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Pulmonary Function Abnormalities and their Association in Children with Beta-Thalassemia Major Age (10-18 years)

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Abstract: ***Objective: The objective of the study was to study prevalence of pulmonary function abnormality, severity and correlation with serum ferritin level. Materials and Methods: This was an observational Study done in tertiary care hospital setting, Inclusion criteria: Children with confirmed cases beta-thalassemia major aged 10–18 years on regular blood transfusion and chelation therapy for more than 6 years were included in the study. Exclusion criteria: Already diagnosed cases of pulmonary dysfunctions, CHD were excluded from the study. We performed a thorough clinical and physical examination before enrolling children to our study and blood sample were sent for Hb and serum ferritin before blood transfusion (BT). PFT was done within 24 h of BT using spirometer (Helios-401). Statistical analysis was done using SPSS (Version22). Results: 60 children enrolled in the study of age group 10 -18 year with M:F ratio 2:1. The pulmonary dysfunction was present in 33 (55%), but none of them had respiratory symptoms. The pulmonary dysfunction observed was restrictive 31 (51.7%), obstructive 1 (1.7%), and combined 2 (1.7%). A reduced forced vital capacity (FVC) % in 33 (73.3%). Risk factors such as, age at 1st transfusion, and serum ferritin level were significantly associated with pulmonary dysfunction (P< 0.05). There was no correlation between duration of chelation therapy. However, PFT values were found to be decreased in patients with a high serum ferritin (>2500 ng/ml), these differences were statistically significant. Conclusion: Abnormal patterns of lung function were common (restrictive type, predominant), even though none of these children had any respiratory symptoms.***

Keyword: thalassemia major, pulmonary function abnormalities, restrictive abnormality, serum ferritin

1. Introduction

Thalassemia is most common monogenic disorder of autosomal origin worldwide. About 10% of the total world thalassaemic are born in India every year.[1] In India, the prevalence of beta-thalassemia is 1–17% and carrier frequency is 3–4%.[2]As treatment of thalassemia evolved over years like availability of blood transfusion and chelation therapy had lead dramatic improvement in quality of life in these children. Regular BT causes generalized iron overloading in organs such as heart, liver, and pancreas. Lung impairment in thalassemia is also noted. Although, it does not produce any symptoms and is not the most significant clinical manifestation of thalassemia.[3]

Although pulmonary dysfunction is not the most significant clinical manifestation of chronically transfused thalassemic patients but a certain reduction of pulmonary functions has been reported to occur in most subjects with β-thalassemia.[4]Different types of pulmonary function abnormalities have been described in β-thalassemia major patients. A restrictive pattern has been reported as the most frequent abnormality in the pulmonary function test in thalassemia patients in the literature. However, airway obstruction, diffusion impairment or small-airway disease are also reported.[5]

The main pathology in causing pulmonary dysfunction is not well defined in literature, but in various studies positive association has been found with high serum ferritin levels. However, lung dysfunction has never been adequately focused upon and remains to be one of the least understood complications, hence, we propose this study to know the pattern of lung function abnormalities and prevalence. The reported prevalence of pulmonary function abnormality in literature varies between 36.1% to 95%. We planned this study to collect the data on the prevalence andspectrum of various pulmonary function abnormalities in regularly transfused beta thalassemic children in North Indian tertiary care centre. We also looked for the correlation between pulmonary function abnormalities and various parameters like serum ferritin levels, average pre transfusion haemoglobin and duration of chelation therapy if any.

2. Material and Method

It was a prospective observational study done in North Indian setting during February 2019 toJune 2020, in children aged between 5 and 18 years with beta-thalassemia major in outpatient department and Thalassemia day care center (TDCC), department of Paediatrics and department of Pulmonary and Critical care Medicine, PGIMS Rohtak.

Inclusion Criteria

Children with beta thalassemia major in age group of 10-18 years who were otherwise asymptomatic and on regular blood transfusions and chelation therapy for at least last 5 years.

Exclusion Criteria

1) Children less than 10 and more than 18 years
2) Children having recent/past history of allergies /asthma or any respiratory illness in last two weeks.
3) Children with known cardio-pulmonary, CNS or musculoskeletal illness likely to alter the study results.
4) Parents denied consent or not willing for follow up.
5) Children with observed forced vital capacity (FEV1) less than 1 litre as it was not supposed to be interpreted by the spirometry machine we used for the study.

Sample Size:

At commencement of study there were 112 registered thalassaemic patients between age group of 10-18 years at Thalassemia day care center (TDCC) of our institute. Depending on a very high prevalence ranging between 36.1 % to 95% of reported pulmonary function abnormalities in various previous studies. Expecting around 70-80% consent rate by the patients initially we expected 75-80 patients to be eligible as cases for present study. We screened every patients between 10-18 years for enrollment but due to COVID pandemic finally we were able to enroll 60 patients for our study.

3. Methodology

We took ethical clearance from ethical committee before commencement of the study. Children who fulfill the inclusion/exclusion criteria for the study were selected. Informed and written consent was obtained from parents of all cases. All enrolled children were enquired forS detailed clinical history including age at first BT, Haemoglobin at first BT, duration of iron chelation therapy, and general physical examination findings which were recorded. Pretransfusion blood samples for haemoglobin and serum ferritin estimation were collected. All selected patient were subjected to pulmonary function test in the day or day after depending upon availability of slots for PFT.

The following parameters were recorded in the spirometry – forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1), ratio of FEV1/FVC, peak expiratory flow rate (PEFR), and forced expiratory flow between 25 and 75% vital capacity (FEF 25–75%). Interpretation of PFT was done according to the recommended guidelines by asthma training module.[17]

Statistical Analysis

All statistical procedures were performed using the Statistical Package for Social Sciences (SPSS) Window. Data was summarised by the mean ± SD or number (percentage). For the comparison of means, unpaired, independent sample *t*-test was used. For the comparison of qualitative variables, a χ^2 test was used. For comparison between more than two groups, the anova test was used. The Spearman correlation coefficient will be used to rank different variables as either positive or inverse. The degrees of association between pulmonary function tests (PFTs) and other parameters, including serum ferritin levels, and pre-transfusion Hb were determined using the Spearman/ Pearson correlation test. The variables were investigated using visual histograms and probability plots. A *P*-value <0·05 was considered statistically significant.

4. Results

Total number of children included in the study was 60 cases out of which 40 (66.7%) male cases and 20 (33.3%) female cases. [Table 1]

Out of 60 children with thalassemia major 33(55%) had abnormal PFT. Among 33 children with pulmonary dysfunction, 31 (88.5%) children had restrictive pattern, 1 (1.7%) children had obstructive pattern, and 1(1.7%) children had combined pattern out of which 16 (26.7%), 11(18.3%), 2(3.3%) and 4(6.7%) showed mild, moderate, moderate to severe and severe pulmonary function abnormalities respectively 16(26.7%) had mild restrictive, 10(16.7%) had moderate, 1(1.7%) had moderate to severe restrictive and 4(6.7%) showed severe restrictive pattern[Table 2]. Mean serum ferritin levels in children with normal PFT, restrictive pattern, obstructive pattern, and combined pattern were 2474.70 ± 2150.58, 3051.10 ± 1463.54,1453, and 1430, respectively.[Table 3]. There was statistically significant difference in mean values of PFT parameters and serum ferritin level and age at diagnosis between groups those who had restrictive pattern were diagnosed at later age than others[Table 4] however there was no significant association of age, BMI, and pre-transfusion Hb and duration of chelation therapy with respect to serum ferritin levels; however, FVC and FEV1, PEFR, and PEF 25–75% values were decreased in children with a high ferritin level (>2500 ng/ml) in our study as compared with children with a low ferritin level (<2500 ng/ml), but these differences were statistically not significant.

Table I: Baseline epidemiological profile of the study subject at enrollment

Parameters	Mean±SD	Range
Age at enrollment for study (years)	13.23 ± 2.55	7.00 - 18.00
Mean age at diagnosis (months)	9.45 ± 5.30	1.00 - 24.00
Weight (kg)	33.22 ± 9.10	20.00 - 58.00
Height (cm)	140.67 ± 12.91	112.00 - 165.00
BSA (m^2)	1.15 ± 0.20	0.82 - 1.62
Duration of chelation therapy (years)	6.45 ± 2.18	5.00 - 15.00
Age at 1st Transfusion (Months)	9.42 ± 5.31	1.00 - 24.00
Hemoglobin at 1st Transfusion (g/dL)	4.76 ± 0.93	1.00 - 7.00
Frequency of Transfusion (Days)	17.02 ± 2.66	15.00 - 25.00
Average Pre-transfusion Hemoglobin in Last 1 Year (g/dL)	8.13 ± 0.38	7.00 - 9.00
Average Serum Ferritin in Last 1 Year (ng/mL)	2739.57 ± 1806.57	521.00 - 11000.00

Table 2: Abnormalities of Pulmonary Function Test (PFT) in study participants (n=60)

PFT Interpretation		Number (Percentage)
PFT Abnormalities	Present	33 (55.0%)
	Absent	27 (45.0%)
Pattern of PFT Abnormalities	None	27 (45.0%)
	Obstructive	1 (1.7%)
	Restrictive	31 (51.7%)
	Mixed	1 (1.7%)
Severity of PFT Abnormalities	None	27 (45.0%)
	Mild	16 (26.7%)
	Moderate	11 (18.3%)
	Moderate-Severe	2 (3.3%)
	Severe	4 (6.7%)
PFT Interpretation	Normal	27 (45.0%)
	Mild Restrictive	16 (26.7%)
	Moderate Restrictive	10 (16.7%)
	Moderate-Severe Restrictive	1 (1.7%)
	Severe Restrictive	4 (6.7%)
	Moderate Obstructive	1 (1.7%)
	Moderate-Severe Mixed	1 (1.7%)

Table 3: Comparison of the 4 Subgroups of the Variable Pattern of PFT Abnormalities in Terms of Average Serum Ferritin in Last 1 Year (ng/mL) (n = 60)

Average Serum Ferritin in Last 1 Year (ng/mL)	Pattern of PFT Abnormalities				Kruskal Wallis Test	
	None	Obstructive	Restrictive	Mixed	$\chi 2$	p value
Mean (SD)	2474.70 ±2150.58	1543.00 (NA)	3051.10 ±1463.54	1430.00 (NA)	9.567	0.023
Median (IQR)	1676 (1340.5-2521)	1543 (1543-1543)	2800 (2050-3450)	1430 (1430-1430)		

Table 4: Comparison of the 4 Subgroups of the Variable Pattern of PFT Abnormalities in Terms of Age at Diagnosis (Months) (n = 60)

Age at Diagnosis (Months)	Pattern of PFT Abnormalities				Kruskal Wallis Test	
	None	Obstructive	Restrictive	Mixed	$\chi 2$	p value
Mean (SD)	7.33 ± 4.17	8.00 (NA)	11.32±5.69	10.00 (NA)	11.165	0.011
Median (IQR)	7 (6-8)	8 (8-8)	9 (8-12)	10 (10-10)		
Range	4 - 24	8 – 8	4 – 24	10 – 10		

5. Discussion

Pulmonary abnormality is among the least studied complication in children with beta-thalassemia major, most probably due to the lack of any pulmonary symptoms or if presents masked by anaemia or cardiac causes (cardiomyopathy).[6] To look for prevalence of pulmonary abnormalities we conducted this study on our centre.In study conducted in our centre out of 60 enrolled patients between 10-18 years, 40 were males and 20 were female with mean serum ferritin of 2740±1806ng/dl. Out of 60 patients 55 % showed some pulmonary function abnormalities which were higher in females (40%) as compare to males (33.3%). The restrictive abnormality was found in 31 (88.5%), obstructive 1 (5.7%), and combined 1 (5.7%). Prevalence of pulmonary abnormality in our study was 55%(33 out of 60%), in which 16 (26.7%) had mild pulmonary dysfunction 11 (16%) had moderate, 2 patient (3.3%) had moderate to severe and 4(6.7%) had severe restrictive lung function abnormality. In other studies also restrictive abnormality was majorly found.[7-16] In other studies Boddu et al[8]on 42 thalassemia major children 95% were having restrictive type of respiratory dysfunction as in our study(94%). Majority (59.5%) had moderate lung dysfunction in our study majority had mild dysfunction (26.7%). The mean serum ferritin value in patients with severe respiratory dysfunction was 6275 ug/l, which is significantly higher when compared to moderate (4249 ug/l) and mild (3066 ug/l), mean serum ferritin(2474±2150ng/) level in our study were quite lower than previous as we had enrolled only those patient who were on regular chelation for 5 years we observed a higher serum ferritin of serum 3051ng/dl as compare to obstructive1430ng/dl and mixed group1543ng/dl in other studies also similar results were found[17,18]. From previous various studies it was found that serum ferritin of >1500ng/dl was significantly associated with restrictive abnormality.[18] Explanation to their finding was that, level of serum ferritin is indicator of iron overload, more the ferritin more will be iron overload state, deposition of iron in pulmonary capillaries and alveoli, restrict the area for diffusion and gas exchange thereby causing restrictive abnormality[17]. In many other studies, different etiopathogenetic mechanisms for the development of restrictive lung dysfunction were reported such as multiple BT,[18] hypoxia, iron overload,[17]

We analyzed various risk factors for abnormal lung function including age, height, BMI, number of BT, duration of chelation therapy similar to previous studies[5].We observed a positive correlation between serum ferritin and age at diagnosis whereas no correlation found between age at enrolment and years of chelation therapy with pulmonary function abnormality.

Forced vital capacity (FVC%), forced expiratory volume in 1st second (FEV1%) values were lower in boys when compared to girls. PFT showed a restrictive pattern in the

study group (FEV1/FVC=>0.7) with significant involvement in 73.5% of cases (FEV1<80%). A statistically significant negative correlation was observed between age and FEV1% (r=-0.577, p=<0.01) highlighting the importance of duration of iron overloadfrom repeated blood transfusion.

In our study mean age at diagnosis (11.18±5.55Months) is significantly associated with presence of pulmonary function abnormality. We observed that those who were diagnosed and transfused early had pulmonary function abnormality less than who diagnosed at later age and received 1st transfusion at later age and also who present later had severely anemic than those who presents and diagnosed earlier this may probably explained by greater duration of hypoxic changes in their pulmonary capillaries that may result in restrictive Limited literature is available on significance of age at diagnosis and age at first transfusion on prevalence of pulmonary function abnormality.

In our study restrictive abnormality is significantly associated with serum ferritin level with p value of 0.023. Those who showed restrictive abnormality had serum ferritin(3051ug/dl) higher than those with none(2474ug/dl), obstructive(1540ug/dl) and mixed abnormalities(1430ug/dl). Serum ferritin levels were higher in moderate(2657ug/dl) to severe(3427ug/dl) group as compare to mild restrictive(2783ug/dl) group. Those with higher serum ferritin levels, also had greater reduction in FVC, FEV1, PEFR and increased FEV1/FVC results were concordant to previous studies[16,17]Serum ferritin levels >2500 ng/mL was strongest predicting factor for restrictive dysfunction.Guidotti[17] et al also reported that serum ferritin of>2500 associated with restrictive abnormality.

6. Conclusion

Although none of our patient show any respiratory complain almost 28.3% patient had mod to severe pulmonary function abnormalities out of 55% of prevalence. We suggest pulmonary function should be screened annually for all thalassaemic patient to prevent sequele and also some chest physiotherapy can be advised if pulmonary abnormalities were found to increase compliance of lung.

Declaration of patient consent
Patient consent taken before enrolment in study.

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Provided by institute in the form of permission for PFT assessment in thalassaemic children- No money burden imposed on attendant test was free of cost provided.

Conflicts of interest
There are no conflicts of interest

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