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Original Research Article

Study of pulmonary function tests in multitransfused children with beta thalassemia major: an observational study

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ABSTRACT

Background: Thalassemia is a hemoglobinopathy requiring multiple blood transfusions leading to iron deposition in various organs. Abnormalities in pulmonary function in thalassemia major patients have been found in various studies. Our aim was to study pulmonary function tests (PFT) in multitransfused children with beta thalassemia major.
Methods: PFT was done in forty beta thalassemia major (TM) patients and forty normal healthy age and sex matched individuals and the results were analyzed.
Results: Out of 40 thalassemia major patients, 20 (50%) had normal PFT and the rest 20 (50%) had an abnormal PFT out of which 18 (90%) had restrictive PFT and 2 (10%) had obstructive PFT. Out of 40 controls, all 40 (100%) had normal PFT.
Conclusions: Alteration of pulmonary function can be seen even in well-chelated TM patients. The respiratory system should be evaluated annually by PFTs even in asymptomatic patients to prevent pulmonary sequelae.

Keywords: Beta thalassemia major, Hemoglobinopathy, Pulmonary function tests

INTRODUCTION

Beta thalassemia major (β-TM) is caused by reduced βglobin chain synthesis.[1-3] Depending on the mutation and degree of fetal hemoglobin production, transfusions in thalassemia major (TM) are necessary beginning in the 2nd month to second year of life.[4,5] Signs of ineffective erythropoiesis like growth failure, bone deformities secondary to marrow expansion, hepatosplenomegaly are important variables in determining transfusion initiation.[6] Hemosiderosis develops after 1 year of chronic transfusion leading to alteration of lung functions with reduced lung volumes and capacities, lung fibrosis, interstitial edema and reduced diffusing capacity of the alveolar-capillary membrane.

The purpose of our study is to evaluate the pulmonary status in multitransfused children with beta TM by means of pulmonary function test (PFT) as in spite of chelation, many patients develop complications due to iron overload in multiple organs.

Objective of the study was PFT in multitransfused children with beta TM.

METHODS

This was a hospital based observational study conducted in the department of pediatric medicine, SMS medical college, Jaipur from May 2015 to June 2016.

Our study included 40 patients with β-TM, who were managed at dept. of paediatrics, SMS medical college, Jaipur, Rajasthan for monthly examination and blood transfusion during 2014-15 and also 40 age and sex matched healthy individuals used as control.

Eligibility criteria of study group included inclusion criteria in which children aged 6 year and above, diagnosed with beta TM, receiving multiple transfusions and whose parents give positive consent.

Exclusion criteria included children diagnosed with beta thalassemia major but less than 6 year or with respiratory or cardiac diseases.

Inclusion criteria were normal healthy age and sex matched individuals whose parents give positive consent.

Exclusion criteria were children with respiratory or cardiac diseases

All patients were older than 6 years of age and were able to perform pulmonary function test. At the time of the study, all patients were clinically stable and not in overt congestive heart failure or respiratory distress. These patients were receiving regular blood transfusion according to a standard protocol and chelation of iron with an aim to prevent high serum ferritin concentration. Written informed consent was obtained from the parents or patients before doing PFTs. Proforma containing general information like name, age, sex, father's name, address and contact number was filled. Relevant clinical history was taken including age at diagnosis, age at first transfusion, number of transfusions, duration of iron chelation therapy, if any. Physical examination was done recording vitals and systemic examination. Haemoglobin and serum ferritin levels were recorded. PFT was performed on the day scheduled for blood transfusion. Spirometer (Med Gv3 Jaeger) corrected for temperature, pressure and saturation of environment by a sensormedics was used.

The lung function tests were carried out and the results were expressed as a percentage of normal. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, peak expiratory flow (PEF), and forced expiratory flow between 25 and 75% of the exhaled vital capacity ($FEF_{25-75\%}$) were measured. Each test was performed 3 times and the best performance was selected. For the purpose of this study, the threshold of abnormality was identified as fewer than 80% of the predicted value for all parameters except $FEF_{25-75\%}$ for which 60% was taken as the threshold shown in the (Table 1).

Obstructive airway disease was defined as reduced FEV1 and reduced FEV1/FVC ratio i.e. less than 80% and restrictive airway disease was defined as a reduction of FVC less than 80% and FEV1/FVC equal to or more than 80%. The pulmonary deficits were classified as mild when FEV1 values were between 70 and 79% of predicted, moderate when between 60 and 69% of predicted and severe when <60% of predicted.[7] The results were presented as mean±SD.

Statistical analysis was performed with the Statistical package for social sciences (SPSS), trial version 23 for Windows statistical software package (SPSS inc., Chicago, Il, USA) and primer. The categorical data were presented as numbers (percent) and were compared among groups using chi square test. Normally distributed variables were summarized using mean±SD, and non-normally distributed variables were summarized using median and range. Differences among the groups was analyzed using the student T test for parametric data and Mann-Whitney U test for the non-parametric data. The test of normality was done by Kolmogorov-Smirnov test as observed FEV1:FVC% and PEF% were non parametric data.

Correlation analyses were performed using Pearson correlation coefficient (r=at least 0.8 very strong, 0.6 up to 0.8 moderately strong, 0.3 to 0.5 good and <0.3 is poor). Significance level for tests were determined as 95% ($p<0.05$). $P<0.05$ was considered statistically significant.

Table 1: Cut off values of pulmonary function test indices.

PFT indices	Normal (%)	Restrictive (%)	Obstructive (%)
FEV_1	≥80	<80 or normal	<80
FVC	≥80	<80	<80 or normal
FEV_1: FVC	≥80	≥80	<80
$FEF_{25-75\%}$	≥60	≥60	<60

RESULTS

The mean age of cases was 10.65 year and that of controls was 9.55 year. Among 40 cases, 31 (77.5%) were male while 9 (22.5%) were female with the male:female ratio being 3.4:1 The mean age at diagnosis was 1.84 year, the mean age at first transfusion was 1.85 year and the mean duration of transfusion was 8.8 year. The mean haemoglobin level was 8.05 g/dL and the mean serum ferritin level was 1459.13 ng/mL. The mean FEV_1 was 84.83% among cases and 101.43% among controls. The mean FVC was 85.88% among cases and 96% among controls.

The mean FEV1:FVC was 98.17% among cases and 106% among cases. The mean $FEF_{25-75\%}$ was 84.32% among cases and 83.35% among controls. The mean PEF was 79.3% among cases and 102.5% among controls (Table 2). Out of 40 thalassemic, 20 (50%) had normal PFT and the rest 20 (50%) had an abnormal PFT out of which 18 (90%) had restrictive PFT and 2 (10%) had obstructive PFT. Out of 40 controls, all 40 (100%) had normal PFT.

Table 2: Correlations.

Variables		No. of transfusions	Ferritin (mg%)	Duration of chelation (year)	Hemoglobin (gm%)	FEV1%	FVC%	FEV1:FVC%	FEF $_{25-75\%}$	PEF (%)
	N	40	40	40	40	40	40	40	40	40
FEV1%	Pearson Correlation	0.130	-0.140	0.182	0.014	1	0.857**	0.457**	0.279*	0.619**
	Sig. (2-tailed)	0.423	0.390	0.260	0.930		0.000	0.000	0.012	0.000
	N	40	40	40	40	80	80	80	80	80
FVC%	Pearson Correlation	0.285	0.027	0.296	-0.066	0.857**	1	-0.018	0.165	0.534**
	Sig. (2-tailed)	0.074	0.870	0.064	0.685	0.000		0.875	0.143	0.000
	N	40	40	40	40	80	80	80	80	80
FEV1:FVC%	Pearson Correlation	-0.332*	-0.183	-0.255	0.060	0.457**	-0.018	1	0.305**	0.292**
	Sig. (2-tailed)	0.036	0.258	0.113	0.715	0.000	0.875		0.006	0.009
	N	40	40	40	40	80	80	80	80	80
FEF$_{25-75\%}$	Pearson Correlation	-0.116	-0.134	-0.046	-0.002	0.279*	0.165	0.305**	1	0.398**
	Sig. (2-tailed)	0.476	0.410	0.777	0.993	0.012	0.143	0.006		0.000
	N	40	40	40	40	80	80	80	80	80
PEF%	Pearson Correlation	0.110	-0.257	0.064	0.170	0.619**	0.534**	0.292**	0.398**	1
	Sig. (2-tailed)	0.500	0.110	0.694	0.294	0.000	0.000	0.009	0.000	
	N	40	40	40	40	80	80	80	80	80

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

In our study we found that the mean age of cases was found to be 10.65±2.92 year and that of controls was 9.55±1.99 year which was similar to that of other studies.[8]

Out of forty thalassaemic, 20 (50%) had normal PFT and the rest 20 (50%) had an abnormal PFT out of which 18 (90%) had restrictive PFT and 2 (10%) had obstructive PFT. Out of 40 controls, all 40 (100%) had normal PFT. One of the earliest studies conducted by Cooper et al reported restrictive lung disease in 70% of their patients.[9] Similarly, a study by Boddu et al showed that restrictive dysfunction affected 40 out of 42 (95%) cases while the rest 2 (5%) had normal PFT.[10]

A study by Alyasin et al studied thirty-three boys and 17 girls (median age 12.5 years) with β-thalassemia in which respiratory abnormality was observed in 35 (70%) out of 50 patients. Six out of 35 (17%) had a restrictive pattern, 4 (11%) had an obstructive pattern while the rest 25 (72%) had small airway disease.[8] A recent study by Bourli et al included fifty-two children and young adults (mean age: 21.33±6.24 years) with β-TM on conventional treatment (transfusions and iron chelation therapy) and showed that 20 patients (38.46%) had restrictive pulmonary pattern that was preferentially observed in older and shorter patients.[11] Multiple other studies also had a predominantly restrictive PFT.[12-16]

A study by Parakh et al showed that PFTs were normal in 51.61% cases while the D_{LCO} (diffusion capacity of carbon monoxide) was impaired in 41.16%.[17] Other studies too have shown an impaired D_{LCO} among transfused thalassemia patients.[18-20] There was no statistically significant association between the pattern of PFT and age (p=0.57), sex (p=1.0), duration of transfusion (p=0.95) or haemoglobin (p=0.82).[10,14,18]

Limitations

This study is a cross sectional assessment of lung function. Measurement of hepatic iron content by liver biopsy gives the best quantitative estimate of total body iron. However, such a procedure is invasive and was not suitable in our study.

CONCLUSION

Our study concluded that lung can be a site of organ damage, and alteration of pulmonary function can be seen even in well-chelated TM patients. The respiratory system should be evaluated annually by PFTs even in asymptomatic patients to prevent pulmonary sequelae. Patients with abnormal PFT should be re-evaluated for compliance of chelation therapy and transfusion program.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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