OBSTRUCTIVE SLEEP APNEA AMONG CHILDREN WITH SEVERE BETA-THALASSEMIA

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Abstract. The aim of this study was to determine the prevalence and associated factors for obstructive sleep apnea (OSA) among children with severe beta-thalassemia. Children with severe beta-thalassemia without a history of bone marrow transplantation were studied. Polysomnography (PSG) was performed in those who habitually snored to identify OSA. One hundred twenty children (aged 9.3±3.7 years; 42% male) were studied. Nineteen patients (15.8%) habitually snored. Sixteen had PSG performed. OSA was demonstrated in 10 patients. Six had moderate-to-severe OSA. The estimated prevalence of OSA was 8.3%. All OSA patients had adenoid hypertrophy and 80% had associated tonsil enlargement. The OSA group had a higher serum ferritin level compared to the non-OSA group (3,785±1,780 *vs* 1,885±677 ng/ml; p=0.03). Six of 10 patients who had OSA underwent adenotonsillectomy. Reactive lymphoid hyperplasia was demonstrated in all cases. The estimated prevalence of OSA in children with severe beta-thalassemia was high (8.3%) and some had severe OSA. Adenotonsillar lymphoid hyperplasia was common among those who had OSA. A high serum ferritin level was associated with the occurrence of OSA. A history of snoring and OSA symptoms should be periodically assessed in children with severe beta-thalassemia.

Keywords: beta-thalassemia, obstructive sleep apnea, pediatrics

INTRODUCTION

Beta-thalassemia is a common inherited hemoglobin disorder in Southeast Asia and many parts of the world. It is characterized by ineffective erythroipoiesis and hemolytic anemia (Galanello and Origa, 2010). Children with severe beta-thalassemia require frequent blood transfusions and are at risk for increased extramedullary hematopoiesis. There was a report of OSA secondary to extramedullary hematopoiesis in a child with thalassemia intermedia (Kapelushnik *et al*, 2001) and a report of sleep disruption in children with beta-thalassemia and congenital dyserythropoietic anemia (Tarasiuk *et al*, 2003). There have also been reports of OSA in children with sickle cell disease, another inherited hemoglobinopathy that shows clinical features of chronic hemoly-

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sis and increased extramedullary hematopoiesis, as in beta-thalassemia (Maddern and Reed, 1989; Samuels *et al*, 1992; Salles *et al*, 2009). Studies of OSA among children with severe beta-thalassemia are few. We investigated the prevalence of OSA among children with severe beta-thalassemia and determined the associated factors.

MATERIALS AND METHODS

Children aged 3-15 years diagnosed with severe beta-thalassemia who had been followed up at the Division of Pediatric Hematology, King Chulalongkorn Memorial Hospital, Thailand, were included in the study. Severe beta-thalassemia was defined as patients with homozygous beta-thalassemia or beta-thalassemia/hemoblobin E and requiring at least one blood transfusion every 3-4 weeks. Patients with a history of bone marrow transplantation, adenotonsillectomy, upper airway obstruction caused by other etiologies (such as congenital craniofacial anomalies, subglottic stenosis, tracheomalacia), neuromuscular diseases, congenital cyanotic heart diseases or acute respiratory tract infection within 2 weeks prior to the study were excluded from the study. All eligible patients were asked whether they habitually snored (snored ≥ three nights/week). Those who habitually snored were scheduled for an overnight polysomnography (PSG) and a nasopharyngeal X-ray. Written informed consent was obtained from the legal guardian prior to the study. The study protocol was approved by the Ethics Committee for Human Research Study, Faculty of Medicine, Chulalongkorn University.

The overnight PSG was performed at the sleep lab, King Chulalongkorn Memorial Hospital using the Easy II System® (Cadwell Laboratories, Seattle, WA). The test was performed by the same trained technician for all subjects. Patients presented to the sleep lab at 8:30 PM and was discharged at 7:00 AM the following day. A parent or caregiver was allowed to stay with the patient duration the PSG. The following parameters were monitored and recorded during sleep: eight-channel electroencephalogram (two frontal, two occipital, two temporal, and two central leads), bilateral electro-occulogram, chin and anterior tibial electromyograms, electrocardiogram, oro-nasal airflow (using a thermocouple), thoracic and abdominal wall movement (using strain gauge electrodes), body position (using body position detector), arterial pulse oxygen saturation (SpO_2) [using a pulse oximeter; Capnocheck PLUS® (BCI International, WI)] and end-tidal carbon dioxide tension ($P_{ET}CO_2$) [using a capnometer; Capnocheck PLUS® (BCI International, WI)].

The study was interpreted by a pediatric neurologist and pediatric pulmonologist trained and experienced in pediatric PSG. The interpreters were the same throughout the study period. Sleep stages and arousals/awakenings were scored by the pediatric neurologist while respiratory events during sleep were scored by the pediatric pulmonologist. All were scored in accordance with the criteria set by the American Academy of Sleep Medicine (AASM) (Iber *et al*, 2007). Sleep efficiency was defined as the percentage of total sleep time (TST) per the total time in bed. The arousal index was the number of arousal events per hour of TST. Arousals induced by the technician were not counted.

Central, obstructive, and mixed apneic events were scored according to AASM

criteria. OSA was diagnosed if the patient demonstrated the events of obstructive apnea- hypopnea at a rate of ≥ 1 per hour TST [obstructive apnea/hypopnea index (AHI) ≥ 1 per TST]. The severity of OSA and hypoventilation were categorized as mild, moderate and severe in accordance with criteria previously described by Katz and Marcus (2005).

Adenoid enlargement and nasopharyngeal airway narrowing were diagnosed by lateral nasopharynx X-ray by a pediatric radiologist not involved in the study who was the same throughout the study. An adenoidal-nasopharyngeal ratio ≥ 0.6 and ≥ 0.8 were used to diagnose adenoid enlargement and nasopharyngeal airway narrowing, respectively (Fujioka *et al*, 1979).

Collected data included demographic data, a history of habitual snoring, a history of passive smoking, a history of splenectomy and iron chelation, other underlying diseases (such as allergic rhinitis, obesity, malnutrition), grading of adenotonsillar hypertrophy and the presence of hepatosplenomegaly. Hemoglobin and serum ferritin levels at 4 and 6 weeks, respectively, prior to the study, were also recorded. Clinical data were compared between the OSA and non-OSA groups using an unpaired Student's *t*-test for continuous variables and the Fisher exact test for categorical variables to identify factors associated with OSA. OSA patients were categorized as either mild or moderate-to-severe. Clinical data were compared between the two groups using applicable statistics to identify factors associated with OSA severity. A two-tailed *p*-value of < 0.05 was considered significant. The statistical analysis was performed using GraphPad InStat (GraphPad Software, San Diego, CA).

RESULTS

One-hundred twenty children with severe beta-thalassemia were eligible for the study. The mean age was 9.3±3.7 years (range 3-15 years). The male:female ratio was 1:1.4. The age at diagnosis of severe beta-thalassemia was 4.4±2.6 years (range 8 months-12.6 years). Eighty-four patients (70%) had desferrioxamine for iron chelating therapy and 24 patients (20%) had a splenectomy.

Nineteen patients (15.8%) habitually snored. Sixteen of these had an overnight PSG and a nasopharyngeal X-ray, the rest refused the test. All 16 patients had adenoid hypertrophy and 11 (68.8%) had associated tonsil enlargement (Table 1). The PSG revealed an average TST of 7±0.5 hours (range 5.8-7.9 hours). The average sleep efficiency was 93.1±6.6% (range 77-99%). The average duration of REM sleep was 11.4±4.5% of TST (range 6-30%TST). The median arousal index was 3.8/hour (range 0.3-23.1/hour) and the median obstructive AHI was 2.3/hour (range 0-65/hour). The average baseline SpO_2 was 97±1% (range 94-99%) and the average baseline $P_{ET}CO_2$ was 48±6 mmHg (range 36-60 mmHg). The average nadir SpO_2 was 81±9% (range 67-92%) and the average peak $P_{ET}CO_2$ was 55±7 mmHg (range 43-70 mmHg).

Of the 16 patients who had PSG, 10 had OSA (4 mild, 1 moderate and 5 severe); 5 had mild hypoventilation (mean $P_{ET}CO_2$ 49±3 mmHg; range 46-54 mmHg) and paradoxical breathing during sleep without OSA. One of the 16 patients had a mildly abnormal PSG. She had two brief episodes of mild desaturation following central apneic events (lowest SpO_2: 89%) and one brief episode of mild desaturation (SpO_2 88%) following an obstructive

Table 1
Comparison of clinical data between OSA and non-OSA patients.

Clinical data	OSA (*N*=10)	Non-OSA (*N*=6)	*p*-value
Mean age ± SD (years)	9.7 ± 3.8	8.7 ± 3.3	0.7
Percent male	30	33.3	1.0
Mean % weight for height ± SD	101.1 ± 8	107.8 ± 6.6	0.1
Passive smoking	3 (30%)	4 (67%)	0.3
Allergic rhinitis	1 (10%)	0	1.0
Obesity (% weight for height ≥120)	1 (10%)	0	1.0
Malnutrition (%weight for height <90)	0	0	-
Mean age thalassemia diagnosed ± SD (years)	5 ± 1.8	5.6 ± 1.37	0.5
Desferrioxamine therapy	8 (80%)	4 (67%)	0.6
Mean duration of desferrioxamine therapy± SD (years)	4.9 ± 1.7	3.8 ± 1.6	0.32
Splenectomy	7 (70%)	1 (16.7%)	0.1
Tonsil enlargement	8 (80%)	3 (50%)	0.3
Mean liver span ± SD (cm)	8.2 ± 1.7	7.2 ± 2.6	0.35
Mean splenic span ± SD (cm) in non-splenectomized patients	3 ± 1.3 (*N*=3)	3.2 ± 1.3 (*N*=5)	0.06
Mean hemoglobin level ± SD (g%)	7.5 ± 0.7	7 ± 0.6	0.52
Mean serum ferritin level ± SD (ng/ml)	3,785 ± 1,780	1,885 ± 677	0.03
Adenoid enlargement	10 (100%)	6 (100%)	-
Nasopharyngeal narrowing	5 (50%)	2 (33%)	0.6

apneic event. She had no hypoventilation but did have some episodes of paradoxic breathing during sleep.

Of the 10 patients who had OSA, the male:female ratio was 1:2.3. The mean age was 9.7±3.8 years (range 4-15 years). The mean age at onset of habitual snoring was 3.6±2.1 years (range 1-10 years). The duration of habitual snoring prior to the diagnosis of OSA was 6.1±3.1 years (range 1.3-12.3 years). All OSA patients had adenoid hypertrophy; 8 of these (80%) had associated tonsil enlargement (Table 1). The median obstructive AHI was 9.9/hour (range 1.1-65/hour). The median arousal index was 8.7/hour (range 0.6-23.1/hour). The average baseline SpO_2 was 97±2% (range 94-99%) and the average baseline $P_{ET}CO_2$ was 48±7 mmHg (range 36-60 mmHg). The average nadir SpO_2 was 76±7% (range 67-83%) and the average peak $P_{ET}CO_2$ was 56±8 mmHg (range 43-70 mmHg).

A comparison of the clinical data between the OSA and non-OSA groups is found in Table 1. OSA patients had higher serum ferritin levels compared to non-OSA patients (3,785±1,780 *vs* 1,885±677 ng/ml; p=0.03) (Table 1). Those who had moderate-to-severe OSA tended to have a higher serum ferritin level compared to those who had mild OSA (4,606±1,784 *vs* 2,554±913 ng/ml; p=0.07; Table 2).

Of the 10 patients who had OSA, six underwent adenotonsillectomy. All reported marked improvement in snoring

Table 2
Comparison of clinical data between mild OSA and moderate-to-severe OSA patients.

Clinical data	Mild OSA (*N*=4)	Moderate-to-severe OSA (*N*=6)	*p*-value
Mean age ± SD (years)	8.8 ± 3.6	11.6 ± 3.8	0.3
Percent male	25	33	1.0
Mean % weight for height ± SD	104.8 ± 11.6	99.1 ± 4.5	0.3
Passive smoking	0	3 (50%)	0.2
Allergic rhinitis	1 (25%)	0	0.4
Obesity (% weight for height ≥120)	1 (25%)	0	0.4
Malnutrition (% weight for height <90)	0	0	-
Mean age thalassemia diagnosed ± SD (years)	4.1 ± 2.8	5.8 ± 0.7	0.2
Desferrioxamine therapy	3 (75%)	5 (83%)	1.0
Mean duration of desferrioxamine therapy± SD (years)	5.6 ± 1.8	4.5 ± 1.7	0.41
Splenectomy	2 (50%)	5 (83%)	0.5
Tonsil enlargement	3 (75%)	5 (83%)	1.0
Mean liver span ± SD (cm)	7.5 ± 1.9	8.7 ± 1.5	0.31
Mean splenic span ± SD (cm) in non-splenectomized patients	1.5 ± 0.7 (*N*=2)	1 (*N*=1)	0.67
Mean hemoglobin level ± SD (g%)	8 ± 0.6	7.3 ± 0.8	0.22
Mean serum ferritin level ± SD (ng/ml)	2,554 ± 913	4,606 ± 1,784	0.07
Adenoid enlargement	4 (100%)	6 (100%)	-
Nasopharyngeal narrowing	1 (25%)	4 (67%)	0.5

and quality of sleep. Histopathology showed reactive lymphoid hyperplasia in all cases.

DISCUSSION

In this study, the estimated prevalence of OSA in children with severe beta-thalassemia was 8.3%. This prevalence could be underestimated since we only performed the PSG in those who habitually snored. Some children with OSA might have no history of snoring and were not identified as OSA cases in this study. The estimated prevalence of OSA in this population was high compared to a report by Anuntaseree *et al* (2001) who reported a 0.7% prevalence of OSA in Thai school aged children (aged 6-13 years). Sixty percent of children with OSA had moderate-to-severe OSA. The average AHI among children with OSA was also high compared to general Thai school-aged children (1.1-65/hour *vs* 0.6-4.7/hour) (Anuntaseree *et al*, 2001).

There have been several reports of OSA among children with sickle cell disease, another inherited hemoglobinopathy that has clinical features of chronic hemolysis and increased extramedullary hematopoiesis, similar to beta-thalassemia (Maddern *et al*, 1989; Samuels *et al*, 1992; Salles *et al*, 2009). Our findings of a high prevalence of OSA and more severe

OSA were in accordance with the findings of Kaleyias *et al* (2008) who reported a high prevalence of sleep-disordered breathing and severe OSA in children with sickle cell disease. The mechanism of these findings is unknown and needs to be investigated.

In this study, the average age at the onset of habitual snoring was 3.6±2.1 years. This is comparable to the general pediatric population (Katz and Marcus, 2005). However, the mean age when OSA was diagnosed was 9.7±3.8 years, showing a long delay until diagnosis, suggesting OSA symptoms were not recognized in these children.

The mechanism of OSA in children with severe beta-thalassemia has not been well established. Kapelushnik *et al* (2001) reported the case of a child with thalassemia intermedia and OSA. They found extramedullary hematopoiesis in the nasopharygeal airway to be the cause of OSA (Kapelushnik *et al*, 2001). In our study, all OSA patients had adenoid hypertrophy and 80% had associated tonsil enlargement. Six patients with OSA underwent adenotonsillectomy. All of the adenotonsillar lymphoid tissues showed reactive lymphoid hyperplasia without the evidence of extramedullary erythropoiesis on histopathology. This suggests lymphoid hyperplasia was the cause of nasopharyngeal airway narrowing and OSA in children with severe beta-thalassemia. This is the same as in the general pediatric population and in children with sickle cell disease (Maddern *et al*, 1989). The mechanism for persistent lymphoid hyperplasia in these children is not known. Several mechanisms have been proposed, including compensatory lymphoid hyperplasia in response to splenectomy and repeated adenotonsillar infections with encapsulated organisms (Maddern *et al*, 1989).

In this study, we found a higher average serum ferritin level in the OSA group than the non-OSA group. Those who had more severe OSA tended to have a higher serum ferritin level than those who had milder disease. An increased serum ferritin level is generally found in patients with severe beta-thalassemia who require frequent blood transfusions. It reflects the number of blood transfusions and iron chelation. A higher serum ferritin level may reflect more severe disease, more frequent blood transfusions, facial bone changes and upper airway narrowing. Serum ferritin is also a non-specific inflammatory marker. Several studies have suggested OSA induces a systemic inflammatory response and rising levels of several proinflammatory cytokines, such as C-reactive protein, interleukin-8 and interferon gamma (Kheirandish-Gozal *et al*, 2006; Tam *et al*, 2006; Li *et al*, 2008). The higher serum ferritin levels in thalassemia children with OSA may reflect more inflammation induced by OSA in these children.

Pulmonary hypertension is common in patients with beta-thalassemia (Aessopos and Farmakis, 2005; Phrommintikul, 2006). Several mechanisms of increased cardiac output and pulmonary vascular resistance have been proposed as the pathogenesis for pulmonary hypertension in these patients (Aessopos and Farmakis, 2005; Phrommintikul, 2006). OSA is a known risk factor for pulmonary hypertension in the general pediatric population but has not been reported in children with beta-thalassemia. Our finding of a high prevalence of OSA in children with severe beta-thalassemia who habitually snored suggests this could

be a predisposing factor for pulmonary hypertension in this group of patients. A history of snoring and OSA symptoms should be periodically assessed in these children during their routine follow-ups at hematology clinics.

In conclusion, we reported a high prevalence of OSA among children with severe beta-thalassemia. Most of them had moderate-to-severe OSA. Adenotonsillar lymphoid hyperplasia was commonly found in those with OSA. A high serum ferritin level was associated with the occurrence of OSA and may be related to its severity. A history of snoring and OSA symptoms should be periodically assessed in children with severe beta-thalassemia. Further investigations regarding the mechanism of persistent adenotonsillar lymphoid hyperplasia and the relationship between OSA and pulmonary hypertension in children with severe beta-thalasemia are needed.

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