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Sleep Disordered Breathing in Patients With Primary Ciliary Dyskinesia

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Summary. Background: Upper airway manifestations of primary ciliary dyskinesia (PCD) can cause obstructive sleep apnea syndrome (OSAS). Also abnormalities of lung mechanics and gas exchange may lead to sleep abnormalities in these patients. Objectives: To determine the rate of OSAS and sleep quality in PCD patients, and whether these are related to upper respiratory system manifestations and severity of lung disease in these patients. Methods: Twenty-nine PCD patients and healthy controls were included to the study. Respiratory symptoms within the previous month were separately scored with the severity of the symptoms. Physical examination, pulmonary function tests, and ear–nose–throat assessments were obtained. All patients completed the Turkish version of Pittsburgh Sleep Quality Index (PSQI), sleep questionnaire, and underwent overnight polysomnography. Categorical variables were compared with chi-square and Fisher's exact test while continuous variables were compared with Student's *t*-test. Results: Eleven PCD patients reported themselves to be "poor" sleepers, compared to only one subject in the control group ($P = 0.002$). Sixty-five percent of PCD patients had habitual snoring (HS). Fifty-two percent of the PCD patients had OSAS in polysomnography. OSAS rate was higher in PCD patients who snored ($P = 0.008$). HS and OSAS were more common in PCD patients who had cigarette smoke exposure in their homes ($P < 0.001$ and $P = 0.02$, respectively). Conclusions: Patients with PCD have decreased sleep quality and higher rate of sleep disordered breathing compared to controls and higher rate of OSAS compared to population rates. Cigarette smoke exposure is an important risk factor for OSAS in PCD patients. Assessment and treatment of sleep disorders in PCD should be a part of disease management. **Pediatr Pulmonol. 2013; 48:897–903.** © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

The syndrome of primary ciliary dyskinesia (PCD) is a spectrum of conditions caused by a failure of mucociliary clearance related to ciliary abnormalities. Upper airway manifestations of PCD include chronic rhinosinusitis and nasal polyposis, which can increase upper airway resistance which in turn can cause obstructive sleep apnea syndrome (OSAS). Some PCD patients develop bronchiectasis with airflow obstruction and air-trapping, which may lead to hypoxemia and hypercapnia. Abnormalities of lung mechanics and gas exchange may lead to sleep abnormalities similar to those seen in patients with asthma, cystic fibrosis (CF), and non-CF bronchiectasis.[1–6]

Sleep disruption may significantly impair daytime functioning and health-related quality of life. In order to optimize the medical management of PCD patients, it is important to understand the magnitude of sleep disorders in this population and to identify the predictors of at-risk patients in whom further evaluation may be indicated.

There have been no previous studies evaluating the rate of sleep disordered breathing in PCD patients. The objective of this study was to determine the rate of OSAS and sleep quality in PCD patients, and whether

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these are related to upper respiratory system manifestations and severity of lung disease. We hypothesized that patients with PCD have impaired sleep quality compared to healthy controls and sleep disordered breathing is more prevalent in these patients; also these sleep problems are associated with presence of upper airway pathologies as well as severity of lung disease.

MATERIALS AND METHODS

Subjects

All patients followed with a diagnosis of PCD in Marmara University Hospital, Division of Pediatric Pulmonology were asked to join the study. PCD was diagnosed by electron microscopy in patients with chronic upper and lower respiratory symptoms or patients with dextrocardia and chronic respiratory symptoms were diagnosed by PCD, even if the electron microscopy studies were not conclusive. Electron microscopy studies showed both inner and outer, only outer, only inner dynein arm deficiency in 43%, 36%, and 21% of patients, respectively. Demographic data were also recorded. Cough, sputum production, sputum color, amount of sputum, wheezing, and breathlessness within the previous month was separately scored with the severity of the symptoms. A scoring system between 0 and 3 was used (0 = none, 1 = mild, 2 = moderate, 3 = severe). Patients were asked to complete a sleep questionnaire which was previously validated.[7,8] Sleep questionnaires were completed by parents on the night of sleep study. Sleep questionnaire included questions on smoke exposure in the house. Snoring more than 3 days a week was defined as habitual snoring (HS).

Height, weight, physical examination, pulmonary function tests (PFT), SpO_2, and ear–nose–throat (ENT) assessments were obtained within 3 days of the overnight polysomnography. All patients with PCD were evaluated with echocardiography to evaluate dextrocardia and other cardiac pathologies.

Healthy, age-matched control subjects were enrolled from the well-child clinics. Control subjects completed sleep questionnaires and PSQI and performed PFTs. However computerized tomography (CT) scans and polysomnography were not performed in these patients due to ethical reasons. The protocol was approved by the Marmara University Medical School Ethics Committee and informed consents were obtained from each parent.

Pulmonary Function Tests

Vital capacity and flow rates were measured by spirometry according to the criteria of the American Thoracic Society while patients were awake and in the seated position.[9] The values of spirometry were expressed as the ratio of percentage of normal values based on age, gender, and height. The best value of a minimum of the three adequate measurements was taken. Reference values obtained by Knudson et al.[10] were used.

Ear, Nose, and Throat Assessment

All patients were evaluated by the ENT specialists for the following parameters:

(1) Tonsil size assessment by Brodsky[11] scoring system.
(2) Deviation of the nasal septum, nasal patency, hypertrophy of the conchae, nasal polyps.
(3) Paranasal sinus CT in case of any suspicion of rhinosinusitis.

Radiological Evaluation

High resolution computed tomography scans obtained within the last 6 months were scored by the same radiologist. Images were scored using a modified Bhalla scoring system.[12,13] The total score was derived by adding the scores for each abnormality, and ranged from 0 to 37.

Evaluation of sleep quality

Evaluation of sleep quality was performed with PSQI. A PSQI score of ≥ 5 indicates that a person is a "poor sleeper."[14] This questionnaire was translated to Turkish and validated by a previous study.[7]

Overnight Polysomnography

Each patient underwent overnight polysomnography (Alice 5, Respironics, Murrysville, PA). Staging of sleep and the scoring of respiratory events and arousals were performed according to the standards of the American Academy of Sleep Medicine.[15–18] An apnea hypopnea index (AHI) of >1/hr signified a positive polysomnography result and, hence, the diagnosis of OSAS.[19] Mixed apneic events were counted as obstructive.

Statistical Analysis

Statistical analyses were performed by SPSS 16.0. Continuous variables were described through means, standard deviations, whereas categorical variables were presented as proportions. Categorical variables were compared with chi-square and with Fisher's exact test when 20% of the expected frequencies were <5. Continuous variables between two groups were compared with Student's *t*-test, since the data followed a normal distribution. The effect of the cigarette smoke exposure on HS and OSAS was evaluated with chi-square test. Bivariate correlations were evaluated through Spearman's

rank correlation and presented as correlation coefficients. A P-value <0.05 was considered as statistically significant.

RESULTS

Twenty-nine patients with PCD (14 female) aged between 6 months and 24 years (mean ± SD: 10.0 ± 5.9) were enrolled to the study. Control group consisted of 29 healthy subjects (15 female) without any chronic disease, their ages were between 6 months and 24 years (mean ± SD: 10.0 ± 5.6; Table 1). There was no statistically significant difference between PCD patients and control group in terms of age and gender ($P > 0.05$).

Twenty-one PCD and 18 control patients performed PFT. Mean forced vital capacity (FVC, % predicted normal), forced expiratory volume in 1 sec (FEV_1, % predicted normal), FEV_1/FVC (% predicted normal) values in PCD patient and control groups were 74 ± 17, 74 ± 17, 100 ± 12, 99 ± 22, 104 ± 15, and 107 ± 7, respectively. Compared with control subjects, PCD patients had significantly lower FVC and forced expiratory volume in 1 sec (FEV_1) values ($P < 0.001$; Table 1). Twelve PCD patients had restrictive, one patient had obstructive and one patient had mixed pattern of the flow-volume curve. There was no patient in the control group who had restrictive, obstructive, or mixed pattern.

HS, witnessed sleep apnea, difficulty breathing during sleep, and increased parental anxiety about child's sleep were more prevalant in PCD patients compared to control group (Table 1). Mean PSQI scores in PCD patient and control groups were 3.9 ± 2.1 and 2.3 ± 1.1, respectively. There was no statistically significant difference between the two groups in terms of mean PSQI scores. However, 11 out of the 29 PCD patients (38%) reported themselves to be "poor" sleepers, that is, to have a PSQI of ≥5 compared to only one subject in the control group ($P = 0.002$; Table 1).

Mean CT scores were 16.5 ± 8.8 in PCD patients. PCD patients who were more symptomatic had worse CT scores as expected ($P = 0.02$). There was no correlation between CT scores and PFT's in PCD patients ($P > 0.05$).

Symptoms, physical examination, and ENT evaluation of the patients are summarized in Table 2.

PCD patients with rhinosinusitis were more likely to be poor sleepers ($P = 0.04$). There was no relation between poor sleep quality and presence of tonsillar hypertrophy, deviation of the nasal septum, nasal patency, presence of nasal polyps, or hypertrophy of the conchae in PCD patients ($P > 0.05$). There was no statistically significant correlation between PSQI and respiratory symptom scores ($P > 0.05$). Also, there was no correlation between PSQI and CT scores or PFT's ($P > 0.05$).

Nineteen of the 29 (65%) PCD patients had HS (i.e., snored more than 3 days a week). There was no statistically significant difference between PCD patients with HS and without HS in terms of having poor sleep quality, night-time cough, and mean PSQI scores. Fifteen of the 29 PCD patients had OSAS in polysomnography (52%). Fourteen of them had mild, one of them had moderate–severe OSAS. OSAS rate was higher in PCD

TABLE 1— Demographic, Pulmonary Function, Sleep Questionnaire, and PSQI Data for Primary Ciliary Dyskinesia Patients and Control Subjects

	PCD (n = 29)	Control (n = 29)	*P*
Age (years)	10 ± 5.9	10 ± 5.6	NS
Male/female	15/14	14/15	NS
Weight *Z*-score	−0.87 ± −0.90	0.10 ± 1.35	0.002
Height *Z*-score	−1.35 ± 0.87	0.10 ± 1.26	<0.001
FVC (% predicted normal)	74	99	<0.001
FEV_1 (% predicted normal)	74	103	<0.001
FEV_1/FVC (% predicted normal)	101 ± 12	107 ± 7	NS
Habitual snoring (%)	65.5	6.9	<0.001
Witnessed sleep apnea (%)	27.6	0	0.002
Excessive daytime sleepiness (%)	20.7	3.4	0.04
Difficulty breathing during sleep (%)	27.6	3.4	0.011
Increased parental anxiety about child's sleep (%)	48.3	3.4	<0.001
Restless sleep/irritability (%)	27.6	0	0.002
Profuse sweating (%)	24.1	3.4	0.02
Blue color during sleep (%)	3.4	0	NS
Parental shaking for apnea (%)	13.8	0	0.03
PSQI	3.9 ± 2.1	2.3 ± 1.1	NS
Poor sleepers	11	1	0.002
Good sleepers	18	28	

NS, non significant, FVC, forced vital capacity, FEV_1, forced expiratory volume in one second, PSQI, Pittsburgh Sleep Quality Index.

TABLE 2— Symptoms, Physical Examination, and ENT Evaluation of the PCD Patients

Symptoms		N	%
Cough	None	0	0
	Mild	18	62.1
	Moderate	7	24.1
	Severe	4	13.8
Sputum production	None	2	6.9
	Mild	11	37.9
	Moderate	7	24.1
	Severe	9	31.1
Wheezing	None	7	24.1
	Mild	10	34.5
	Moderate	6	20.7
	Severe	6	20.7
Breathlessness	None	13	44.8
	Mild	10	34.5
	Moderate	4	13.8
	Severe	0	0
Physical examination			
	Wheezing	11	37.9
	Rales	14	48.3
	Clubbing	5	17.2
ENT evaluation			
Adenoidal hypertrophy		6	20.7
Tonsil size	Stage 1	23	79.3
	Stage 2	4	13.8
	Stage 3	2	6.9
	Stage 4	0	0
Deviation of nasal septum		6	20.7
Hypertrophy of conchae		9	31
Nasal polyps		2	6.9
Nasal patency		6	20.7
Rhinosinusitis		9	31
Allergic rhinitis		8	27.6
Otitis		18	62.1

TABLE 3— Sleep Characteristics of the PCD Patients

	Mean ± standard deviation
Total sleep time (min)	382 ± 76
Sleep efficiency (%)	86.1 ± 6.9
Arousal index (n/hr)	13.3 ± 2.8
Stage 1 (%TST)	6 ± 3
Stage 2 (%TST)	46 ± 8
Slow wave sleep (%TST)	28 ± 8
Rapid eye movement sleep (%TST)	20 ± 6
Mean saturation (%)	95 ± 2
Mean lowest saturation	92 ± 5
Obstructive apnea (n/hr)	6.8 ± 8.8
Mixed apnea (n/hr)	1 ± 1.9
Hypopnea (n/hr)	2.7 ± 2.8
Apnea–hypopnea index (n/hr)	1.6 ± 2

patients who snored ($P = 0.008$). Thirteen out of 15 patients with OSAS had snoring but two patients who did not complain of snoring had OSAS on polysomnography. These two patients without snoring had mild OSAS.

There was no statistically significant difference between PCD patients with or without OSAS in terms of upper airway physical examination findings, respiratory symptom scores, rhinosinusitis, and respiratory examination findings ($P > 0.05$). There were no correlations between AHI and PSQI, CT scores, SpO_2 measured during examination, FVC, FEV_1 ($P > 0.05$).

Sleep characteristics of the PCD patients are summarized in Table 3. There was no relationship between sleep architecture parameters and PSQI. In patients with PCD; AHI was positively correlated with mean desaturation index ($r = 0.36$, $P = 0.05$), negatively correlated with mean saturation ($r = -0.36$, $P = 0.05$), and mean lowest saturation ($r = -0.49$, $P = 0.007$). There was no correlation between upper airway physical examination findings, respiratory symptom scores, respiratory examination findings, and mean desaturation index, mean saturation, mean lowest saturation, and total sleep time ($P > 0.05$).

HS was more common in PCD patients with cigarette smoke exposure in their houses (100% vs. 37.5%, respectively, $P < 0.001$). Also, PCD patients with OSAS had more frequent cigarette smoke exposure in their houses in comparison to those without OSAS (73.3% vs. 28.6%, respectively, $P = 0.02$).

DISCUSSION

To our knowledge this is the first study which provided both objective and subjective assessment of sleep in patients with PCD. The objective measure of OSAS provided by polysomnogarphy and the subjective measures provided by PSQI and questionnaires completed by patients and their parents demonstrated that patients with PCD have impaired sleep quality as well as increased incidence of snoring and OSAS. Sleep questionnaire, ENT and respiratory system examination did not predict the presence of OSAS in these patients.

Sleep problems are common in many childhood chronic disorders including asthma, CF, and non-CF bronchiectasis.[4–6] Factors causing sleep abnormalities in these patients such as wheezing, cough, sputum, rhinitis may also cause impaired sleep quality in patients with PCD. Camhi et al.[20] reported wheezing as a risk factor for disorders of initiating and maintaining sleep and Redline et al.[21] found that persistent wheezing was an independent risk factor of sleep-disordered breathing. Non-CF bronchiectasis patients with night-time wheezing and breathlessness had sleep disruption and wheezing patients had more difficulties in falling asleep in a recent study.[6]

Compared to polysomnography, PSQI is simple to perform, inexpensive, could be followed over time, and does not involve a hospital stay. If the PSQI suggests poor sleep quality, then polysomnography studies may

be obtained for further evaluation of the underlying sleep disorders. Some studies showed inverse correlations between PSQI scores and polysomnography measured sleep efficiency in CF patients.[5,22] PSQI appears to be a useful screening tool to identify patients who are at risk for sleep disturbance.[5,22,23] We found that poor sleep quality was more prevalent in patients with PCD compared to control group. But there was no correlation between PSQI and CT scores, FEV_1, AHI, obstructive apnea, mixed apnea, hypopnea in PCD patients. Night-time coughing, respiratory symptom scores, respiratory examination findings could not predict poor sleep quality with PSQI in this patient group.

The major polysomnography findings of the current study were threefold. First, OSAS incidence was higher in patients with PCD. Second, sleep questionnaire, ENT and respiratory system examination could not predict the presence of OSAS. Finally, PCD patients with OSAS in comparison to those without OSAS were more frequently exposed to cigarette smoke in their homes.

HS is recognized as an important manifestation of OSAS in patients. Numerous risk factors for HS and OSAS have been reported, including adenotonsillar hypertrophy, obesity, allergies, or other causes of nasal obstruction, and exposure to tobacco smoke.[21–30] Although HS, presence of apnea, and difficulty in breathing have been found to be associated with OSAS in number of studies, some children with OSAS have no snoring history reported by their families.[27,31–34] In our study group, two patients had OSAS without any report of HS.

The incidence of OSAS in children is estimated to be 2%.[21,31] There are no data about incidence of OSAS in PCD patients. Current study showed that OSAS incidence was high in patients with PCD. In 1984, a study reported a high accuracy for a diagnostic questionnaire for OSAS in children with adenotonsillar hypertrophy.[32] But further studies proved that the use of this questionnaire as a substitute for polysomnography would lead to numerous false-positive and false-negative results in the diagnosis of OSAS.[35,36] Questionnaires and clinical history alone are helpful but not adequate in clinical practice to distinguish childhood primary snoring from OSAS and therefore additional diagnostic testing is needed.[35,37] However, HS, presence of apnea, and difficulty breathing have been found to be associated with OSAS in a number of studies[27,32,33] OSAS rate was higher in PCD patients who snored in our study. Nocturnal sleep laboratory based polysomnography is considered the gold standard for the diagnosis and assessment of OSAS in patients and two patients were diagnosed with OSAS despite the lack of reported HS.[34]

As the upper and lower airways are primarily affected by PCD, symptoms can be divided into ENT manifestations and pulmonary symptoms. ENT symptoms include chronic rhinitis, recurrent and chronic rhinosinusitis, and recurrent otitis media. A recent study documented that 59% of PCD patients had recurrent problems concerning the paranasal sinuses in terms of rhinosinusitis.[38] In the current study, PCD patients with rhinosinusitis had higher incidence of poor PSQI but not OSAS. ENT examination did not predict the presence of OSAS in PCD patients.

PCD is caused by a congenital reduction or absence of the function of the normal mucociliary escalator, an important primary airway defence mechanism, due to impaired or absence of ciliary beating. Second-hand smoke exposure may cause decreased bronchial and nasal mucociliary clearance secondary to inflammation of the airways, increased production of mucus particularly of more viscous mucins, and decreased ciliary beat frequency possibly coupled with morphologic changes of ciliated cells and cilia. Side-stream tobacco smoke exposure acutely alters human nasal mucociliary clearance.[39] Second-hand smoke exposure has been reported as a risk factor for snoring and sleep disordered breathing in children and adults.[8,40–42] An association between the father's smoking and HS was identified in an epidemiologic study of 6- to 13-year-old children in Thailand.[30] Corbo et al. also found a highly significant association between parental smoking, the number of cigarettes consumed by parents and HS. Ersu et al.[8] reported that maternal smoking had more impact on HS.[43] In the current study, HS and OSAS were more common in PCD patients with cigarette smoke exposure in their homes.

One of the major limitation of this study was that polysomnography and CT were not performed in the control group. We used sleep questionnaires in both groups and we compared the incidence of OSAS to the previous studies performed in healthy children which included a study from Turkey. Another limitation of this study was the small number of sample size.

This is the first study assessing sleep quality, sleep disordered breathing, and OSAS in patients with PCD. We showed that patients with PCD have decreased sleep quality and higher rate of sleep disordered breathing compared to controls. Also these children had higher rate of OSAS compared to a population study performed in Turkey. Patients with rhinosinusitis had increased risk of poor sleep quality. So effective treatment of rhinosinusitis may be an important therapeutic strategy in these patients. Our data suggest that cigarette smoke exposure is an important risk factor for OSAS. Lack of awareness of association between PCD and sleep disordered breathing can lead to a vicious cycle of poor control of disease, impaired daytime

activity and behavioral problems with impaired school performance. Assessment and treatment of sleep disorders in PCD should be a part of disease management.

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