HK J Paediatr (new series) 2012;**17**:24-30

Daytime Sleepiness and Obstructive Sleep Apnoea from Children to Young Adults with Beta-thalassaemia Intemedia: A Pilot Study

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Abstract ***Objective:*** This pilot study assessed the prevalence of daytime sleepiness and obstructive sleep apnoea (OSA) from children to young adults with beta-thalassaemia intermedia. ***Methods:*** Patients diagnosed with beta-thalassaemia intermedia and attended the four participating hospitals (Prince of Wales, Tuen Mun, Queen Elizabeth and Princess Margaret) for regular evaluations were recruited. All subjects were examined by a paediatrician and underwent overnight polysomnography (PSG). The subjects were also invited to undergo magnetic resonance imaging (MRI) of the upper airway. Serum haemoglobin and ferritin levels were measured after overnight PSG. A detailed sleep apnoea questionnaire and a Chinese version of the Epworth Sleepiness Scale were completed by parents of subjects under 18 years old or by subjects themselves if they were aged 18 or more. ***Findings:*** A total of 19 beta-thalassaemia intermedia patients (15 males and 4 females) aged 3-28 years were enrolled. Their mean age at diagnosis was 3.54 years. Four subjects were found to have OSA using obstructive apnoea hypopnoea index (OAHI) >1 as cut-off. Epworth sleepiness score, haemoglobin and ferritin levels, PSG parameters and sleep related symptoms were similar between subjects with and without OSA. All 4 OSA subjects and 7 non-OSA patients underwent MRI, and no significant differences between their upper airway parameters were noted. ***Conclusion:*** Prevalence of OSA maybe higher amongst patients with beta-thalassaemia intermedia but this has to be confirmed by further studies with larger sample size.

Key words Beta-thalassaemia; Magnetic resonance imaging; Sleep apnoea, obstructive

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Received November 18, 2010

Introduction

Sleep is defined as a reversible behavioural state of decreased responsiveness and interaction with the environment.[1] The essential function(s) of sleep however, remain to be fully elucidated. Most of the information known about the possible function of normal sleep is based on studies investigating the effects of sleep deprivation and anecdotal evidence documenting the effects of sleep loss. Sleep deprivation studies in adult humans and animals have focused on physiologic and immunologic consequences of sleep loss and suggest that sleep is involved in maintenance of normal bodily functions and optimal immune performance.[2,3] Specifically, sleep is believed to play a role in the growth and healing of body tissues, learning and processing of memory, and central nervous system repair.[4] Obstructive sleep apnoea (OSA) is commonly recognised as an important cause for inadequate sleep quality and quantity.[5] Subjects with this condition if untreated can develop cardiovascular and neurocognitive complications.[5,6]

Beta-thalassaemia is a hereditary condition characterised by chronic haemolytic anaemia resulting from mutations that affect haemoglobin synthesis. Ineffective erythropoiesis causes osteoporosis and expansion of marrow space in the skull and facial bones thus predisposing this group of patients to upper airway obstruction especially during sleep.[7] A case report documented the presence of OSA in a child with beta-thalassaemia intermedia. Computed tomographic scanning demonstrated obstruction of the nasopharynx as a result of extramedullary erythropoiesis.[8] Tarasiuk et al performed polysomnography (PSG) on patients with thalassaemia and found significantly more arousals and periodic limb movements in patients compared to normal controls. This study, however, consisted of only 10 patients of whom six were of thalassaemia major type.[9] It is nowadays rare for thalassaemia major patients to have significant facial skeletal deformity as early diagnosis and regular blood transfusion would have kept extramedullary erythropoiesis at a minimum. This may not hold true for those with thalassaemia intermedia as chronic anaemia would still provide a stimulus for bone marrow expansion and hence a risk for airway obstruction. There is accumulating evidence to suggest that OSA is associated with endothelial dysfunction and cardiovascular diseases especially hypertension.[10-12] It is therefore of paramount importance to identify OSA in thalassaemic patients especially those with thalassaemia intermedia who are already at risk of suffering from myocardial strain as a result of chronic anaemia so that further insult to myocardial function is minimised. This study determined the presence and severity of daytime sleepiness and OSA in children, adolescents and young adults with beta-thalassaemia intermedia. The correlation between degree of objective sleepiness with haemoglobin and ferritin levels was also described.

Methods

Subjects diagnosed with beta-thalassaemia intermedia and attended the four participating hospitals (Prince of Wales, Tuen Mun, Queen Elizabeth and Princess Margaret) for regular evaluations were recruited. For patients with beta-thalassaemia intermedia, they were able to maintain a haemoglobin level of at least 6-7 g/dL at the time of diagnosis without the need for regular blood transfusions. None of the participants had medical conditions that may disturb sleep such as depression, intracranial pathology or use of medications that could interfere with sleep. Patients who had undergone any upper airway surgery were excluded. Informed consent was obtained from both subjects (those ≥18 years of age) and their parents. This study was approved by the institution ethics review board.

Clinical Evaluation

All subjects were examined by a paediatrician. Apart from asking about detailed symptomatologies, further information was obtained on sleep patterns, symptoms suggestive of other physical or sleep disorders and previous treatment history. Parents of the subjects under 18 years old completed a OSA symptom questionnaire[13] and a Chinese version of the Epworth Sleepiness Scale (ESS). For subjects aged 18 years or above, they completed the questionnaires themselves.

Demographics and detailed medical history of each subject were recorded for subsequent regression analysis to assess for factors that were associated with the presence of OSA. The height and weight of each subject were measured for determining the body mass index (BMI). Standing height without shoes was measured using a Harpenden stadiometer (Holtain, UK) to the nearest 0.1 cm. Body weight was measured with the lightest clothing to the nearest 0.1 kg by an electronic weighing scale (Tanita BF-522, Japan).

Polysomnographic Study

All subjects underwent overnight PSG assessment. A model 1000P PSG machine was used to record the

following parameters: electroencephalogram from four leads (C_3/A_2, C_4/A_1), bilateral electrooculogram, electromyogram of mentalis activity and bilateral anterior tibialis. Respiratory movements of the rib cage and abdomen were measured by pneumatic effort belt. Electrocardiogram and heart rate were continuously recorded from two anterior chest leads. Arterial oxyhaemoglobin saturation (SaO_2) was measured by an oximeter (Ohmeda Biox 3900 Pulse Oximeter) with finger probe. Respiratory airflow pressure signals and end tidal CO_2 were concurrently measured via a triple-port nasal catheter placed at the anterior nares and connected to a pressure transducer and a capnograph (BCI Capnocheck Plus) respectively. Snoring was measured by a snoring microphone placed near the throat. Body position was monitored via a body position sensor. Obstructive apnoea (OA) was defined as absence of airflow with persistent respiratory effort lasting longer than 2 baseline breaths, irrespective of SaO_2 changes. Central apnoea (CA) was defined as absence of respiratory effort associated with absence of airflow. Those of greater than 20 seconds with or without oxygen desaturation or arousals, and those of any duration but associated with oxygen desaturation of at least 4% and/or arousals were quantified. Obstructive apnoea index (OAI) was defined as the number of OA per hour of sleep. Hypopnoea was defined as a reduction of 50% or more in the amplitude of the airflow signal. It was only quantified if longer than 2 baseline breaths and associated with oxygen desaturation of at least 4% and/or arousals. Obstructive apnoea hypopnoea index (OAHI) was defined as the total number of obstructive apnoeic and hypopnoeic episodes per hour of sleep. Oxygen desaturation index (ODI) was defined as the total number of dips in arterial oxygen saturation greater than 4% per hour of sleep. Arousal was defined as an abrupt shift in EEG frequency during sleep. In rapid eye movement sleep, arousals were scored only when accompanied by concurrent increases in submental electromyography amplitude. We defined an adequate overnight PSG as one with sleep efficiency of >80%. OAHI >1 was used as the diagnostic cutoff for OSA. All subjects had blood testing for serum ferritin and haemoglobin levels after overnight PSG.

Magnetic Resonance Imaging of the Upper Airway

All subjects were invited to undergo upper airway magnetic resonance imaging (MRI) using a 1.5T MR unit (Siemens, Sonata, Erlangen, Germany). Patient was imaged supine with the cervical spine in neutral position. A three-dimensional localiser image was obtained. Sagittal and transverse fast spin-echo fat suppressed images as well as sagittal and transverse T1-weighted spin-echo images were obtained.[14] The midline sagittal image was obtained mainly to define the anatomy of the supraglottic airway and to evaluate the level(s) of obstruction. Nasopharynx was defined as the aerated space bordered by soft palate anteriorly, adenoid posteriorly, and nasal turbinates anteriorly and superiorly. The inferior border was defined by the inferior tip of the uvula. Oropharynx was defined as the aerated spaced bordered by the hard palate superiorly, tongue inferiorly, and soft palate posteriorly. Hypopharynx was defined as the aerated spaced bordered by posterior aspect of the tongue anteriorly, posterior pharyngeal wall posteriorly, and inferior aspect of soft palate anterior. The inferior border is defined by the inferior extent (or base) of the tongue. The maximal AP diameter of the nasopharynx, oropharynx and hypopharynx were measured and the site of obstruction will be recorded. The fast SE fat suppressed images were obtained mainly to evaluate the tonsillar tissue, which appears bright. The maximal dimensions of the adenoids, palatine tonsils and lingual tonsils are recorded. Presence of glossoptosis or collapsing hypopharynx was recorded if noted. The transverse T1-weighted image was obtained to evaluate the effect of expansion of marrow space in the skull and facial bones.

Statistical Analysis

Data processing was done using SPSS for Windows14 (SPSS, Inc., Chicago, IL). Descriptive data were presented as percentage and median with interquartile range (IQR). Associations between severity of OSA and continuous parameters were assessed by Spearman's rank correlation coefficient and between categorical variables by Chi-square test or Fisher's exact test as appropriate. Mann-Whitney U test was used to compare the difference of the laboratory and PSG results between the OSA and non-OSA groups. Statistically significant difference was set at 5% for all comparisons.

Results

A total of 19 beta-thalassaemia intermedia patients (15 males and 4 females) aged 3-28 years were recruited. Their mean and median age at diagnosis was 3.54 years and 6.3 years, respectively. Ten out of these 19 patients had received at least one blood transfusion, and the average was 5.3 times of blood transfusion after the diagnosis of beta-thalassaemia intermedia was made.

None of the subjects reported to suffer from any atopic diseases (such as asthma, allergic rhinitis and eczema) and no cardio-pulmonary abnormalities were detected on clinical examination. Eleven patients gave consent to undergo MRI examination.

Four subjects were identified to suffer from OSA using OAHI >1 as cut-off. They all had mild disease, their OAHI ranged from 1.2 to 2.8/hr. There was no significant difference in clinical, laboratory parameters and ESS between subjects with and without OSA (Table 1). Sleep parameters in terms of total sleep time, sleep efficiency, sleep staging, and apnoea index were similar between the two groups except for periodic leg movements (PLM) index. The tonsillar, adenoidal and airway size were similar between subjects with and without OSA (Table 2). In addition, there was no correlation found between degree of objective sleepiness (ESS) with haemoglobin and ferritin levels.

The details of the distribution of sleep related symptoms among the 19 beta-thalassaemia intermedia patients are listed in Table 3. No difference was found between OSA and non-OSA subjects.

Table 1 Characteristics of subjects divided into non-OSA and OSA groups

	Non-OSA (n=15)		OSA (n=4)	
	Median	**IQR**	**Median**	**IQR**
Age	12.4	(8.3-18.6)	13.7	(7.7-25.3)
Height (cm)	139.0	(129-168)	144.0	(120-169.5)
Weight (kg)	37.7	(21-51.1)	40.7	(21.6-54.2)
Body mass index (kg/m^2)	15.8	(14.5-18.8)	17.0	(14.8-21.1)
Epworth sleepiness scale	6.0	(4-8)	4.5	(2.3-12)
Red blood cell (10^{12}/L)	3.6	(3.17-4.37)	3.7	(3.1-4.4)
Haemoglobin (g/dL)	8.5	(8-9.6)	9.5	(8.7-10.3)
Haematocrit (L/L)	0.3	(0.3-0.3)	0.3	(0.3-0.3)
Platelets (10^9/L)	723.0	(442-839)	707.0	(286.3-806)
White blood cell (10^9/L)	13.5	(7.7-24)	28.3	(10.5-58.2)
Serum ferritin (ug/L)	2345.5	(1217-3186)	1411.0	(739-2819)
Right tonsil length (cm)	1.8	(1.3-1.9)	1.5	(1.4-1.8)
Right tonsil width (cm)	1.8	(1.3-1.9)	1.8	(1.6-2.3)
Right tonsil (cm^2)	3.3	(1.7-3.4)	2.7	(2.2-4.1)
Left tonsil length (cm)	1.4	(1.2-1.8)	1.5	(1.2-2.1)
Left tonsil width (cm)	1.4	(1.3-1.8)	1.4	(1.4-2.0)
Left tonsil (cm^2)	2.1	(1.6-2.8)	2.2	(1.6-2.7)
Airway AP	0.7	(0.4-1.0)	0.6	(0.5-1.1)
Airway TS	0.8	(0.5-1.1)	0.6	(0.5-1.0)
Adenoid length (cm)	2.4	(2.4-2.6)	2.7	(2.4-3.0)
Adenoid width (cm)	1.2	(1.1-1.3)	1.3	(1.2-1.6)
Adenoid size (cm^2)	2.7	(2.6-3.1)	3.6	(2.8-4.5)
Total sleep time (hr)	8.1	(7.4-8.9)	7.2	4.8-8.8)
Sleep efficiency (%)	92.2	(85.9-93.8)	82.8	(58.4-93.8)
Stage rapid eye movement (%)	20.1	(17.5-22.2)	20.1	12.0-21.5)
Stage 1(%)	2.1	(1.2-3.9)	3.5	(0.3-13.1)
Stage 2(%)	47.4	(31.3-49.7)	48.0	(40.8-58.0)
Stage 3(%)	8.6	(7.8-12.5)	8.7	(5.6-10.1)
Stage 4(%)	22.8	(15.4-31.9)	20.1	(8.7-29.6)
Periodic leg movements index*	1.6	(0.5-7.1)	10.6	(5.2-20.2)
Oxygen desaturation index	0.3	(0-0.5)	0.7	(0-1.4)
Obstructive apnoea index	0.0	(0-0.3)	0.1	(0-0.3)
Obstructive apnoea hypopnoea index*	0.2	(0-0.6)	1.3	(1.2-2.8)
Total arousal index	12.0	(10.2-16.2)	17.6	(13-25)
Respiratory arousal index	10.3	(8.8-14.4)	15.4	(9.3-21.1)

IQR: interquartile range

*P <0.001

Table 2 Comparison of MRI measurements between subjects with and without OSA

	Non-OSA (n=4)		OSA (n=4)	
	Mean	**IQR**	**Mean**	**IQR**
Right tonsil length (cm)	1.6	(1.3-1.9)	1.5	(1.4-1.7)
Right tonsil width (cm)	1.7	(1.4-1.9)	1.8	(1.6-1.9)
Right tonsil (cm^2)	2.7	(1.7-3.4)	2.7	(2.2-3.3)
Left tonsil length (cm)	1.5	(1.3-1.8)	1.5	(1.2-1.9)
Left tonsil width (cm)	1.5	(1.3-1.7)	1.4	(1.4-1.5)
Left tonsil (cm^2)	2.3	(1.6-2.8)	2.2	(1.6-2.8)
Airway AP (cm)	0.7	(0.4-0.9)	0.6	(0.5-0.6)
Airway TS (cm)	0.8	(0.5-1.0)	0.6	(0.5-0.8)
Adenoid length (cm)	2.5	(2.3-2.6)	2.7	(2.4-3.0)
Adenoid width (cm)	1.2	(1.1-1.3)	1.3	(1.2-1.5)
Adenoid size (cm^2)	3.1	(2.6-3.1)	3.6	(2.8-4.5)

IQR: interquartile range

Table 3 Distribution of sleep related symptoms among the 19 subjects

Sleep related symptoms	**Non-OSA**	**OSA**
	n (%)	n (%)
Difficulty in getting to sleep	5 (21.4)	2 (50.0)
Feeling anxious or afraid when falling asleep	0 (0.0)	0 (0.0)
Repetitive actions such as rocking or head banging while falling asleep	1 (5.3)	0 (0.0)
Startles or jerks parts of body while falling asleep	4 (26.7)	1 (25.0)
Night sweating during sleep	9 (64.3)	4 (100.0)
Sudden awakenings	2 (13.3)	1 (25.0)
Nocturnal breathing difficulty	1 (6.7)	1 (25.0)
Nocturnal mouth breathing	4 (26.7)	1 (25.0)
Gasps for breath or unable to breathe during sleep	0 (0.0)	0 (0.0)
Lips turning blue during sleep	0 (0.0)	0 (0.0)
Sleep restlessly	13 (86.7)	1 (25.0)
Prone position	5 (33.3)	1 (25.0)
Nocturnal teeth grinding	6 (40.0)	1 (25.0)
Nocturnal enuresis	1 (13.3)	1 (25.0)
Sleep talking	5 (33.3)	1 (25.0)
Nightmares	4 (26.7)	2 (50.0)
Early morning awakenings	3 (20.0)	2 (50.0)
Morning dry-mouth	8 (53.3)	2 (50.0)
Difficulty getting out of bed in the morning	8 (53.3)	1 (25.0)
Feeling unrefreshed after getting up in the morning	4 (26.7)	2 (50.0)
Headache after getting up in the morning	3 (20.0)	1 (25.0)
Feeling tired during the day	3 (20.0)	1 (25.0)
Habitual snoring	1 (13.3)	2 (50.0)

All are non-significant using by Chi-square test or Fisher's exact test as appropriate

Discussion

Our study provided an insight into sleep related symptoms and prevalence of obstructive sleep apnoea among beta-thalassaemia intermedia patients in Hong Kong. Four subjects out of a total of 19 were found to have OSA, a prevalence of around 20%, which is high taking into account the prevalence of OSA among healthy children being 2.3 to 4.5%.[15] We cannot exclude the possibility that we studied a selected population. That means subjects with sleep symptoms were more likely to participate and that would have inflated the OSA prevalence in patients with beta-thalassaemia intermedia. On the other hand, this figure of 20% could be a genuine reflection of a higher OSA prevalence among this group of at risk subjects. All subjects identified to have OSA had only mild disease, as their OAHI was between 1 and 5. In our experience, subjects with mild OSA do not tend to have significant OSA symptoms.[16,17] As shown in table 3, sleep related symptoms were similar between subjects with and without OSA. Furthermore, the subjects with OSA were not sleepier than those without the disease, as their Epworth sleepiness scores were similar. Interestingly, unlike adults with OSA, children with OSA do not tend to present with daytime sleepiness, rather they are hyperactive with poor attention.[18] Having said that, there is accumulating evidence to suggest mild childhood OSA is associated with important complications.[10,19] Nocturnal systolic blood pressure was significantly higher in children with mild OSA compared to healthy controls.[10] Children with mild disease were found to have neurobehavioural abnormalities that improved with surgical intervention.[19] Therefore it is important to identify individuals with OSA early, even it is of mild degree and without significant symptoms, so that appropriate treatment can be instituted and follow-up arranged.

In this study, the prevalence of sleep related symptoms was discrepant between the groups with and without OSA as shown in Table 3 (differences of >25% were noted in difficulty in getting to sleep, night sweating during sleep, sleep restlessly, early morning awakenings, difficulty getting out of bed in the morning, and habitual snoring), though it was not to the extent of being statistically significant. In our previous research work on validating a screening OSA questionnaire, snoring and night sweating were identified to be useful in predicting the presence of OSA.[13] Since this was a pilot study with a small sample size, these "subtle" differences will have to be confirmed by further studies with larger sample size.

Overnight sleep study remains the gold standard for diagnosing OSA but the service is not widely available. Furthermore, it is expensive and labour intensive, thus current waiting time for sleep study in certain units is unacceptably long.[17] The findings of this study suggested that even in otherwise healthy beta-thalassaemia intermedia patients, PSG should be offered as symptoms alone are inaccurate in separating those with and without OSA.

We were unable to find any correlation between blood parameters like ferritin and haemoglobin levels with any of the sleep or OSA parameters. A previous report has linked iron deficiency anaemia / ferritin levels with limb movements at night.[9] The negative result in this current study may relate to the small sample size.

There were certain limitations in this study. We involved 4 paediatric haematology units in Hong Kong, yet we only managed to recruit 19 subjects. This limited sample population could explain the many insignificant findings between subjects with and without OSA. As mentioned, the "high" OSA prevalence as documented in this study needs to be confirmed by further studies. Furthermore, as a result of the small sample population, we were unable to assess risk factors for OSA in this group of patients.

In conclusion, the current study suggested that OSA maybe more prevalent in the beta-thalassaemia intermedia population. We failed to detect any statistically significant differences in the MRI measurements and sleep related symptoms between OSA and non-OSA patients. Further studies of larger sample size are required to ascertain or refute these findings.

Acknowledgements

The study was supported by Children's Thalassaemia Foundation (Project no. 2006/01). We would like to thank the medical professionals from the four participating hospitals (Prince of Wales, Tuen Mun, Queen Elizabeth and Princess Margaret) for their kind support and assistance with enrolment and information collection.

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