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Original Article

Paediatrics Section

Clinical Profile and Cardiac Complications of Haemoglobinopathies in Children at Tertiary Care Centre in Hyderabad, India: A Cross-sectional Study

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ABSTRACT

Introduction: Haemoglobinopathies include a group of inherited, chronic haemolytic anaemias which are transfusion dependent. Haemolytic Anaemia is a public health problem and has a high prevalence in Asian countries. Cardiac morbidity and mortality are burdens of these disorders as a result of chronic anaemia and iron overload despite iron chelation therapy. For this reason, it is recommended that regular cardiac evaluation should be done for all patients with haemoglobinopathies.

Aim: To study the clinical and laboratory profile of haemoglobinopathies and, the cardiac complications in transfusion-dependent patients by conventional echocardiography.

Materials and Methods: This hospital-based, cross-sectional observational study was conducted in Department of Paediatrics at Niloufer Hospital, Hyderabad, Telangana, India, from March 2020 to February 2022. Diagnosis was confirmed clinically or by laboratory including 2D Echocardiography (ECHO). Variable measures are demographic data of the child, clinical features, laboratory changes, and 2D ECHO changes. Continued variables (quantitative) were analysed calculating mean and standard deviation and performing T-test or Mann-Whitney's test.

Results: Total 68 patients who received blood transfusions were part of the research. The mean age of children with haemoglobinopathy was 4.8±2.86 years. Patients with serum ferritin >1000 mg/dL had more than 10 transfusions per year in 33 cases. The 2D ECHO was abnormal in 65% of patients, among these 61% of patients showed increased Left Ventricular (LV) mass/m^2 in ECHO, and 39% had normal LV mass/m^2. The mean ejection fraction in the patients was 64.82%. Pulmonary hypertension was seen in 25% of patients and 42 patients had mild tricuspid regurgitation.

Conclusion: There is a possibility of reducing the disease burden by health education and avoiding parental consanguinity as almost half of the patients have parental consanguinity. Serial echocardiography is recommended to screen for early discoveries of cardiac abnormalities in asymptomatic children and timely initiation of appropriate therapy.

Keywords: Anaemia, Chelation therapy, Echocardiography, Ferritins, Stroke volume

INTRODUCTION

Anaemia is the most prevalent problem in the world, particularly in developing countries. Haemolytic anaemia accounts for 5% of all anaemias affecting the paediatric population with a varied incidence in different parts of the world [1]. Haemoglobinopathies are the world's most common group of monogenic disorders with an estimated 7% of the global population carrying these diseases [2]. Haemoglobinopathies are Haemoglobin (Hb) defects include sickle cell anaemia (unstable Hb disease, HbC, HbD, HbE), thalassaemia (α or β-thalassaemia) and sickle cell β-thalassaemia, HbE β-thalassaemia, HbD β-thalassaemia, double heterozygous disorders [3].

Thalassaemia syndrome is estimated to be more than 200 million carriers of the β-thalassaemia gene all over the world, 40 million of them are in India alone. According to World Health Organisation (WHO), more than 40000 babies are born with thalassaemia each year, of whom about 25,500 have transfusion-dependent thalassaemias [4]. The carrier rate for the β-thalassaemia gene varies from 1% to 2% in Southern India, to 3-15% in northern India. Nearly 20 million people are affected in India by sickle cell anaemia. The term "sickle cell disease" includes all manifestations of abnormal HbS levels (proportion of HbS >50%). These include homozygous sickle cell disease (HbSS) and a range of mixed heterozygous haemoglobinopathies (HbS/β-thalassaemia, HbSC disease) [5]. Haemolysis is the premature destruction of RBCs. Anaemia results when the rate of destruction exceeds the capacity of the marrow to produce RBCs. Normal RBC survival time is 110-120 days (half-life is 55 to 60 days), and approximately 0.85% of most senescent RBCs are removed and replaced each day [6]. The marrow can increase its output to 2 to 3 folds actually with a maximum of 6-8 fold in long-standing haemolysis. The erythroid hyperplasia resulting from chronic haemolytic aneamia may so extensive that leads to extramedullary haematopoiesis and expansion of marrow spaces [7]. Haemoglobinopathies usually present with severe pallor, jaundice, hepatosplenomegaly, and growth failure. Features suggestive of thalassaemia are thalassaemia facies, pathological bone fractures, and cachexia. Sickle cell aneamia may be presented with pain due to vasooclusive crisis, dactilitis, cholecystitis, priapism, and acute splenic sequestration. Patients with β-thalassaemia major have severe chronic haemolytic anaemia and require regular blood transfusions from early childhood with iron chelators [8].

These complications are caused by chronic anaemia, hypoxia, secondary to iron overload. The mortality in haemolytic anaemia is usually caused by cardiac complications [9]. Common cardiac complications seen in these patients are congestive cardiac failure, cardiomyopathy, pulmonary hypertension, and arrhythmias [10]. With the introduction of blood transfusions and chelation therapy, morbidity and mortality have been delayed to decade later [11]. Though many studies are there regarding complications of haemoglobinopathies, this study gives special focus to cardiac complications. Early detection of cardiac involvement using ECHO leads to the prompt initiation of aggressive chelation therapy during the early stages when the condition can still be reversed. This was the reason, special emphasis was given to echocardiography and serum ferritin's role in the detection of early cardiac complications. This study was mainly aimed at low-resource settings where cardiac Magnetic Resonance Imaging (MRI) is not available. By carrying out this survey many management

requirements, including serum ferritin measurement, chelation therapy and echocardiography were met. Therefore, it is necessary to establish such services and prevent problems through cardiac screening.

The objective of this study was to

- To know the clinical profile of patients with abnormal haemoglobinopathy at the Hyderabad Paediatric Centre.
- Role of Echocardiography in diagnosing early cardiac complications.
- To find out the relationship between blood ferritin levels and cardiac function.

MATERIALS AND METHODS

This was a hospital-based, cross-sectional observational study conducted in Department of Paediatrics at Niloufer Hospital, Hyderabad, Telangana, India, from March 2020 to February 2022. The Institutional Ethical Committee's approval (ECR/300/inst/TN/2019/RR-16) and informed consent of parents was taken.

Sample size calculation: The sample size was calculated with prevalence based on previous studies with precision of 5% and type one error of 5% as 52 (mean prevalence of 3.5%) [12].

Inclusion criteria: This study included patients with abnormal haemoglobinopathy who received regular blood transfusions between the ages of 2 and 12 years. The diagnosis was confirmed clinically or by a laboratory that included a 2D ECHO.

Exclusion criteria: Patients with known cardiovascular complications or congenital heart disease, and patients or parents who do not consent to participate in the study were excluded from the study.

Study Procedure

Variable measures are demographic data of the child, clinical features, laboratory changes, and 2D ECHO changes. Clinically, it is difficult to diagnose haemolytic anaemia in the younger age group. Hence, these patients need laboratory investigations for diagnosis and early detection of complications and their management for a better outcome.

Laboratory investigation: The diagnostic workup for haemoglobinopathies is based on based on systematic, step-by-step examinations including medical history, clinical features, red blood cell morphology, hematological indicators with increased reticulocyte count, and echocardiography of complication. If the underlying defect remains unexplained despite rigorous testing, a genetic diagnosis is needed [13].

Test to establish the specific cause of haemolytic anaemia

- Sickling test
- Haemoglobin electrophoresis: it is the confirmatory test to detect haemoglobin defects

Tests to detect complications due to disease and due to management of the disease

- Tests to detect Iron overload: Serum Iron and serum ferritin. Serum ferritin should be estimated once every 6 months. Iron chelation therapy is started if the levels are elevated above 1000 ng/mL [14]. Serum ferritin greater than 2000 ng/mL or LIC greater than 15 mg/g dry weight was associated with an increased risk of complication and death. Serum ferritin remains an important predictor of survival but weakly correlates with the degree of cardiac siderosis [15].
- Tests to evaluate cardiac complications: Electrocardiogram (ECG), 2D Echocardiogram (2D Echo). The chest x-ray may show cardiomegaly.
- T2 weighted cardiac MRI is useful in assessing the severity of cardiac iron overload

Echocardiography is the most commonly used non-invasive technique for systolic and diastolic functions, ventricular size assessment, and evaluation for pulmonary arterial hypertension. Functional assessment and anatomic measurements by echocardiogram have been used to know the risk of cardiac iron load [16].

STATISTICAL ANALYSIS

Continues variables (quantitative) are analysed calculating mean and standard deviation and performing T-test or Mann-Whitney test. Categorically (qualitative data) are analyzed by calculating by frequency and performing the Chi-square test and Fisher's exact test. Statistical analysis was done by using Statistical Package for Social Sciences (SPSS) version 22.0 and Epi Info software for epidemiology developed by Centers for Disease Control and Prevention (CDC), United States of America. The p-value <0.05 was considered as statistically significant.

RESULTS

Total 68 patients who received blood transfusions were part of the research. The mean age of children with haemoglobinopathy was 4.8±2.86 years. There were 41 (60.30%) male and 27 (39.70%) female, with male:female ration of 1.51:1. Male were more affected by thalassaemia and sickle cell disease whereas, female were more affected by sickle thalassaemia. The mean age of both sexes is not significantly different (p-value=0.6783). The mean age of children with different haemoglobinopathies was significantly different (p-value <0.05). Thalassaemia was predominant clinical disease 47 (69.1%) followed by sickle cell disease in 13 (19.1%) and sickle thalassaemia in 8 (11.8%) [Table/Fig-1].

Disease phenotype	Frequency	Percentage (%)	95% Confidence limitation	
Sickle cell disease	13	19.1%	10.6	30.5
Sickle thalassaemia	8	11.8%	5.2	21.9
Thalassaemia	47	69.1%	56.7	79.8
Total	68	100.0%		

[Table/Fig-1]: Frequency and distribution of different haemoglobinopathies. Chi-square=39.735; Degree of Freedom=2; p-value <0.0001 (p-value <0.05 was considered as statistically significant)

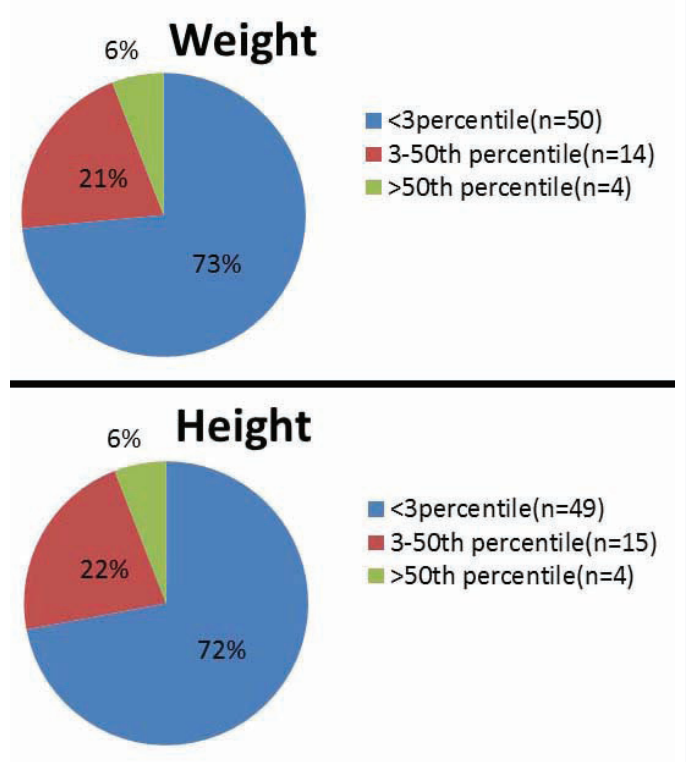
Most of the children are from a rural area (75%; n-51). Parental consanguinity (2nd degree consanguineous) was observed in 33 (48.5%) of cases, and there was no difference in parental kinship between different abnormal haemoglobinopathies. Most of the children are having significant growth impairment in both weight (<3 perentile- 73.50%; n=50) and height (<3 perentile- 72.10%; n=49). Pallor with weakness was noted in all cases. About 27 (39.70%) of children had haemolytic facies predominantly in β-thalassaemia (42%). Other features noted were icterus (28, 41.20%), joint pain (21, 30.90%), pain abdomen (20, 29.90%) and dactylitis (5, 7.4%). Cardiomegaly was noted in 4 (20.60%) of cases.

The predominant blood group observed was "O" (34, 50%) and Rh positive (67, 98.50%). Mean haemoglobin was similar in groups. Mean haemoglobin in sickle cell anaemia was 5.28 gm/dL, in sickle thalassaemia was 5.53 gm/dL and in thalassaemia was 4.54 gm/dL. Median reticulocyte count was 3% with a range of 2% to 28%. All disease groups had microcytosis (98.50%) and hyperchromasia (97.10%) [Table/Fig-2,3]. Sickle cells were noted in sickle cell disease and sickle thalassaemia. Mean serum ferritin by disease group is depicted in [Table/Fig-4]. Patients with serum ferritin >1000 mg/dL had more than 10 transfusions per year in 33 cases. Patients on Oral Chelation were 32.40% (n=22) and all received folic acid [Table/Fig-5].

In this study, 38 (56%) patients had tachycardia at admission, and ECG was abnormal in 25 (37%) of cases and normal in 43 (63%) cases. In the present study, 21 (24%) ferritin levels were normal, while 47 (76%) cases had serum ferritin levels above 1000 ng/dL. Right Ventricular Hypertrophy (RVH) was seen in a total of 6 (8.8%) patients, among these serum ferritin level was high in 4 (66%) and

Diagnosis	Consanguinity		Total
	No	Yes	
β-thalassaemia	17	25	42 (61.8%)
β-thalassaemia intermedia	4	1	5 (7.4%)
Sickle-β-thalassaemia	4	4	8 (11.8%)
Sickle cell disease	3	2	5 (7.4%)
Sickle trait	7	1	8 (11.8%)
Total	35 (51.5%)	33 (48.5%)	68 (100%)

[Table/Fig-2]: Association between haemoglobinopathies and parental consanguinity. Chi-square=7.972; Degree of Freedom (DF)=4; p-value=0.0926; contingency coefficient=0.324; (p-value <0.05 was considered as statistically significant)



[Table/Fig-3]: Weight and Height Frequency (Percentile) in study group.

Variables	Observations	Total	Mean	Variance	Standard deviation
Sickle cell disease	4	4966.7	1241.67	829682.35	910.86
Sickle thalassaemia	2	1726	863	284258	533.15
Thalassaemia	35	65906	1883.02	1673173.317	1293.51

[Table/Fig-4]: Mean serum ferritin levels in different Haemoglobinopathies.

Serum ferritin (ng/dL)	Frequency of transfusion (n, %)			
	<5	6-10	>10	Total
<1000	15 (78.94%)	5 (33.33%)	1 (2.94%)	21 (30.88%)
≥1000	4 (21.05%)	10 (66.66%)	33 (97.05%)	47 (69.11%)
Total	19	15	34	68

[Table/Fig-5]: Association between serum ferritin level and frequency of blood transfusion.
χ^2=33.0421, Degree of Freedom (DF)=2, the p-value <0.00001 (the result is significant at p<0.05)

normal in 2 (33.3%). Whereas, 24 patients had Left Ventricular Hypertrophy (LVH) in echocardiography [Table/Fig-6]. Of the 24 patients, 21 (87.5%) had serum ferritin levels above 1000 ng/dL. The ECHO was abnormal in 44 (65%) of patients, among these 27 (61%) of patients showed increased left ventricle mass/m^2 in ECHO and 17 (39 %) had normal LV mass/m^2. The mean ejection fraction in the study patients was 64.82% [Table/Fig-7]. Pulmonary hypertension was observed in 17 (25%) of patients, and 42 (61.76%) patients showed mild tricuspid regurgitation.

Serum ferritin	Right Ventricular Hypertrophy (RVH)		Total	Left Ventricular Hypertrophy (LVH)		Total
	Yes	No		Yes	No	
<1000 (ng/dL)	4 (66.66)	43 (69.35)	47 (69.11)	21 (87.5)	32 (72.72)	53 (77.94)
≥1000 (ng/dL)	2 (33.33)	19 (30.64)	21 (30.88)	3 (12.5)	12 (27.27)	15 (22.05)
Total	6	62	68	24	44	68

[Table/Fig-6]: Association between ventricular hypertrophy and serum ferritin.

Variables	No. of patients	Minimum	Maximum	Mean±SD	Variance
Ejection fraction (Normal range-56% to 78%)	68	48	80	64.82±8.203	67.29

[Table/Fig-7]: Ejection fraction mean and SD in study group.

DISCUSSION

Haemoglobinopathy is one of India's major public health problems. Most common cause of mortality in these patients were cardiac complications. The structure and function of the heart in these patients is primarily affected by increased cardiac output and iron overload. Also, the deposition of iron in the myocardium mainly leads to a decline in left ventricular function. A continuous and holistic approach is needed to prevent them and succeed in fighting. In this study children with haemoglobinopathies attending a government teaching hospital were studied to know the clinical, laboratory, and cardiac complications at the time of admission. In the current study, males (60.30%) were more affected than females (39.70%), similar to other studies done by Usha BK [17]. As 48.5% were born to consanguineous parents, the relatives of carriers should be screened and genetic counseling can prevent these births. Most of the children are from rural and tribal areas, their remoteness of living area contributes to infrequent medical care, follow-up, and complications.

Most of the children are found to have severe anaemia at admission and this explains the severe growth impairment. The mean age of the thalassaemia group of children is significantly lower than the mean age of sickle cell disease and sickle thalassaemia groups. The mean age of β-thalassaemia (4.13 years) was significantly different from that of sickle β-thalassaemia (6.92 years) and sickle cell disease (7.48 years). As most of the affected thalassaemia children present in infancy at around 4-6 months of age, this finding was significant as these children were screened for thalassaemia after the death of their elder siblings. Total 9 (14.1%) of these patients had a sibling who was affected with haemoglobinopathy. Mean haemoglobin values in the present study were sickle 5.28, 5.28 gm/dL in sickle cell disease, 5.53 gm/dL in sickle thalassaemia, 4.54 gm/dL in β-thalassaemia. Chronic, anaemia can cause growth retardation pulmonary hypertension.

Most of the children with haemolytic anaemia of different disease groups are having microcytic, hypochromic anaemia. In the present study, patients were further classified based on the serum ferritin value into those who had values more than 1000 ng/mL and the ones with less than 1000 ng/mL to know the extent of iron overload. Many children are showing elevated levels of serum ferritin, with a mean of 1481 ng/mL. Many patients are not in a position to get the serum ferritin levels monitored appropriately and need this test to be done as a free medical service. The thalassaemia group of children received significantly more blood transfusions.

Serum ferritin values were compared with the chest X-ray, ECG, and echocardiography findings to know the relation between cardiac function and iron overload. Left Ventricular Hypertrophy (LVH) had occurred more frequently than Right Ventricular Hypertrophy (RVH) and was seen more in patients with serum ferritin >1000 mg/dL. Cardiomegaly was observed in 14 (21%) children and can be due to chronic anaemia and volume overload rather than iron overload alone. Echocardiography showed that 25%patients had mild pulmonary hypertension and 61% had increased LV mass. Similar findings were

observed in a study done by Mohammad AM, and Koohi F et al., [18,19]. However, serum ferritin had a poor positive correlation with LV mass and pulmonary hypertension, hence it cannot be used as a single marker for cardiac iron load in transfusion dependant patients. An increase in LV mass and LV mass index is multifactorial includes chronic anaemia, tissue hypoxia, and iron overload. The ejection fraction was found to be mildly elevated than the normal values for age. Tissue doppler ECHO can able to identify systolic dysfunction even when left ventricular ejection fraction is still preserved [20].

Ibrahim MH et al., conducted a case-control study with 100 thalassemic patients below 18 years old to evaluate the value of tissue velocity imaging for early detection of myocardial dysfunction. Patients with thalassaemia were found to have right and LV systolic dysfunction on the basis of abnormal myocardial velocities [21]. Though T2 MRI is the gold standard in the diagnosis of cardiac iron deposition Echocardigraph still is used as a screening test [22]. Various specific cardiological parameters have been assessed to find out the efficacy in identifying early myocardial iron overload in thalassemic, to prevent cardiac complications [23].

According to literature, the major cardiovascular disorders of sickle cell disease are pulmonary hypertension, left ventricular diastolic dysfunction, and hypoxic myocardial ischemia [24]. Hypertrophy of the left ventricle in patients with sickle cell anaemia occurs significantly early and causes myocardial myopathy. The development of effective and inexpensive techniques for screening haemoglobin diseases is of great importance, especially in countries with high rates of these diseases [25].

Hence, echocardiography combined with an electrocardiogram should be used for regular periodic monitoring of transfusion-dependent thalassaemia patients. There is a significant burden of haemoglobinopathies and need to prevent it by health education and counseling, avoiding consanguineous marriages, and prenatal detection for necessary intervention.

Limitation(s)

Because the majority of children come from rural or tribal areas that are far from residential areas, medical procedures and follow-up were not feasible. Echocardiographic changes should be compared to MRI and followed-up on a regular basis. Community-level outcomes cannot be predicted because this was an institutional study. Another limitation of this study was the small sample size.

CONCLUSION(S)

Thalassaemia is the commonest haemoglobinopathy, followed by sickle cell disease. There is a possibility of reducing the disease burden by health education and avoiding parental consanguinity as almost half of the patients have parental consanguinity. Cardiac complications are common in patients with haemoglobinopathies due to chronic anaemia as well as transfusional iron load. Serial echocardiography is recommended to screen early discoveries of cardiac abnormalities in asymptomatic children and timely initiation of appropriate therapy. Though serum ferritin is useful to assess cardiac iron deposition, cardiac MRI which is considered as gold standard should be used.

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