Natural History of Primary Snoring in School-aged Children: A 4-Year Follow-up Study

Albert M. Li, MD[1]*; Yin Zhu, MM[1]*; Chun T. Au[1], MPhil; Dennis L. Y. Lee[2], MB; Crover Ho[3], RPSGT; Yun K.Wing[3], MB

* Joint first author

[1]Department of Pediatrics, [2]Department of Otorhinolaryngology - Head and Neck Surgery, [3]Department of Psychiatry, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong.

ABSTRACT

Background: To examine the natural history of childhood primary snoring (PS) and to identify predictive clinical symptoms and risk factors associated with PS progression to obstructive sleep apnea (OSA).
Methods: Children aged 6-13 years who were diagnosed to have PS in our previous community-based OSA prevalence study were invited to undergo repeat polysomnography (PSG) at 4-year follow-up. Subjects with an obstructive apnea hypopnea index (OAHI) ≥1 were classified as having OSA at follow-up.
Results: Seventy children (60% boys) with a mean age of 14.7±1.8 years was analysed in this follow-up study. The mean duration of follow-up was 4.6±0.6 years. At follow-up, 26 subjects (37.1%) progressed to OSA, of whom 5 (7.1%) had moderate-to-severe disease (OAHI≥5). Twenty-two (31.4%) remained as PS and 18 (25.7%) had complete resolution of their snoring with normal PSG. Persistent snoring had a positive predictive value (PPV) of 47.7% and a negative predictive value (NPV) of 86.4% for predicting progression from PS to OSA. Multivariate logistic regression analysis showed that persistent overweight/obesity was a significant risk factor for the development of OSA at follow-up, with odds ratio of 7.95 (95%CI 1.43-44.09).
Conclusions: More than one third of school-aged children with PS progressed to OSA over a 4-year period, though only 7.1% developed moderate-to-severe disease.Weight control may be an important component in the management of PS as obesity was found to be a significant risk factor for PS progression.

Snoring is a common symptom of pediatric sleep-disordered breathing (SDB), and the reported prevalence of habitual snoring ranges from 4.0% to 34.5%.[1-4] SDB includes a spectrum of diseases with severity ranging from primary snoring (PS), upper airway resistance syndrome (UARS) to obstructive sleep apnea (OSA).[5, 6] In contrast to

OSA, PS which is defined as snoring without apnea, frequent arousals or gas exchange abnormalities[7] has been positioned at the milder end of the SDB severity continuum, [8] and treatment is usually not prescribed.[9]

Nevertheless, whether deferment of treatment for PS is safe has aroused more research recently. Kwok et al found that children with PS had increased casual daytime blood pressure and reduced arterial distensibility.[10] Our research group further demonstrated that nighttime blood pressure was also elevated in children with PS.[11] A more recent study found that PS was a risk factor for hyperactive and inattentive behavior and poor school performance in children.[12] Accumulating evidence suggests PS may be associated with a variety of clinical sequelae, and therefore it should no longer be considered as completely benign.[13]

Another important issue that relates to whether PS if left untreated progresses to OSA, persists or resolves over time is still poorly defined. To our knowledge, only three research studies that examined the natural history of PS in children have been published. The three studies repeated polysomnography (PSG) in cohorts of 20, 9 and 31 children with PS over a 2-year, 3-year and 6-month period respectively. All three studies concluded that PS in children generally did not evolve to OSA over time.[14-16] These studies, however, had small sample size and consisted of hospital-based subjects.

In this study, we aimed to determine (1) the natural history of PS in school-aged children recruited from the community over a 4-year period and (2) clinical symptoms and risk factors predictive of PS progression to OSA.

METHODS AND MATERIALS

Subjects

This was a prospective study of a cohort established between 2003 and 2005 for a childhood OSA epidemiologic study.[17] Children aged 6-13 years from 13 primary schools were randomly recruited. A total of 619 subjects underwent PSG, and 161 were defined as PS (see below for definition). For this follow-up study, as a result of limited resources, only the first 99 consecutive subjects with PS were invited to undergo repeat assessment. Subjects were excluded from the study if they had cardiovascular, renal or neuromuscular diseases, chromosomal abnormalities, acute illness within two weeks of PSG, or if they had undergone upper airway surgery or started on continuous positive airway pressure treatment during the follow-up period. Written informed consent and assent were obtained from the parents and subjects respectively. The study was approved by the Clinical Research Ethics Committee of

the Chinese University of Hong Kong (CRE_2007.363).

Sleep symptom questionnaire

A validated sleep symptom questionnaire[18] was completed by parents of recruited subjects at baseline and follow-up, and the following information was extracted: (1) snoring frequency and other sleep-related symptoms rated on a 6-point scale: 0=never; 1=less than one night per month; 2=one to two nights per month; 3=one to two nights per week; 4=three nights or more per week; 5=unclear. Snoring and other OSA-related symptoms were defined as present if their frequency scored 2-4. (2) Clinical features: history of allergic rhinitis and asthma. (3) Socioeconomic and environmental factors. We defined 'persistent' as having positive history at both time-points.

Anthropometry assessment

The weight, height and Tanner stage of all subjects were assessed on the day of PSG. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Weight, height and BMI were converted to z-scores appropriate for age and gender,according to local reference.[19] Overweight and obese children were defined as a BMI z-score ≥ 1.036 and 1.645, corresponding to the 85th and 95th percentile, respectively. We defined 'persistent overweight/obesity' as being overweight or obese at both baseline and follow-up. Pubertal stage was evaluated using a self-assessment questionnaire to categorize Tanner stages.[20] Prepubertal was defined as Tanner stage 1, and pubertal defined as Tanner stage 2 or greater.

Tonsil and adenoid size assessment

The examination was carried out in the morning after overnight PSG by an otorhinolaryngologist. The size of tonsils and adenoids were evaluated by a 4mm rigid rhinoscope (Storz endoscopy, Tuttingen, Germany) and a flexible laryngoscope (P4, Olympus) respectively. The size of tonsils and adenoids was reported as a percentage of the oropharyngeal and nasopharyngeal airway respectively. A large tonsil or adenoid was defined as the soft tissue occupying ≥50% of the corresponding airway. Tonsils and adenoids were further classified as 'persistently large' if they were large at both time-points.

Polysomnography (PSG)

All recruited children underwent initial and follow-up standard overnight PSG at a dedicated sleep laboratory with CNS 1000P polygraph (CNS Inc, Chanhassen, Minnesota, USA). In brief, the central and occipital electroencephalogram, bilateral electrooculogram, submental electromyogram, bilateral leg electromyogram and electrocardiogram were recorded. The positions of the subject, respiratory airflow (nasal cannula connected to pressure transducer), respiratory efforts (strain gauge), arterial oxyhaemoglobin saturation (SpO_2, by Ohmeda 3700 pulse oximeter, Boulder, CO, USA) were measured. All data were scored by experienced PSG technologists. At baseline standard criteria described in our previous publication was used for scoring.[21, 22] While at follow-up, the new AASM 2007 pediatric polysomnography scoring criteria was used.[23] Therefore all the baseline data of PS subjects who participated in our follow-up study was rescored using AASM criteria. Those who were not classified as PS by the new criteria were excluded.

Obstructive apnea hypopnea index (OAHI) was defined as the total number of obstructive apneic and hypopneic episodes per hour of sleep. Oxygen desaturation index (ODI) was defined as the total number of dips in arterial oxygen saturation >3% per hour of sleep. The oxygen saturation nadir (SpO_2 nadir) was also noted. Arousal index (ArI) was defined as the total number of arousals per hour of sleep.

Children who snored were diagnosed to have PS if their OAHI<1 and SpO_2 nadir≥90%. At follow-up, children were diagnosed to have OSA if their OAHI≥1. Normal subjects were defined as non-snorers with OAHI<1 and SpO_2 nadir≥90%.

Statistical Analysis

Student t tests, Mann-Whitney U tests and chi square tests were used to detect difference between subjects who participated in this study and those who did not for parametric, non-parametric and categorical data respectively. Paired t tests, Wilcoxon signed rank tests and McNemar tests were used to examine intra-group differences between baseline and follow-up for parametric, non-parametric and categorical data respectively. Sensitivity, specificity, PPV, NPV, positive likelihood ratio and negative likelihood ratio together with their 95%CI of OSA-related symptoms were calculated using an online software http://vassarstats.net/clin1.html. Binary logistic regression analyses were performed to investigate factors associated with progression of PS to OSA and resolution of PS to normal at follow-up seperately. All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois), and a p value <0.05 was considered statistically significant.

RESULTS

Of the 99 subjects invited, we failed to contact 6 and 18 refused to participate. One case who had received tonsillectomy for recurrent tonsillitis during the follow-up period was excluded. Therefore 74 subjects with PS participated in this follow-up study. There were no significant differences in demographic, clinical, environmental, socioeconomic or polysomnographic characteristics between the 74 who participated and the 87 who did not (Table 1). Four participants had OAHI⩾1 at baseline using AASM 2007 criteria during rescoring, so a total of 70 subjects were included for final analysis. Mean time of reevaluation was 4.6±0.6 (range 3.4-6.2) years after the initial assessment.

Subjects' characteristics at baseline and follow-up

For the whole group, changes in anthropometric and PSG parameters over the follow-up period are shown in Table 2. As expected, subjects had significant increase in weight and height however their average BMI z-score remained unchanged. The proportion of pubertal children increased from 12.9% to 100%. Only six subjects had large tonsils at baseline, of whom 3 had persistently large tonsils at follow-up. Three subjects had large adenoids at baseline but none at follow-up. None of the subjects had new onset of large tonsils or adenoids at follow-up. OAHI, ArI and ODI increased while SpO_2 nadir decreased significantly over the follow-up period (Figure 1 and Table 2).

Twenty-six of the 70 subjects (37.1%) developed OSA at follow-up. Their median OAHI was 2.05 (ranging from 1.00 to 13.01), and 5 subjects (7.1%) had OAHI≥5. Amongst the remaining subjects without OSA at follow-up, 22 (31.4%) remained as PS and 18 (25.7%) became normal. Four subjects were unclassified at follow-up, of whom 2 had OAHI<1 but unclear snoring status and 2 had OAHI<1 but their SpO_2 nadir <90%.

Predictive clinical symptoms and risk factors for PS progression to OSA

Among the OSA-related clinical symptoms, only persistent snoring was significantly different between those who did and did not develop OSA at follow-up (p=0.007). Persistent snoring had a relatively high sensitivity (87.5%, 95%CI 66.5%-96.7%) and negative predictive value (NPV) (86.4%, 95%CI 64.0%-96.4%) despite poor specificity (45.2%, 95%CI 30.2%-61.2%) and positive predictive value (PPV) (47.7%, 95%CI 32.7%-63.1%) for the development of OSA. The positive

likelihood ratio and negative likelihood ratio of persistent snoring was 1.60 (95%CI 1.17-2.19) and 0.28 (0.09-0.84) respectively for the development of OSA.

We analysed the effects of several potential factors in predicting progression, persistence or resolution of PS using logistic regression models (Table 3). In identifying the risk factors for worsening of PS, the univariate analysis showed only the presence of persistent overweight/obesity was significantly associated with progression to OSA, with odds ratio of 7.33 (95% CI=1.41-38.13). In a multivariate model adjusted for baseline age, gender, persistently large tonsils and persistent snoring, the presence of persistent overweight/obesity remained the only significant predictor, with odds ratio of 7.95 (95% CI=1.43-44.09). In contrast, no factors were found to be significantly associated with remission of PS.

DISCUSSION

In this community-based follow-up study of children with PS, we demonstrated that more than one third of the subjects progressed to OSA over a period of 4 years. Persistent snoring had a relatively high NPV for PS progression. Persistent overweight/obesity placed children with PS at an increased risk for such progression. To our knowledge, this study on the natural history of PS in children is the first to report a significant proportion of subjects with disease progression to OSA and its associated risk factors.

Studies examining natural history of PS are scarce in both adults and children. The comparison between our study and the other three published pediatric studies is shown in Table 4. None of the previous studies found significant changes in respiratory parameters for the group as a whole, and the proportion of subjects progressed to OSA was much lower than in our study.[14-16] One possible explanation for this discrepancy is our longer follow-up period, which would allow subjects greater exposure time to risk factor(s) leading to disease progression. One such risk factor was persistent overweight/obesity. This is understandable as obesity is a well-established risk factor for OSA.[17, 24] Our present study provided robust evidence that obesity is a significant risk factor in causing disease progression along the SDB severity spectrum in children. Therefore weight reduction may play an important role in preventing PS from pregressing to OSA for overweight/obese children. However in our study cohort the overall magnitude of change in BMI z-score was only moderate, and we were unable to demonstrate a significant association between chang in BMI z-score and progression of PS. Further intervention study to verify this hypothesis is needed.

The age range in our study was older than the other series. At follow-up all of our

subjects had reached puberty. We however, failed to find a significant effect of puberty on PS progression. Previous studies showed that AHI had no correlation with Tanner stage in healthy adolescents.[25] It has also been suggested that changes in sex hormones were not a primary modulator of upper airway function during transition from childhood to adulthood.[26] Thus the role of puberty in SDB remains undefined at present. On a similar note, we failed to identify gender as a significant risk factor for PS progression in this current study.

There is also discrepancy in the percentage of resolved PS across the four studies (Table 4), likely a result of different definitions used for PS resolution. All three published studies only used decreased questionnaire-based symptom scores to define resolution of PS. We however, classified resolution of PS as absence of snoring together with normal PSG findings. Adenotonsillar hypertrophy was not found to be associated with PS progression in this study. It may be because the mean age of our cohort at baseline and follow-up were both beyond the peak age of lymphoid hypertrophy.[27] This data was however not fully analysed in previous studies where they included younger participants (Table 4).

In school-aged children, PS is not necessarily a stable status, especially those who remained overweight or obese. Moreover, presence of persistent snoring can also be used as a guide for disease progression. Persistent snoring has a relatively high NPV for development of OSA, meaning that if a child with PS did not continue to snore it was less likely that he/she would develop OSA. Thus a clinician could give priority for repeat assessment for children with PS who remain overweight or obese and/or with persistent snoring.

There were a few limitations in this study. Firstly, esophageal pressure monitoring was not used thus cases with UARS would have been missed. Nevertheless nasal pressure was monitored in our study, which made up for this potential source of error to some extent. Secondly, other potential factors associated with progression or resolution of PS such as change in craniofacial structure or fat deposition in the upper airway were not performed in this study.

In summary, more than one third of children with PS progressed over a 4-year period to develop OSA, and persistent overweight/obesity was a significant risk factor. Therefore in the management of school-aged children with PS, great attention should be paid to weight control. As accumulating evidence suggest PS is also associated with important sequelae, further studies should examine the potential beneficial effects of intervention for this common pediatric problem.

Table 1. Characteristics of children with PS who did and did not participate in the follow-up study

	Participants (n=74)	Non-participants (n=87)	p value
Age (years)	10.1(1.7)	10.3(1.7)	.52
Male gender (n,(%))	50 (67.6)	55 (63.2)	.56
Weight (kg)	34.5 (9.7)	35.2 (10.4)	.65
Height (cm)	137 (11.2)	139 (11.2)	.25
BMI (kg/m^2)	18.0 (3.1)	17.9 (3.3)	.74
BMI z-score	0.47 (0.95)	0.38 (1.08)	.52
Puberty (n,(%))	13 (17.6)	17 (19.5)	.75
Large tonsils (n,(%))	7 (9.5)	13 (14.9)	.29
Large adenoids (n,(%))	3 (4.1)	6 (6.9)	.43
Snoring (n,(%))			.52
Sometimes	19 (25.7)	20 (23.5)	
Often	30 (40.5)	30 (34.5)	
Frequently	25 (33.8)	37 (42.5)	
Allergic rhinitis (n,(%))	62 (83.8)	67 (77.0)	.28
Asthma (n,(%))	11 (14.9)	9 (10.3)	.39
Household smoking (n,(%))	16 (21.6)	28 (32.2)	.13
Share bedroom with others (n,(%))	58 (78.4)	62 (71.3)	.30
Share bed with others (n,(%))	17 (23.0)	25 (28.7)	.41
Household area (n,(%))			.09
≤400 sq ft	14 (18.9)	29 (33.3)	
401-800 sq ft	45 (60.8)	47 (54.0)	
>800 sq ft	15 (20.3)	11 (12.6)	
Family income (n,(%))			.09
≤HK$10,000	14 (18.9)	29 (33.3)	
HK$10,001-20,000	45 (60.8)	47 (54.0)	
>HK$20,000	15 (20.3)	11 (12.6)	
Paternal education (n,(%))			.58
Primary or below	7 (9.5)	13 (14.9)	
Secondary	56 (75.7)	62 (71.3)	
Tertiary or above	11 (14.9)	12 (13.8)	
Maternal education (n,(%))			.81
Primary or below	9 (12.2)	10 (11.5)	

Secondary	55 (74.3)	68 (78.2)	
Tertiary or above	10 (13.5)	9 (10.3)	
OAHI (/hr)	0.12 (0.00-0.46)	0.15 (0.00-0.50)	.63
SpO_2 nadir (%)	93 (92-95)	93 (92-94)	.67

Mean (SD), median (IQR) and number (%) are presented for parametric, non-parametric and categorical data, respectively.

BMI: body mass index; OAHI: obstructive apnoea hypopnoea index; SpO_2 nadir: oxygen saturation nadir.

Table 2. Anthropometric and polysomnographic data of the subjects (n=70) at baseline and follow-up

	Baseline	Follow-up	P value
Age (year)	10.2 (1.7)	14.7 (1.8)	<.001
Weight (kg)	35.0 (9.7)	55.7 (13.2)	<.001
Weight z-score	0.36 (0.96)	0.59 (1.02)	<.01
Height (cm)	138 (11.5)	162 (8.8)	<.001
Height z-score	-0.02 (1.11)	0.35 (1.27)	.01
BMI (kg/m^2)	18.2 (3.1)	21.1 (3.9)	<.001
BMI z-score	0.50 (0.94)	0.53 (0.90)	.68
Tanner stage (n,(%))			<.001
Tanner 1	61 (87.1)	0 (0)	
Tanner 2	5 (7.1)	9 (12.9)	
Tanner 3	3 (4.3)	25 (35.7)	
Tanner 4	1 (1.4)	32 (45.7)	
Tanner 5	0 (0)	4 (5.7)	
Large tonsils (n,(%))	6 (8.6)	3 (4.3)	.49
Large adenoids (n,(%))	3 (4.3)	0 (0)	.25
Sleep efficiency (%)	86.0 (77.4-89.2)	87.0 (77.0-92.2)	.54
Sleep latency (min)	15 (8-24)	12 (9-17)	.01
REM latency (min)	132 (96-168)	93 (75-171)	.13
Stage N1 (% TST)	7.1 (2.8)	8.5 (3.9)	<.01
Stage N2 (% TST)	46.2 (6.2)	48.7 (6.0)	<.01
SWS (% TST)	25.1 (5.8)	21.4 (6.4)	<.001
REM (% TST)	20.2 (4.3)	21.4 (4.1)	.04
OAHI (/hr)	0.25 (0-0.61)	0.50 (0.08-1.50)	<.001
SpO_2 nadir (%)	93 (92-95)	93 (91-94)	.04
ArI (/hr)	5.5 (4.6-7.5)	6.7 (5.1-8.7)	.03
ODI (/hr)	0.12 (0-0.35)	0.19 (0-0.59)	<.01

Mean (SD), median (IQR) and number (%) are presented for parametric, non-parametric and categorical data, respectively.
BMI, body mass index; REM, rapid eye movement; TST, total sleep time; SWS, slow wave sleep; OAHI, obstructive apnoea hypopnoea index; SpO_2 nadir, oxygen saturation nadir; ArI, arousal index; ODI, oxygen desaturation index.

Table 3. Logistic regression analysis assessing the potential factors associated with the worsening or remission of PS

	PS at follow-up vs OSA at follow-up		PS at follow-up vs normal at follow-up	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Male gender	2.25 (0.69-7.32)	—	0.64 (0.18-2.25)	—
Baseline variables				
Age	0.91 (0.65-1.29)	—	0.76 (0.50-1.15)	—
BMI z-score	1.40 (0.75-2.64)		1.18 (0.59-2.36)	
Overweight/obesity	3.40 (0.97-11.98)		0.77 (0.18-3.21)	
Tanner stage	0.46 (0.11-1.90)		0.73 (0.30-3.21)	
Large tonsils	2.74 (0.26-28.41)		0.38 (0.03-4.58)	
Large adenoids	—		—	
Allergic rhinitis	0.43 (0.10-1.91)		0.37 (0.04-3.93)	
Asthma	0.38 (0.06-2.28)		1.18 (0.29-11.04)	

Change over follow-up period				
Change in BMI z-score	1.00 (0.41-2.43)		1.40 (0.54-3.59)	
Persistent overweight/obesity	7.33 (1.41-38.13)	7.95† (1.43-44.09)	0.80 (0.10-6.32)	— §
Persistent nonoverweight/ obesity	0.71 (0.23-2.23)		0.60 (0.17-2.18)	
Persistently large tonsils	—	—	—	—
Persistent snoring	—	—		

†Adjusted for baseline age, gender, persistently large tonsils and persistent snoring. § Adjusted for baseline age, gender and persistently large tonsils. — Without significance.

Table 4. Comparison of our findings and previous studies on natural history of PS in children

	Li et al	Marcus et al	Topol et al	Nieminen et al
Number of PS subjects who underwent repeat PSG	70	20	9	31
Mean Age at initial assessment (year)	10.2±1.7	6±4	7.2±2.4	6.0±1.8
Male gender (n,(%))	42(60.0)	12(60)	5(55.5)	17(54.8)
Mean Follow-up period	4.6 years	2 years	3.2 years	6 months
Baseline BMI	18.2±3.1	17.6±4.3	NA	NA
Change in BMI z-score	Not significant	Not significant[(1)]	NA	NA
Change in PSG parameters	Significant	Not significant	Not significant	Not significant
Progression to OSA (n,(%))	26(37.1)	2(10)	1(11.1)	1(3.2)
Resolution of PS (n,(%))	18(25.7)	2(10)	5(38.4)[(2)]	16(43.2)[(3)]

NA, not available.

(1) Chang in BMI

(2) Thirteen subjects completed sleep questionnaires.

(3) Thirty-seven subjects (31 primary snorers and 6 children with mild OSA) completed sleep questionnaires.

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