ORIGINAL ARTICLE

Respiratory function in patients with thalassaemia major: relation with iron overload

A M Li, D Chan, C K Li, E Wong, Y L Chan, T F Fok

Arch Dis Child 2002;87:328-330

See end of article for
authors' affiliations

Correspondence to:
Dr A M Li, Department of
Paediatrics, The Chinese
University of Hong Kong,
Prince of Wales Hospital,
Shatin, Hong Kong SAR,
China;
albertmli@cuhk.edu.hk

Accepted 15 May 2002

Aims: (1) To determine the pattern of respiratory impairment in children with thalassaemia major (TM); (2) to assess the relation between the degree of respiratory impairment and total body iron content.

Methods: Twenty nine TM patients were recruited. All underwent physical examination, standardised pulmonary function tests (spirometry, lung volume, and single breath diffusion capacity for carbon monoxide), and magnetic resonance imaging measurements of the liver. Serum ferritin was measured. The signal intensity ratio of liver to that of paraspinal muscle (T1 weighted sequence) and serum ferritin were used as surrogate index of body iron content.

Results: Sixteen boys and 13 girls (median age 14.2 years) were studied. None had clinical evidence of congestive heart failure. Sixteen had normal lung function. Impairment of diffusion capacity (median DL_{CO} 83.5% predicted) was the most common abnormality, being observed in 34% of patients. Pure restrictive and obstructive ventilatory impairment was found in one and two patients respectively. Five patients had a combination of ventilation and diffusion defects. There was no correlation between the degree of impairment of each respiratory abnormality and body iron content.

Conclusion: Diffusion impairment was the commonest abnormality found in our cohort of paediatric TM patients. Our data did not support the notion that respiratory function impairment was correlated with body iron content.

Thalassaemia major (TM) is a disorder of abnormal haemoglobin synthesis. This leads to impaired oxygen delivery to the tissues, ineffective erythropoiesis, and iron overload.¹ Management of these patients involves regular blood transfusions which can be complicated by progressive tissue deposition of iron and organ damage.

A variety of pulmonary function abnormalities have been described in TM patients. Of these, restrictive abnormalities are the most frequent, being reported in up to 80% of patients.²⁻⁵ The precise aetiology of the pulmonary dysfunction remains unknown. Previous postmortem studies have shown the presence of iron in the lungs of TM patients.⁶ Filosa and his group⁷ showed that TM patients with abnormal pulmonary function had higher serum ferritin levels compared to those with normal pulmonary function. In a study by Factor and colleagues,³ an inverse correlation between total lung capacity and lifetime estimates of transfusional iron load was established. It was thus proposed that iron overload may play an important part in causing pulmonary abnormalities in these patients. However, such a claim was not supported by a subsequent study by Tai and colleagues⁴; the method of lifetime estimates of iron overload was also criticised for being inaccurate.

The aims of our study are: (1) to determine the predominant pulmonary function abnormality in paediatric TM patients; and (2) to re-examine the relation between respiratory abnormalities and body iron content. Unlike previous studies, our study assessed body iron content by means of magnetic resonance imaging (MRI) measurements of the liver and serum ferritin.

METHODS

Subjects

Twenty nine patients with homozygous β thalassaemia major participated in the study. They were all managed at a tertiary university haematology centre according to a standard protocol which aimed to maintain a haemoglobin concentration of

greater than 95 g/l. Each participant attended our centre for monthly examination and blood transfusion. Serum ferritin level was checked every six months. All patients were receiving chelation therapy with subcutaneous administration of desferrioxamine five to seven times a week. One patient had previously undergone splenectomy. Two patients had been diagnosed with asthma; their symptoms were well controlled. Only one of these was receiving regular prophylactic inhaled steroids. None of the participants were smokers or carriers of hepatitis C. None had a history of congestive heart failure. At the time of this study, all were in a stable condition without limitations in their daily activities. Informed consent was obtained from the parents and patients who underwent physical examination, pulmonary function testing, and MRI. The number of years of blood transfusion received by each subject was also recorded.

Pulmonary function testing

All pulmonary function studies were performed within two days prior to the scheduled transfusion. A pretransfusion haemoglobin was checked. The lung function tests were carried out by the same team of technicians according to the recommended standard.⁸ Spirometry was measured by a SensorMedics 2130 spirometer using the Enhanced Spirometry Program. The best of at least three technically acceptable values for forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), maximum mid-expiratory flow rate (MMEFR), and flow-volume curves were selected. Functional residual capacity (FRC), residual volume (RV), and total lung capacity (TLC) were measured by body plethysmography

Abbreviations: FEV₁, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; MMEFR, maximum mid-expiratory flow rate; MRI, magnetic resonance imaging; ROI, region of interest; RV, residual volume; TLC, total lung capacity; TM, thalassaemia major

(SensorMedics 6200) and expressed in litres corrected for body temperature, atmospheric pressure, and saturation with water vapour. Diffusion capacity of carbon monoxide was measured by single breath technique and the values obtained were corrected for haemoglobin concentration (SensorMedics 6200 Autobox DL, Single Breath Diffusion Capacity DLco SB Program).⁹ The pulmonary function results were expressed as percentages of predicted normal values.¹⁰ For the purpose of this study, the threshold of abnormality was identified as under 80% of the predicted value. Restrictive disease was defined as a reduction in TLC to less than 80%; diffusion impairment as a reduction in DL_{co} to less than 80%; and obstructive airway disease as reduced FEV₁/FVC ratio to less than 80%. The pulmonary deficits were classified as “mild” (>70%), “moderate” (<70% and >60%), “moderately severe” (<60% and >50%), and “severe” (<50%).¹¹

Magnetic resonance imaging studies

MRI was performed in a 1.5 Tesla MR Imager (Gyrosan ACS NT, Philips Medial System, Best, Netherlands) with a body coil. Breath hold axial modified spin echo T1 weighted images were obtained with the following parameters: repetition time 120 ms, echo time 13 ms, 135 degrees flip angle, 15 slices at three slices per breath, slice thickness 10 mm with 10% gap, number of excitations two, field of view 375 mm, matrix 192–256×256.

Signal intensities were measured by a single radiologist with the use of operator defined regions of interest (ROIs). ROIs of more than 100 pixels were chosen in a homogeneous area without blood vessels at the lower part of the right lobe of the liver. The lateral boundary of the ROI was about 1 cm from the liver surface. Liver signal intensity was averaged from three ROIs. The signal intensity of the right paraspinal muscle was measured with a single ROI encompassing more than 30 pixels on the same slice. The ratio of the signal intensities of liver to muscle was obtained. This ratio was inversely related to hepatic iron content.

Statistical analysis

Percentage predicted was calculated for each respiratory impairment. Median and interquartile range were presented for various interval parameters including anthropometric measurements and various pulmonary function parameters. Spearman's rank correlation coefficient was used to assess the association between the median liver/muscle intensity ratio, median serum ferritin level, and the various pulmonary function parameters and anthropometric measurements including age. SPSS for Windows statistical software (Release 10.0, SPSS Inc., Chicago, Illinois) was used in the analyses. The level of significance was set at 5% in all comparisons, and all statistical testings were two sided.

RESULTS

Sixteen boys and 13 girls with a median age of 14.2 years (interquartile range: 10.58 to 16.50) participated in the study. Their median body mass index was 16.3 and none were considered to be obese (<120% ideal body weight for height). None of the subjects had clinical evidence of heart failure detected on physical examination. Table 1 shows the anthropometric and pulmonary function data of the subjects. The median number of years of blood transfusion was 12.3 (interquartile range: 9.5 to 14.5). Median oxygen saturation in room air was 98%. Peak expiratory flow rate was estimated in 25 patients with a median of 260 l/min (interquartile range: 207.5 to 335.0). Sixteen of the 29 patients (55%) had normal lung function, with the remaining showing isolated or combined functional abnormalities. The patient who had splenectomy and the two asthmatic patients had normal pulmonary function. Diffusional impairment was the most frequent abnormality, being observed in 10 patients (34%).

Table 1 Anthropometric and respiratory function data

	Median (interquartile range)
Age (y)	14.2 (10.6 to 16.5)
Sex (male/female ratio)	16/13
Weight (kg)	33.2 (28.4 to 42.5)
Height (cm)	142.8 (130.0 to 148.5)
Haemoglobin (g/l)	102.5 (98.3 to 109)
Transfusion years	12.3 (9.5 to 14.5)
Serum ferritin (pmol/l)	5827.75 (3919.88 to 7939.5)
FVC ₁ (% predicted)	88.0 (81.8 to 96.5)
FEV ₁ (% predicted)	85.0 (71.5 to 97.0)
FEV ₁ /FVC	88.0 (84.0 to 91.0)
FEF _{25–75%} (% predicted)	85.0 (71.5 to 97.0)
TLC (% predicted)	95.5 (88.0 to 107.0)
DL _{co} (corrected % predicted)	83.5 (70.0 to 100.75)
SaO ₂ (% in room air)	98.0 (98.0 to 99.0)

FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; FEF_{25–75%}, forced mid-expiratory flow; TLC, total lung capacity; DL_{co}, diffusion capacity for carbon monoxide; SaO₂, oxygen saturation.

Figure 1 Percentage pulmonary function abnormalities of the subjects.

One patient (3.4%) had pure restrictive impairment, and two (6.8%) had pure obstructive impairment. Three patients (10.3%) had a combination of restrictive and diffusional impairment, and two (6.8%) had a combination of obstructive and diffusional impairment (fig 1). Respiratory abnormalities were detected in a total of 45% of the study subjects, and were all considered to be mild (70–79% of the predicted value). Except for total lung capacity (Spearman's correlation coefficient = -0.469 , $p = 0.016$), there was no correlation detected between age and the other pulmonary function parameters.

The serum ferritin level of each patient was derived by calculating the average measurement over a two year period. The median level was 5827.75 pmol/l (interquartile range: 3919 to 7939). The median liver/muscle intensity ratio was 0.610 (interquartile range: 0.495 to 0.847). There was a negative correlation between the serum ferritin and the liver/muscle intensity ratio (Spearman's correlation coefficient = -0.689 , $p = 0.000$). The liver/muscle intensity ratio was also found to have a negative correlation with age (Spearman's correlation coefficient = -0.426 , $p = 0.019$). However, no correlation was detected between the intensity ratio or serum ferritin with the number of years of blood transfusion or the various pulmonary function parameters (tables 2 and 3).

DISCUSSION

The most common respiratory abnormality observed in our study, affecting 34% of patients with TM, was diffusional impairment. This was in contrast to other published studies which included mainly adult patients, where restrictive abnormalities were the most frequently reported deficit.^{2–5}

Table 2 Spearman's correlation coefficients between liver to muscle signal intensity and pulmonary function

	Liver to muscle signal intensity
Age	-0.426 (p=0.019)
FEV ₁ /FVC	-0.624 (p=0.175)
TLC (% predicted)	-0.250 (p=0.228)
DL _{co} (corrected % predicted)	-0.610 (p=0.761)

Table 3 Spearman's correlation coefficients between serum ferritin and pulmonary function

	Serum ferritin
Age	0.098 (p=0.613)
FEV ₁ /FVC	0.029 (p=0.883)
TLC (% predicted)	0.182 (p=0.814)
DL _{co} (corrected % predicted)	0.047 (p=0.814)
Liver to muscle signal intensity	-0.689* (p=0.000)

*Significant at 5% level.

Iron accumulation from repeated transfusions has been proposed as the likely mechanism causing pulmonary defect in TM patients. Factor and colleagues,³ in their study of 29 patients (mean age 19.8 years), found an inverse relation between total lung capacity and estimates of transfusional iron burden. They suggested that the degree and duration of iron overload might be important in the pathogenesis of the restrictive ventilatory deficit. In a subsequent study by Tai and colleagues,⁴ however, the calculated lifetime iron burden did not correlate with the restrictive impairment in their patients. In these studies, the calculations/estimates of iron overload had not taken into account the amount of iron absorbed through the intestine, which in TM patients may be significant.¹² Another confounding factor was iron chelation therapy, received by most TM patients, which would render such estimation less reliable. A causal relation between pulmonary iron deposition and restrictive abnormalities is not supported by necropsy data on TM patients where iron was found predominantly in bronchial epithelial cells and bronchial glands rather than in the lung parenchyma.¹³ Furthermore, no increase in fibrous tissue was shown in the lung, making a restrictive deficit less likely. Diffusional impairment, on the other hand, may be accounted for by a defective alveolocapillary membrane, which was found in a significant number of TM patients in the study by Tai and colleagues.⁴ One of the limitations of our study is the cross sectional assessment of lung function at one time point. It would be more informative to follow these patients and assess longitudinal changes of their lung function.

Measurement of hepatic iron content gives the best quantitative estimate of total body iron stores in patients with transfusional siderosis.¹⁴ The gold standard for assessing hepatic iron content is by liver biopsy. However, such a procedure is invasive and not suitable as a routine assessment. MRI has been shown to be a reliable and useful non-invasive tool for quantifying hepatic iron in iron overload states.^{15, 16} The MRI measurements are based on the ability of stored intracellular iron to become strongly magnetised in a magnetic field. This magnetisation is quantified by the magnetic susceptibility (the ratio of induced over the applied magnetic field); localised regions of increased magnetic susceptibility are recorded to give an accurate estimate of the iron content.¹⁷

Serum ferritin values have been found to have direct correlation to iron deposition in the liver.¹⁸ Serum ferritin is an acute phase protein as well as a product of hepatocellular

damage. Thus, infection, congestive heart failure, and hepatitis can lead to a falsely increased measurement. None of our patients had clinical evidence of hepatitis or heart failure. The blood samples were taken on a six monthly basis when the patients were clinically well. In our study, we were able to find a good correlation between the average serum ferritin over a two year period and the liver/muscle intensity ratio.

Our data did not support the relation between pulmonary function abnormalities in TM patients and body iron content. It is believed that other potential causative factors also play a part, leading to respiratory dysfunction. It is well known that the increased iron load can promote oxidant tissue injury through the production of free radicals.¹⁹ It has also been postulated that tissue damage is facilitated by certain micro-organisms which are iron dependent. Toxicity secondary to desferrioxamine treatment has also been suggested to be involved.²⁰ It is likely that the cause of respiratory dysfunction in TM patients is multifactorial, but this has yet to be substantiated.

Authors' affiliations

A M Li, D Chan, C K Li, T F Fok, Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, SAR, China
E Wong, Centre for Clinical Trials and Epidemiological Research, The Chinese University of Hong Kong
Y L Chan, Department of Diagnostic Radiology and Organ Imaging, The Chinese University of Hong Kong

REFERENCES

- 1 **Marks PA**. Thalassaemia syndromes: biochemical, genetic and clinical aspects. *N Engl J Med* 1966;**275**:1363-9.
- 2 **Kanj N**, Shamseddine A, Gharzeddine W, et al. Relation of ferritin levels to pulmonary function in patients with thalassaemia major and the acute effects of transfusion. *Eur J Haematol* 2000;**64**:396-400.
- 3 **Factor JM**, Pottipati SR, Rappaport I, et al. Pulmonary function abnormalities in thalassaemia major and the role of iron overload. *Am J Respir Crit Care Med* 1994;**149**:1570-4.
- 4 **Tai DYH**, Wang YT, Lou J, et al. Lungs in thalassaemia major patients receiving regular transfusion. *Eur Respir J* 1996;**9**:1389-94.
- 5 **Fung KP**, Chow DKW, So SY, et al. Pulmonary function in thalassaemia major. *J Pediatr* 1987;**111**:534-7.
- 6 **Cooper DM**, Mansell AL, Weiner MA, et al. Low lung capacity and hypoxemia in children with thalassemia major. *Am Rev Respir Dis* 1980;**21**:639-46.
- 7 **Filosa A**, Esposito V, Meoli I, et al. Evidence of lymphocyte alveolitis by bronchoalveolar lavage in thalassaemic patients with pulmonary dysfunction. *Acta Haematol* 2000;**103**:90-5.
- 8 **British Thoracic Society**, and the Association of Respiratory Technicians and Physiologists. Topical review: guidelines for the measurement of respiratory function. *Respir Med* 1994;**88**:165-94.
- 9 **Cotes JE**, Dabbs JM, Elwood PC, et al. Iron deficiency: its effect on transfer factor. *Clin Sci* 1972;**42**:325-35.
- 10 **Ip MS**, Karlberg EM, Karlberg JP, et al. Lung function reference values in Chinese children and adolescents in Hong Kong. *Am J Respir Crit Care Med* 2000;**162**:424-9.
- 11 **American Thoracic Society**. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;**144**:1202-18.
- 12 **Pippard MJ**, Callender ST, Warner GT, et al. Iron absorption and loading in beta-thalassaemia intermedia. *Lancet* 1979;**20**:819-21.
- 13 **Witzleben CL**, Wyatt JP. The effect of long survival on the pathology of thalassaemia major. *J Pathol Bacteriol* 1961;**82**:1-13.
- 14 **Angelucci E**, Brittenham GM, McLaren CE, et al. Hepatic iron concentration and total body iron stores in thalassemia major. *N Engl J Med* 2000;**343**:327-31.
- 15 **Ernst O**, Sergent G, Bonvarlet P, et al. Hepatic iron overload: diagnosis and quantification with MR imaging. *Am J Roentgenol* 1997;**168**:1205-8.
- 16 **Gomori JM**, Horev G, Tamary H, et al. Hepatic iron overload: quantitative MR imaging. *Radiology* 1991;**179**:367-9.
- 17 **Johnston DL**, Rice L, Vick GW, et al. Assessment of tissue iron overload by nuclear magnetic resonance imaging. *Am J Med* 1989;**87**:40-7.
- 18 **Litsky EA**, Miller F, Worwood M, et al. Serum ferritin in children with thalassaemia regularly transfused. *J Clin Pathol* 1974;**27**:652.
- 19 **Luyt DK**, Richards GA, Roode H, et al. Thalassaemia: lung transfusion with respect to iron studies and oxidant status. *Pediatr Hematol Oncol* 1993;**10**:13-23.
- 20 **Freedman MH**, Grisaru D, Olivieri N, et al. Pulmonary syndrome in patients with thalassaemia major receiving intravenous desferrioxamine infusions. *Am J Dis Child* 1990;**144**:565-9.