferritin level and ejection fraction in both right sided HF and left sided HF are shown in table1. We found that, occurrence of LHF was significantly high (p=<0.001) whose mean age was 12 ± 2 years but relatively older children (mean age 15.5 ± 0.83 years) developed RHF. All children had high iron load having serum ferritin level ranging from 1380 to 5400 ng/dl. But children with RHF had the significantly high serum ferritin level (mean: 2566.66±944.44 ng/dl). All thalassemic children who developed Left sided HF had low Ejection Fraction (EF) ranging from 28% to 44% (mean 34±4%) but all children having Right sided HF had restricted left ventricular (LV) filling and normal EF (mean 65.5±5.33%).

Table-I: Age distribution, S. Ferritin level & EF in children having Thalassemia major at the diagnosis of Heart Failure in DSH (n=32)

<table>
<thead>
<tr>
<th></th>
<th>Left sided HF</th>
<th>Right sided HF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients(n)</td>
<td>25 (78.13%)</td>
<td>6 (18.75%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age(yr)</td>
<td>Mean ± SD</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 ± 2</td>
<td>6-16</td>
<td></td>
</tr>
<tr>
<td>S. Ferritin (ng/dl)</td>
<td>Mean ± SD</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1620±180</td>
<td>3400-1380</td>
<td>0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>Mean ± SD</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34±4</td>
<td>28-44</td>
<td>0.001</td>
</tr>
</tbody>
</table>

In our series, total 14 children died (ten children having LHF and 4 had RHF). The overall mortality was 43.75%. But, we found that individual mortality rate was 40% (10/25) in case of LHF but proportionately higher (66.66%) among the thalassemic children having RHF (Table-II), however the difference was statistically not significant (p=0.238).

Table-II: Individual Mortality rate in children having Thalassemia major with HF

<table>
<thead>
<tr>
<th>Types of HF</th>
<th>No of Patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left sided HF</td>
<td>40% (10/25)</td>
<td>0.238</td>
</tr>
<tr>
<td>Right sided HF</td>
<td>66.66% (4/6)</td>
<td></td>
</tr>
</tbody>
</table>
5. Discussion

The study was conducted in Dhaka Shishu (Children) Hospital thalassemia center, the largest comprehensive referral center for children having thalassemia in Bangladesh. Our observation, there was obvious gradual increase in number of occurring HF among thalassemic children over the study period. Olivieri et al stated that intensified iron chelation therapy has improved the quality of life and survival rate of thalassemic patient, but failed to prevent heart failure yet [28]. Aessopos et al showed a prevalence of heart failure of 2.5% in a series of 202 well-treated patients with thalassemia major. The age of onset of heart failure in thalassemia patient is an important issue that has evolved during last decades. In the current study, we found, the mean age of thalassemic children was 12±2 year who developed left-sided HF and 15.5±0.83 year who developed right sided HF. Kremastinos DT et al found that the mean age in a group of 52 patients having thalassemia with heart failure was 24±5 year [23]. In a another study, Aessopos et a showed that, well treated patients with thalassemia developed heart failure at the mean age of 27±6 year [17]. All these study were conducted among adult population but in our series all patients were within pediatric age group. Probably for this region, in the current study, we found the relatively low mean age at which thalassemic children developed HF.

Our observation, majority of children (78.13%) having thalassemia developed left sided heart failure with left ventricular dilatation and reduced contractility (mean EF 34±4%). This finding is consistent with the study reported by Kremastinos DT et al, they found 83% of cases had left sided HF [23].

Myocardial iron deposition seems to be the triggr for the development of heart failure in thalassemia major [25]. In our series, almost all children with HF had the high serum ferritin level ranging from 1380 to 5400 ng/dl whom on non-optimal iron chelation therapy, but we found that the children who developed Right sided HF had significant (p=0.001) high iron burden but all had restricted left ventricular (LV) filling and normal EF (mean 65.5±5.33%). So, our observation only normal Ejection fraction in echocardiography does not give the total picture regarding thalassemia cardiomyopathy. Majd Z et al did not find any statistically significant relationship between the ejection fraction and serum ferritin levels to predict the complications of iron loading in thalassemic patients [29]. Tanner MA et al also revealed no significant correlation between left ventricular (LV) EF and iron level of the liver [30]. But Eghbali A et al found weak but significant association between ferritin level and echo parameters [31] and Monta zare et al demonstrated significant correlation between serum ferritin and left ventricular EF [32].

The outcome of heart failure in children having thalassemia has substantially improved during last decades. We found that overall mortality was 43.75% but mortality rate was relatively higher among the thalassemic children having RHF, however the difference was statistically not significant (p=0.038). By the five years follow-up in a large cohort of 1048 patients with thalassemia major, Kremastions DT et al found that acute HF developed in 23.4% of patient, majority of whom died within one year and 27.6% of patients developed chronic HF [22]. In 1964, Engle MA et al found that more than half of thalassemic patients with HF died within 3 months of diagnosis [33] and in 2001 Kremastions DT et al showed that with the intensified treatment thalassemic patient who developed HF, the 5 year survival was 48% [23]. In the current study we observe only the immediate outcome of HF in children having thalassemia, it is the limitation of the study. Further a large, multicenter and population-based study with long term follow-up is needed in order to illustrate the outcome of Heart Failure in children having thalassemia in Bangladesh.

6. Conclusions

Occurrence of Left sided HF was significantly high in children having thalassemia major. But mortality was relatively higher in Right sided HF who had normal EF% with restrictive cardiomyopathy, however the difference was statistically not significant.

7. References


