PULMONARY FUNCTION TESTS IN THALASSEMIC PATIENTS

Mea·ad kadhum Hassan & Waleed Khalid Abdul-Lateef

ABSTRACT

Spirometry and body plethsmography were done for forty thalassemic patients (27 male & 13 females) attending the Thalassemia Center of Basrah Maternity and Children Hospital and 38 age and sex matched control subjects. Measured indices include forced vital capacity (FVC), peak expiratory flow rate (REFR), forced expiratory volume in one second (FEV1), the ratio of FEV1/FVC, forced expiratory flow at 25%- 75% of FVC, residual volume (RV) and total lung capacity (TLC). Normal lung function was found in 60% of thalassemic patients, while abnormal lung function was seen in 40% compared to 7.5%in the control group. Restrictive pulmonary disease was the predominant abnormality and it was detected in 32.5%, while obstructive pulmonary disease was found in 7.5%. From this study we conclude pulmonary abnormalities mainly restrictive pattern are frequent in thalassemic patients.

INTRODUCTION

The thalassemia syndromes are a heterogeneous group of inherited anemias characterized by defects in the synthesis of one or more of the hemoglobin tetramer[1]. As a group, thalassemias represent the most common single gene disorder known[1]. The thalassemias has been encountered in virtually every ethnic group and geographic location. In Iraq thalassemias also occur frequently, mainly ß-thalassemia, in Baghdad the frequency of β-thalassemia is 4.4%[2]. In 1999, WHO has estimated that the carrier frequency of β-thalassemia in Iraq is about 3% and the annual births of homozygous are about 571/-year. [3] In Basrah a recent study has revealed that the frequency of β-thalassemia gene is 4.6%[4]. The anatomic and histological changes observed in thalassemia major reflect chronic, severe hemolytic anemia, the long-term effects of hypoxia and consequences of therapy[5]. The clinical manifestations are secondary to decreased oxygen delivery to the tissue, ineffective erythropoesis and iron overload. [1,6] Mild abnormalities of pulmonary function are common in thalassemic patients[1,5]. However, the exact pathophysiology of lung damage is less clearly understood[7]. Some patients exhibit primary restrictive defects[8-10], while in others, pulmonary function studies reveal mild to moderate small airway obstruction and hyperinflation[11]. The reason for these differences is not clear[1,5]. The specific objectives of this study were to systematically classify the pattern of lung function in thalassemic patients.

PATIENTS & METHODS

Forty thalassemic patients were recruited from the Thalassemia Center of Basrah Maternity and Children Hospital during the period from 1/6/2000-1/9/2000.The patients were 27 males & 13 females, their ages ranged from 8-20 years. Twenty-seven patients have homozygos β-thalassemia, and 13 have sickle ß-thalassemia diagnosed by Hb-electrophoresis. Complete physical examination was done for each patient including weight and height, hemoglobin and chest X-ray were checked also. No patient had pulmonary symptoms at time of the study and those with cardiac complications were excluded, all were clinically stable at the time of the study. Thirty-eight subjects matched for the patient age, sex, and height were recruited from the near by primary and secondary schools. Pulmonary function test was carried out using computerized device; Jaegar spirometry 1995 West Germany. Before the measurement, the device was standardized for climate, humidity and level above sea surface. The same technician performed all tests, each subject repeated the test at least twice and the best of two readings were chosen. Spirometry and body plethesmography were done, and in some patients gas diffusion test using helium and CO was performed. Lung function tests were done using spirometry and body plethesmography, the following indices were included in the analysis; forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), the ratio of FEV_1/FVC, forced expiratory flow at 25%-75% of FVC, residual volume (RV) and total lung capacity (TLC). All measured indices were expressed as percent of

Mea·ad kadhum Hassan, MBChB, CABP, Assist. Professor, Department of pediatrics, Basrah Medical College.
Waleed Khalid Abdul-Lateef, MBChB, FICMS, Department of Medicine, College of Medicine, University of Basrah.

predicted normal values. The determination of pattern of lung function was made according to the guidelines of American Thoracic society for the interpretation of lung function testing[12] in to: Normal when the TLC and/ or the FVC, the FEV1, and the FEF_{25-75} were within the normal range (i:e TLC, FVC, and FEV1> 75% of the predicted value, FEF_{25-75} > 65% predicted value and proportional to each other, ***Obstructive*** when the ratio FEV1/ FVC was < 85%, FEF_{25-75} was disproportionately lower relative to FVC, and expiratory flow volume was concave, *Restrictive*; when TLC and /or FVC were lower than 75% of predicted normal value with proportionate decrease in FEV1 and FEF25-75 and FEV1/FVC ratio >85. Statistical analysis was expressed as mean ± SD, t-test and Chi-square test were used to determine the relative importance of various variables. The comparison between groups was performed with one way analysis of variance (ANOVA). P-value at <0.05 was regarded as significant, and <0.01 as highly significant.

RESULTS

Forty thalassemic patients and 38 controls were included in the study, there were no significant differences in age, sex and height of both groups (Table-1) .The results of pulmonary function test from 40 thalassemic patients were analyzed, (Table-2), normal pulmonary function test was found in 24 (60%), restrictive pattern in 13(32.5%) and the rest had obstructive pulmonary disease 3(7.5%). The mean age of thalassemic patients with restrictive pulmonary disease was significantly higher than controls, (Table-2). The same table demonstrates that there is no statistically significant difference in mean weight, height and hemoglobin level among the three groups (P>0.05). The determination of pattern of lung function was made according to the guidelines of American Thoracic society for the interpretation of lung function testing, Table-3 demonstrates the pattern of lung function among thalassemic patients and control group, 44.4% of patients with homozygous β thalassemia have restrictive pattern compared to 7.6% and 2.5% in patients with sickle β-thalassemia and controls. These differences were statistically significant (P-value <0.05 and <0.01 respectively). The indices of lung function for thalassemic patients are presented in Table-4. The FEV1, TLC and RV were significantly lower in those with restrictive pattern compared to patients with normal lung function, while the FEV1/FVC was significantly lower in patients with obstructive airway disease. The impact of age on pulmonary function in thalassemic patients was evaluated (Table-5). It demonstrates that with increasing age there is deterioration in all lung function parameters, which were significantly lower in thalassemic children older than 12 years compared to those younger than 12 years.

Table 1. *Characteristics of patients and controls.*

Characteristic		Thalassemic group	Control group	P -value
Age(year) Mean Range		14± 3 (8-16)	12.7±2.62 (8-18)	P >0.05
Height(cm)		131.4±5	135.3±11.4	P >0.05
Sex	*Male* *Female*	27 13	23 15	P >0.05

Table 2 *Demographic profile of thalassemic patients according to the Pattern of pulmonary function.*

Pulmonary function	Age(year)	Height(cm)	Weight(KG)	Hb(g/dl)
Normal N=24	13±4.2	130±10.5	27±3	9±1.5
Restrictive N=13	16±5.5*	132±3.5	26±6	8.5±1.0
Obstructive N=3	13±2.8	132±2.1	28±5.6	8.7±1.9

Data are expressed as Mean±SD, t-test used
**P < 0.05 (compared normal and restrictive group)*

Table 3. *Pattern of lung function among thalassemic patients and control group*

Type of pulmonary Function	Control N=38	B-thalassemia Group N=27	Sickle/ ß-thalassemia group N=-13
Normal	35 92.5%	14 51.8%	10 76%
Restrictive	1 2.5%	12 44.4%†	1 7.6%*
Obstructive	2 5%	1 3.7%	2 15.3%

Exact fisher test is used for comparison
† P < 0.01 (compared ß thalassemia and control group)
** P <0.05 (compared ß thalassemia and sickle/ ß thalassemia group)*

Table 4. *Indices of lung function in thalassemic patients*

Index	Normal n=24	Obstructive n=3	Restrictive n=13
FVC	74.6±12.7	74±2.8	67.7±14.5
FEV1	76.6±12	67.5±3.3	62.6±14.3*
TLC	99±19.7	107±8.4	67.5±10.8*
FEV1/FVC	92.4±9.7	76.5±6.7	90.3±6.8*
RV	170±74	181±20.2	88.5±46*
PEFR	74.4±22.6	56.25±13	66.2±16.25

** P< 0.05 comparison between groups was done using the ANOVA*

Table 5. *The impact of age on pulmonary function in thalassemic group.*

	<12 year n=25	≥12 year n=15	P-value
DLCO%	86±9.62	72.6±22.4	<0.05
TLC	97.3±20.20	73.5±18.5	<0.01
PEFR	70.30±15.8	57.8±18	<0.05
FEF 25%	70.30±15.3	60.3±20	<0.05
FEF50%	76.8±17.30	65.2±23.1	<0.05
FEF 75%	63.3±26.4	40±24	<0.05
FEV1/FVC	121.6±34	97±10.62	< 0.05

DISCUSSION

With improved survival of thalassemic patients with regular blood transfusions and iron chelation therapy, attention is now focused on long term sequale of the disease and its complications[7]. In this study a detailed analysis of patterns of lung function in thalassemic patients (27 with β-thalassemia major and 13 with sickle/β-thalassemia) was performed. All patients were clinically stable and have no pulmonary or cardiac symptoms. Abnormalities of pulmonary function were detected in 40% of patients compared to 7.5% in the control group. Restrictive disease was the predominant abnormality, which was detected in 32.5% of patients, while obstructive airway disease was found in 3 patients (7.5%). Several studies were done to study the pulmonary function in thalassemic patients with conflicting results. Restrictive pattern was detected in the majority of these studies[7-10,13,14], although the frequency of these abnormalities was variable, ranging from 26.6%[14] up to 86.6%[13]. Few studies had demonstrated a predominantly obstructive airway disease in thalassemic patients[6,11]. These abnormalities were not correlated with hemoglobin level, height or weight of the patients. However, there was an inverse correlation with age, as there was a decline in all lung parameters with increasing age especially for TLC, FEF75% and FEV1/FVC. This result is similar to that of other studies[10,14], while it disagrees with the findings of other studies, which did not demonstrate effect of age on pulmonary function.[9,13] In addition, pulmonary function abnormalities were more frequent in patients with ß-thalassemia major, compared to those with sickle/ß- thalassemia especially restrictive pattern, while the frequency of obstructive airway was more in patients with sickle/ß-thalassemia, many studies had demonstrated that obstructive airway disease was the predominant abnormality in patients with sickle cell disease[15,16]. The exact pathophysiology of lung abnormalities in thalassemic children is not clearly understood. More than one causal mechanism was suggested as lung parenchyma pathology was not related to iron overload[5,7,13,14]. and it was found even in mild cases[8], while other studies suggest that platelet hyperaggregation[8] or alveolar-capillary membrane block[14] may play a role in the pathogenesis of pulmonary disease. From this study we conclude that pulmonary abnormalities mainly restrictive pattern are frequent in thalassemic patients and pulmonary function should be monitored since early age at least once/year.

REFERENCES

1. Forget BG. Thalassmia syndrome. In; Hematology basic principle and practice, Hoffman R, Benz Ejr (eds), 3rd edition. Churchill Livingstone 2000; 485-495.
2. Yahya HI, et al. Thalassemia in gene Bagdad, Iraq. Eastern Med. HealthJ 1996; 2(2); 315-319.
3. Thalassemia international fedration. Management of ß-thalassemia, 6th TIF educational work shop 1999; 18-21.
4. Hassan MK, AL-Naama LM, Widad NM. Prevalence of ß-thalassemia, HB-S and G6PD deficiency in Basrah governorate, Iraq. East. Med.Health J, 2002; in press

5. Benz EI, Schwartz E. The thalassemia syndromes in; Blood disorders in infancy and childhood. Miller DR, Baehner RL (eds). 6th edition, C.V. Mosby CO. 1990; 443-445.
6. Keen TG, Oneal MH, Ortega JA, et al. Pulmonary abnormalities in thalassemic patients on hypertransfusion program. Pediatrics 1980; 65(5): 1013-1016.
7. Piatti G, Allegra L, Ambrosetti U, et al .ß thalassemia and pulmonary function. Hematologica 1999; 84(9): 804-808.
8. Isarangkura P, Chantarajanasiri T, Hathirat P, et al. Pulmonary and platelet function in mild form of HB H disease. South east-Asian J-Trop. Med.-PuplicHealth 1993; 24(1): 210-212.
9. Luyt DK, Richards GA, Roode H, et al. Thalassemia; Lung function with reference to iron studies and reactive oxidant status.Pediatr-Hematol-Oncol. 1993; 10(1): 13-23.
10. Factor JM, Pottipati SR,Rappoport-1, et al .Pulmonary function abnormalities in thalassemia major and the role of iron overload .Am J Resp Crit care Med 1994; 149(6):1570-1574.
11. Hoyt RW, Scarpa N,Wilmatt RW.Pulmonary function abnormalities in homozygos beta thalassemia. J Pediatrics 1986; 109:452-455.
12. American Thoracic society official statement. Lung function testing Am, Rev Resp.Dis. 1991; 144: 1202-1218.
13. Arora M, Chandra J, Suri JC, et al .Pulmonary function test in ß Thalassemia. Indian J Pediatr 2001; 68(3): 239-242.
14. Tai Dy, Wany YT, Lou J, et al. Lungs in thalassemia major patients receiving regular transfusions. Eur Resp. J 1996; 9(7): 1389-1394.
15. Koumbourlis Ac, Zar HJ, Jensen Alt. Prevalence and reversibility of lower airway obstruction in children with sickle cell disease. J Pediatr. 2001; 138(2): 188-192.
16. Leony MA, Dampier C, Varlotta L, et al. Airway hyperreactivity in children with sickle cell disease. J of Pediatr. 1997; 131(2): 268-283.