ABNORMALITIES IN LUNG FUNCTION AMONG MULTIPLY-TRANSFUSED THALASSEMIA PATIENTS: RESULTS FROM A THALASSEMIA CENTER IN MALAYSIA

R Jamal[1], J Baizura[1], A Hamidah[1], N Idris[2], AH Jeffrey[3] and H Roslan[3]

[1]Department of Pediatrics, [3]Department of Community Health, [3]Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Abstract. The aim of this study was to: (1) determine the prevalence and patterns of lung dysfunction among transfusion dependent thalassemics; (2) determine the associated factors that might contribute to this problem. This was a cross-sectional study involving 66 patients with transfusion dependent thalassemia aged 10 years and above. All patients underwent physical examination, standardized pulmonary function tests including spirometry, lung volume, and the carbon monoxide diffusion capacity. A restrictive pattern of lung dysfunction was observed in 22 patients (33.3%) and none showed the presence of obstructive ventilatory impairment. A reduction in the carbon monoxide diffusion capacity (DLCO) was seen 87.9% of the patients, including 7.6% who had evidence of hypoxemia. Ten patients showed a reduction in the $FEF_{25-75\%}$ although they did not fulfil the criteria for small airway disease. No correlation was found between lung dysfunction and serum ferritin levels in the patients. Restrictive lung dysfunction and diffusion impairment were the predominant abnormalities found in our cohort of patients.

INTRODUCTION

The thalassemias are the commonest single-gene disorders in the world. This condition results from defective globin chain synthesis resulting in ineffective erythropoiesis leading to chronic hemolytic anemia. In beta-thalassemia, beta globin chain synthesis is affected leading to an excess of alpha chains in the red blood cells. Three clinically separable forms of beta-thalassemia exist, namely: asymptomatic thalassemia minor, thalassemia intermedia, and thalassemia major (McDonagh and Nienhuis, 1993). In addition to these, compound heterozygotes with HbE-beta thalassemia are also commonly found, especially in the Southeast Asia region.

The two mainstays of treatment for patients with thalassemia major and a proportion of those with thalassemia intermedia are regular blood transfusions and iron chelation therapy. Regular blood transfusions lead to iron accumulation in the tissues and organs, which will lead to organ dysfunction if left untreated. The two important organs affected by iron overload are the heart and the endocrine glands. Thalassemia patients receiving sub-optimal treatment for thalassemia will eventually die in the second decade from complications of iron overload, especially hemochromatotic cardiomyopathy (Olivieri *et al*, 1994, 1999).

Impairment in respiratory function among thalassemia patients has been reported in many previous studies to occur in 29-86% of cases (Cooper *et al*, 1980; Fung *et al*, 1987; Factor *et al*, 1994; Tai *et al*, 1996; Dimopoulou *et al,* 1999; Kanj *et al*, 2000; Arora *et al*, 2001). The predominant type of lung disease also varies from one study to another. Studies which reported the presence of small airway obstruction postulated that this was due to direct narrowing secondary to iron deposition or indirectly through reduction in elastic recoil as well as a disproportionate growth of alveolar mass relative to the airway and chest cage secondary to chronic hypoxia. However, there are other studies reporting the predominance of restrictive lung dysfunction in thalassemia patients. The exact

Correspondence: Dr Rahman Jamal, Pediatric Hematology and Oncology Unit, Department of Pediatrics, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Cheras, 56000 Kuala Lumpur, Malaysia.
Tel: 603-9170-2189; Fax: 603-9173-7827
E-mail: rahmanj@mail.hukm.ukm.my

cause of the abnormal lung function is still not known, however many researchers postulate a relationship between iron overload and parenchymal damage.

There are approximately 2,400 transfusion-dependent thalassemics in Malaysia, which has a population of 24 million people. The carrier rate for beta thalassemia in the population is 3-5% (George, 2001). Local data on the morbidity of these patients are still lacking and this has made it difficult to actually assess the impact of this disease as a whole and more importantly to help plan for resources to be made available to these patients. The aims of the study were to investigate the problem of lung dysfunction among our transfusion dependent thalassemics and the associated factors that might contribute to this problem.

MATERIALS AND METHODS

Subjects

This cross-sectional observational study was carried out during a period from the 1st of January 2002 to the 31st of December 2002 at the thalassemia clinic of the Hospital Universiti Kebangsaan Malaysia, which is a typical daycare center for thalassemia patients. A total of 66 patients who were 10 years and above (based on their ability to perform the pulmonary function test) and on regular blood transfusions were recruited into the study after informed consent. Patients with thalassemia major were on a hypertransfusion regimen aimed at a pre-transfusion hemoglobin (Hb) concentration of 90-100 g/l, whilst those with HbE-beta thalassemia only had transfusions when the Hb dropped below 7 or when they become symptomatic. Those with a previous or current history of asthma or chronic respiratory disease, those with recent lung infection, those with cardiac diseases, those who smoke and those with any musculoskeletal abnormality were excluded. Data regarding the socio-demographic characteristics, diagnosis, frequency of blood transfusions, menstrual history and physical findings were recorded on a standard data collection sheet.

Pulmonary function test

Finger-pulse oximetry was obtained to determine the oxygen's saturation (SaO_2). Peak expiratory flow rate was measured using the Wright's peak-flow meter. The pulmonary function tests were performed by the same team of respiratory technicians before the scheduled blood transfusion for each patient. The tests consisted of spirometry, lung volumes measurement and single breath transfer factor for carbon monoxide. The spirometry and lung volume measurements were performed using a SensorMedics 6200 spirometer with the Enhanced Spirometer Program. The pulmonary function test was performed according to the published standard criteria by the American Thoracic Society (1978) and others (Taussig *et al*, 1980). The spirometry values taken were the FVC, FEV1, FEV1/FVC and $FEF_{25-75\%}$. The lung volumes recorded were the vital capacity (VC), total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC). We used the oriental standard as the reference range for the patients. Carbon monoxide diffusion capacity (DLCO) was measured by a single breath technique and the values obtained were corrected for the hemoglobin concentration (Autobox DL, Single Breath Diffusion Capacity SB Program).

Blood collection and tests performed

A pre-transfusion hemoglobin level was recorded before the performance of the lung function test. Present and past levels of serum ferritin levels were noted and the mean value over a period of 1 year was taken for each patient.

Definitions

We also defined restrictive, obstructive or mixed patterns of airway disease according to published criteria (American Thoracic Society, 1978; Taussig *et al*, 1980). A restrictive pattern was defined by TLC<80% (mild: 70-79%, moderate: 60-69%, severe: <60%) whilst anobstructive defect was defined by an FEV1/FVC ration of <70%. A significant low value for DLCO was taken as <80% of the predicted value and significantly low SaO_2 as <95%. Small airway disease was defined as the presence of $FEF_{25-75\%}$<60%, FEV1/FVC ≥70% and FVC of ≥80%.

Statistical analysis

The data was summarized and analyzed

using the SPSS 10.0 standard version for Windows. The prevalence of lung dysfunction was calculated. The Fisher exact test was used to compare the proportion of patients with and without lung dysfunction with respect to the age groups, sexes and transfusion groups. The *t*-test was used to compare the mean serum ferritin levels between those with and without lung dysfunction. A p-value of less than 0.05 was taken as significant.

RESULTS

A total of 66 patients were eligible and participated in the study. The socio-demographic and clinical characteristics of these patients are shown in Table 1. There were 35 males (53%) and 31 females (47%). The ages ranged between 10 and 24 years with a mean of 15.8±3.5 years. Thirty-seven patients (56.1%) were thalassemia major patients whilst the rest had HbE-beta thalassemia. The mean pre-transfusion hemoglobin before the pulmonary function test was 8.05±1.31 g/dl. Thirty-six patients (54.5%) were on iron chelation therapy. Five patients had oxygen saturations of less than 95%.

Table 2 shows the pulmonary function data for the patients. None of the patients fulfilled the criteria for obstructive airway disease. Restrictive impairment in lung function was seen in 22 patients (33.3%). Ten patients had an isolated reduction of their $FEF_{25-75\%}$ values to less than 60%; however, none of them had other criteria for small airway disease. Table 5 shows the grouping of the patients with lung dysfunction according to the phenotype. Patients with a transfusion interval of less than 8 weeks had a lower mean TLC percentage compared with those who received less frequent transfusions (>8 weeks).

Diffusional impairment was observed in 58 of the 66 patients (87.9%) with 21 of them showing significantly low DLCO values.

Patients who received more frequent blood transfusions (interval <8 weeks) had significantly higher mean serum ferritin values compared to those who received less frequent transfusions. There was a negative correlation found between the TLC and the mean serum ferritin levels (r value of -0.116), however, this was not statistically significant.

DISCUSSION

Despite the standard management on the use of iron chelation in those with iron overload, a significant number of patients in Malaysia were not on chelation therapy mainly due to financial constraints. This factor predicts for a high prevalence of complications arising from iron overload among our patients. For example, short stature was documented in about 55% of our patients and pubertal delay in 21% (Hamidah *et al*, 2001).

Lung dysfunction is among the least studied complications in thalassemia patients, probably

Table 1
Sociodemographic and clinical characteristics of 66 multiply-transfused thalassemia patients.

Characteristics	Number of patients (n=66)	%
Sex		
Male	35	53
Female	31	47
Race		
Malay	39	59.1
Chinese	27	40.9
Diagnosis		
beta thalassemia major	37	56.1
HbE-beta thalassemia	29	43.9
Transfusion intervals		
<8 weeks	39	75
>8 weeks	13	25

Table 2
TLC values in 66 multiply-transfused thalassemia patients.

% Total lung capacity (TLC)	Number of patients (n=66)	%
TLC > 80%	44	66.7
TLC < 80%		
70-79% (mild)	12	18.2
60-69% (moderate)	10	15.1
Total	66	100

Table 3
Comparison of mean % TLC values by sex, type of thalassemia, and transfusion groups in 66 thalassemia patients.

Characteristics	Number of patients (n=66)	Mean % TLC ± SD	p-values
Sex			
Male	35	90.03 ± 14.78	
Female	31	83.29 ± 13.64	0.06
Thalassemia type			
beta thalassemia major	37	87.30 ± 13.52	
HbE-beta thalassemia	29	86.31 ± 15.99	0.79
Transfusion interval			
0-8 weeks	50	85.76 ± 14.26	
>8 weeks	16	90.31 ± 15.38	0.28

Table 4
Comparison of patients with restrictive lung disease (% TLC<80%) according to age groups and thalassemia phenotype.

Characteristics	Number of patients (n=66)	Number of patients with TLC<80%	p-values
Age (years)			
10-14	23	3	
15-19	32	11	
>20	11	8	0.03
Thalassemia type			
beta thalassemia major	37	13	
HbE-beta thalassemia	29	9	0.73

due to the lack of pulmonary symptoms experienced by the patients as compared to those with cardiomyopathy and endocrine complications. Theoretically, the lungs are also at major risk of damage secondary to iron overload.

This study revealed that 33.3% of the patients had restrictive impairment of lung function but none showed an obstructive pattern. The predominance of this type of impairment is comparable to other studies which have reported a prevalence of 70-86% (Factor *et al,* 1994; Dimopoulou *et al*, 1999; Arora *et al*, 2001). The higher prevalence in these studies may be due to the fact that their study patients were mainly thalassemia major patients who received hypertranfusion as compared to our study which consisted of thalassemia major patients as well as those with HbE-beta thalassemia, which is less transfusion-dependent (Tai *et al*, 1996; Kanj *et al*, 2000).

We also found that there was no correlation between mean serum ferritin levels and restrictive lung dysfunction. At least one study showed the presence of an inverse relation between TLC and iron burden, but there are other studies which show that the calculated lifetime iron burden does not correlate with restrictive impairment in lung function (Factor *et al*, 1994; Tai *et al*, 1996). There have been different methods used to estimate body iron, which included the use of MRI with T2, relaxation time, iron content and serum ferritin, as in our study. Serum ferritin is not the best measure of iron overload. The measurement of the liver iron content gives the best estimate of total body iron stores in thalassemia patients. However, this procedure is invasive and requires a liver biopsy specimen.

Diffusional impairment was seen in 87.9% of our patients and this was certainly higher than that reported by Li *et al* (2002) in a study involving 29 patients. This could be explained by the fact that our patients had more severe iron overload. In the 22 patients with restrictive lung disease, only one had a normal DLCO. This diffusional impairment could be attributed to a defect in the alveolo-capillary membrane leading to a ventilation-perfusion mismatch. Another interesting finding was the isolated

reduction in the $FEF_{25-75\%}$ in 10 out of the 66 patients. This is comparable to the findings in a study by Factor *et al* in 1994. Although this is one of the criteria suggestive of the presence of small airway disease, the other two criteria were not present.

Although iron overload is likely to account for lung disease, causing damage either directly or indirectly, there may also be other causative factors responsible. Chronic anemia in these patients may have interfered with the rapid alveolar growth in the first 8 years of life and contributed to the abnormalities found (Cooper *et al*, 1980). Hepatosplenomegaly may also contribute to the restrictive lung defect by impeding the optimal elevation of the diaphragm. This may reduce the lung volume but it does not affect the total lung capacity. Finally, the effect of long-standing use of desferrioxamine has also been reported to cause acute respiratory distress secondary to inflammation, alveolar damage and interstitial fibrosis due to hypersensitivity to the iron chelator. However, none of our patients had any respiratory symptoms. There were also other risk factors which could have effected lung function, such as chronic exposure to environmental air pollution, passive smoking and others.

In conclusion, we found that restrictive lung dysfunction is highly prevalent amongst our patients. The relationship between the severity of iron overload with lung dysfunction requires further evaluation. It is advisable that all thalassemia patients with iron overload have lung function testing done annually. To our knowledge, this is the first study on lung function performed on our local thalassemia patients.

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