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Sleep study abnormalities in patients with Down syndrome.

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Abstract

Children with DS are prone to develop obstructive sleep apnea syndrome because of chronic upper airway obstruction. Untreated OSA results in serious morbidities including pulmonary hypertension (PHT. The aim of our study is to identify the sleep abnormalities in Pediatric patients with DS that are referred to Pediatric pulmonary and general Pediatric clinic from the period Ist Jan-30 Dec 2011 for respiratory symptoms and regular check up. A Prospective Sleep study (Polysomnography) was carried out in the sleep laboratory. Demographic, clinical, diagnostic, morbidity, mortality data, sleep studies abnormalities, and type of medical or surgical interventions were reported. A total of 23 patients confirmed Down syndrome Clinically and by Chromosomal studies. 15 male (65%), 8 female (35%). The most presenting symptoms were: snoring 19 (82%), Shortness of Breath 16 (70%), cough 16 (70%), stopping breathing 16 (70%), increase body movements in 18 (78%), Rhinorrhea in 14 (61%), Sweating 13 (56%), Mouth breathing in 16 (70%), frequent Upper respiratory Tract Infection in 17 (73%), Difficulty in Swallowing in 5 (22%), Difficulty in hearing in 4 (17%), Excessive sleeping during the day in 6 (26%), Enuresis in 5 (22%), Aggressive behaviors in 9 (39%), Asthma in 14 (60%), Recurrent Chest Infection in 13 (57%), Home O2 requirement in 4 (17%), Hypothyroidism in 6 (26%), Gastroesophageal reflux (GER) in 4 (17%). Sleep Study was done in all 23 patients. 19 patients (83%) showed sleep related disorder breathing (SRDB). Abnormal mean Apnea hypopnea index (AHI) of 12.3 (Normal <1.5 %) in 19 patients (83%), mean obstructive apnea index (OAI) of 4.7 in 11 patients (48%), abnormal hypopnea index of 5.6 (N= <1), abnormal periodic leg movements of mean 5.9 in 6 patients (26%). 16 of 23 patients (70%) have Congenital heart disease (CHD). The most common lesions were: ASD in 13 (56%), VSD in 5 (22%), Common A-V Canal in 3 (13%), PDA in 8 (35%). .PHT was detected by Cardiac Cath in 10 patients (43%) with mean PAP 54.6 mmHg ± 4.5. Persistent PHT at follow up was detected in 8 (35%) of patients with mean PAP of 40± 13.5 mmHg. Vasodilator was used in 7 (33%). Sleep related disorder breathing (SRDB) is common in patients with Down syndrome (DS) and has been under estimated by many physicians for a long time. Such patients should be screened for sleep abnormalities specially with significant respiratory or sleep disturbance symptoms. Medical or surgical options should be offered to such patients without delay to prevent complications.

Keywords: Down syndrome, Sleep abnormalities, Pulmonary hypertension

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Introduction

Down syndrome (DS) is a common chromosomal abnormality occurring in about 1 in 961 live births [1]. They are prone to develop obstructive sleep apnoea (OSA) for a combination of reasons, including small upper airway, midfacial hypoplasia, micrognathia and muscular hypotonia. The prevalence of OSA in children with DS has been reported to be between 45%-50%, respectively [1]. Other reports found 38.5% DS children with OSA had no habitual snoring [1-3].

Many reports on Polysomnography studies in DS [2-8] have shown that 50-100% of patients have respiratory sleep disturbance.

In other reports, Children with (DS) have an increased risk of developing pulmonary hypertension (PHT). This may be due to multiple factors, including the presence of congenital heart disease with persistent left-to-right shunts, chronic upper airway obstruction or abnormal pulmonary vasculature growth [9-12].

Untreated OSA results in serious morbidities including failure to thrive, pulmonary hypertension (PHT), poor academic performance, and deterioration in mental function [2-8].

Pediatric Sleep laboratories in Saudi Arabia are scarce, and many of them are geared toward Adult training. In our tertiary care center as a referral for Genetic and cardiac diseases, Down syndrome present a good group for diagnostic and management population.

We selected to prospectively test the benefit of Polysomnography (PSG) test and to identify the sleep abnormalities in Pediatric patients with DS, and to identify the association of PHT and sleep abnormalities.

Material and Method

Prospective selection of patients with DS that are referred to the General Pediatric clinic for regular evaluation and in Pediatric Pulmonary clinic during the period Jan 2010-Dec 2010 with respiratory problems such as cough, shortness of breath, snoring, disturbed sleep, apnea, cyanosis and increase in leg movements during sleep will be booked for sleep study. Consent was obtained from parents for sleep studies.

Polysomnographic assessment

Patients under went a standard over night PSG using XLTEC (Oakville, Canada) and Nicolet (Viasys, Madison,WI) data acquisition and analysis systems. PSG measurements included electro en-cephalogram (EEG), electro-oculogram (EOG), submental electromyogram (EMG) and bilateral anterior tibialis EMG. Respiratory measurements included chest wall and abdominal movement using chest wall and abdominal belts; nasal air flow measurements using nasal air pressure transducer and/ or oro-nasal thermal sensor, oxygen saturation (SaO2). Video and audio recordings were obtained for each study as well as body position, which was documented manually by a registered polysomnographic technician.

Sleep architecture was assessed by standard techniques (Rechtschaffen, 1968). Information obtained from PSG included sleep onset latency and rapid eye movement (REM) onset latency, total sleep time (TST), sleep efficiency, time spent in each sleep stage(minutes and percentage), number and classification of arousals, number of independent leg movements and snoring. Recorded respiratory data included counts and indexes of the following events: OSA, CSA, hypopnea and mixed apnoeas in non- rapid eye movement (NREM) sleep, REM sleep and total sleep. All events were scored according to the current American Academy of Sleep Medicine (AASM) scoring guidelines (Iber et al.2007) [13] by a registered polysomnographic technician. An obstructive apnoea event was scored when air flow dropped at least 90% from baseline with chest and/ or abdominal motion throughout the entire event; the duration of which was at least a minimum of two baseline breaths. A hypopnoea event was scored when air flow dropped at least 50% from baseline, the duration of which was at least a minimum of two baseline breaths. The hypopnea event must have been accompanied by either (i) a minimum 3% drop in oxygen desaturation, (ii) an arousal, or (iii) an awakening (Iber et al., 2007) [13]. Acentral apnoea was defined as acessation of airflow with an absence of respiratory and abdominal effort for a minimum of 20s or of the duration of two prior baseline breaths in which case the event must be accompanied by (i) aminimum 3% drop in oxygen desaturation, (ii) an arousal, or (iii) an awakening. OSA severity was graded according to the obstructive apnoea/ hypopnoea index (OAHI), the number of obstructive apnoeas and obstructive hypopnoeas per hour during sleep. OAHI of <1.5 was considered normal, OAHI from 1.5 to <5 was mild OSA; OAHI from 5 to <10 was moderate OSA and OAHI of 10was considered severe OSA. The central apnoea index(CAI) was defined as the number of central apnoe as pe rhour during sleep. The CSA diagnosis was considered when the CAI was >5 events/ hour sleep.

The following data were also collected: Demographic, clinical, diagnostic, morbidity such as “recurrent chest infections, gastroesophageal reflux (GER), asthma, hypothyroidism, and celiac disease”, mortality data, sleep studies abnormalities, type of cardiac defect, presence of PHT, and type of medical or surgical interventions that have been done to the studied subjects.

Statistical consideration

The statistical analysis of data was done by using the software package SAS version 9.2 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). Descriptive statistics for all the continuous variables are reported as mean ± standard deviation while categorical variables are reported as frequencies and percentages. The categorical variables were compared by using Chi-square test. The statistical level of significance is set at $p < 0.05$

Results

A total of 23 patients confirmed Down syndrome clinically and by Chromosomal studies. 15 male (65%), 8 female (35%). The most presenting symptoms and signs

Sleep study abnormalities in patients with Down syndrome.

Table 1. *Symptoms and signs of patients with Down syndrome (Total 23)*

Symptoms/Signs	Number	Percent
Type of snoring:		
no snoring	14	60.87
Mild	7	30.43
moderate	1	4.35
severe	1	4.35
Difficulty of breathing during sleep	16	69.57
Cough	16	69.57
Increase body Movements during sleep	18	78.26
Recurrent Ear Infection	14	60.87
Restless sleep	19	82.61
Sweating when Asleep	13	56.52
Mouth Breathing when Awake	16	69.57
Frequent Upper Respiratory Tract Infection	17	73.91
Nausea	4	17.39
Difficulty in swallowing	5	21.74
Hearing Problem	4	17.39
Poor Appetite	4	17.39
Excessive Day time Somnolence	6	26.09
Frequent Morning Headache	3	13.4
Nocturnal Enuresis	5	21.7
Recurrent Chest Infection	13	56.6
Home O2	4	17.4

Legend: BMI= Body mass index
CAI- Central apnea index (events/ hr)
AHI- Apnea/ hypopnea index (events/ hr)
PLEGM= periodic leg movements (events/ hr)
AASM- American academy of sleep medicine; BIPAP- bi-level positive airway pressure; CSA- central sleep apnoea; CAI- central apnoea index; CPAP- continuous positive airway pressure
EEG- electroencephalogram; EMG- electromyogram; EOG- Electro-oculogram; NREM- non-rapid eye movement; OSA- obstructive sleep apnoea; OAHI- obstructive apnoeae hypopnea index; SaO2- oxygen saturation; PSG- polysomnography; REM- rapid eye movement; SRDB- sleep-related disordered breathing; TST- total sleep time

(Table 1) were: snoring 19 (82%), Shortness of Breath 16 (70%), cough 16 (70%), stopping breathing 16 (70%), increase body movements in 18 (78%), Rhinorrhea in 14 (61%), Sweating 13 (56%), Mouth breathing in 16 (70%), frequent Upper respiratory Tract Infection in 17 (73%), Difficulty in Swallowing in 5 (22%), Difficulty in hearing in 4 (17%), Excessive sleeping during the day in 6 (26%), Enuresis in 5 (22%), Aggressive behaviors in 9 (39).

Sleep Study was done in all 23 patients. 19 patients (83%) showed sleep related disorder breathing (SRDB) (Table 2). The mean sleep efficiency of 70.5% of total sleep time (N= >90%). Lower stage 2 sleep of mean 37.9 (N=45-55%), and low REM sleep of 10.4 (N= 20-25%). Abnormal mean Apnea hypopnea index (AHI) of 12.3 (Normal <1.5 %) in 19 patients (83%), mean obstructive apnea index (OAI) of 4.7 in 11 patients (48%), abnormal hypopnea index of 5.6 (N= <1), abnormal central apnea index of >5/hr in 2 patients (9%), abnormal periodic leg movements of mean 5.9 in 6 patients (26%) (N<5).

Snoring was detected by polysomnography in only 8 patients (39%) of different degrees (Table 3), but did not have any relation to the degree of respiratory disturbance severity or frequency (Table 3). There were 11 Patients (47.8%) with no snoring detected during the PSG study, but with significant sleep disturbance and AHI of >1, an

Table 2. *Sleep study results of 23 Patients with Down syndrome*

Variable	Normal	Mean	Std Dev
Total sleeping time (hours)		278.4	99.7
Sleep latency (Minutes)		42.2	50.2
Sleep efficiency % of total sleep time	>90%	70.5	20.8
STAGE1 % of total sleep time	2-5%	5.5	5.0
STAGE2 % of total sleep time	45-55%	37.9	13.8
Deep Sleep of total sleep time	3-23%	45.9	16.7
REM Sleep of total sleep time	20-25%	10.4	10.5
Apnea/ Hypopnea Index (events/ hour)	<1.5/ hr	12.3	13.4
Obstructive Apnea Index (events/ hour)	<1.5%	4.7	6.9
Hypopnea Index (events/ hr)	<1.5%	5.6	7.4
Central apnea Index	<5/ hr	1.6	2.2
Lowest Oxygen		80.7	16.0
Mean Oxygen		94.6	4.4
Arousal Index (events/ hour)	<5/ hr	11.3	6.4
leg movements Index (events/ hour)		5.9	9.1

Table 3: *Relationship of snoring and respiratory disturbance*

Variable	No snoring # (%)	Mild # (%)	Moderate # (%)	Severe # (%)	Prob
BMI <=30	14 (60.87)	6 (26.09)	1 (4.35)	0	0.0067
BMI > 30	0(0.00)	1 (4.35)	0	1 (4.35)	
CAI <= 5	13 (56.52)	6 (26.09)	1(4.35)	1(4.35)	0.9170
CAI > 5	1(4.35)	1(4.35)	0	0	
AHI <= 1	3 (13.04)	1(4.35)	0	0	0.8903
AHI > 1	11(47.83)	6 (26.09)	1(4.35)	1(4.35)	
PLEGM<= 5	11(47.83)	4 (17.39)	1(4.35)	1(4.35)	0.5967
PLEGM> 5	3 (13.04)	3 (13.04)	0	0	

1 patient with no snoring but CAI > 5, and 3 patients with no snoring but periodic leg movements >5 (Table 3).

2 patients had Tonsillectomy and adenoidectomy before the study period. 3 patients had tracheostomy before the study period for subglottic stenosis.

Patients with tracheostomies had normal PSG studies, but abnormal periodic leg movements.

16 of 23 patients (70%) have congenital heart disease (CHD). Ten of the patient had cardiac catheterization. The most common lesions were: ASD in 13 (56%), VSD in 5 (22%), Common A-V Canal in 3 (13%), PDA in 8 (35%).

The most common associated diseases were: Autism in one patient (4.35%), Asthma in 14 (60.8%), Celiac disease in 2 (8.7%), Hypothyroidism in 6 (26%), GER in 4 (17%), and other medical condition in 18 patients (78%) as anorectal malformation, 2 patients with Morgagni hernia, bladder Extrophy, Duodenal atresia

PHT was detected by Cardiac Cath in 10 patients (43%) with mean PAP 54.6 mmHg ± 4.5, and mean tricuspid regurgitation velocity (TR) of 3.6 ± 0.2. Persistent PHT at follow up was detected in 8 (35%) of patients with mean PAP of 40± 13.5 mmHg, and mean TR velocity of 3 ± 0.6. Vasodilator was used in 7 (33%). The most common vasodilators used were: Sildenafil in 1 patient (14%), Bosentan in 2 (29%), combination of Sildenafil and Bosentan in 3 (43%), and combination of Bosentan and iloprost inhalation in one patient (14%).

Discussions

OSA syndrome is seen in only 0.7% to 2.0% of the general pediatric population [14, 15], Marcus et al [3] retrospectively evaluated a group of 53 subjects with DS, ages ranging from 4 weeks to 51years (mean age, 7 years), and found sleep abnormalities to be as high as 100%.With this high incidence, the question became whether all children with DS should be evaluated objectively for sleep abnormalities, especially OSAS, and at what age this evaluation should be performed [3].

Adenotonsillectomy and adenoidectomy have markedly improved symptoms in approximately 70-85% of patients with OSA [8]; others may need more extensive surgical procedure like uvulopalatophryngoplasty (UPPP), or Tracheostomy [14-27].

Oral appliances and Non-invasive ventilation as CPAP or BiPAP may be used in some cooperative patients [16].

Asaf et al. (2) reported a study that included 23 children with DS, compared with 13 children with primary snoring. All underwent a 6- to 8-hour sleep study. He found that the respiratory disturbance index was significantly higher in the children with DS (2.8 ± 2.3 events/h vs 0.6 ± 0.4 events/h; $P < .05$). Sleep was significantly fragmented in children with DS, who had a significantly higher arousal/awakening (A/Aw) index (24.6 ± 7.9 events/h) compared with the comparison group (17.6 ± 4.0 events/h) ($P < .02$). A higher percentage of jerks associated with A/Aw and respiratory event-associated A/Aw was observed in patients with DS (45.2% ± 25% and 8.6% ± 6.4%, respectively) compared with the control patients (10.2% ± 4.5% and 1.5% ±2.1%) ($P<.02$). The median length of occurrences of stage 2 sleep was 27% shorter in the DS group ($P < .03$). The number of shifts from “deeper” to “lighter” stages of non-rapid eye movement sleep was 30% greater ($P < .02$) in the DS group. His conclusion was that Children with DS have significant sleep fragmentation, manifested by frequent awakenings and arousals, which are only partially related to obstructive sleep apnea syndrome.

Hui et al. (5) reported on 22 DS patients and 22 snoring controls that completed the overnight PSG. The mean age of DS children and snoring controls was 10.82 +/- 5.93 and 10.27 +/- 5.68 years, respectively. The prevalence of OSA was 59 percent in DS children and 32 percent in

snoring controls. Median and interquartile range (IQR) of AHI of DS children (median 1.80, IQR is 0.40 to 7.10) were significantly higher than those of controls (median 0.50, IQR is 0.00 to 2.03, p-value equals 0.041). Out of 13 DS children with OSA, eight of them (61.5 %) had no habitual snoring. His conclusion was that 59 % of DS children were found to have OSA and they were more likely to develop OSA than controls. Nearly 40 % of DS children with OSA did not have habitual snoring.

The fact that 60% of DS children with OSA had no habitual snoring nor observed apnoea in the Hui et al. study highlighted the difficulty of screening OSA in DS children by clinical history. Moreover, AHI in DS children were positively correlated to age. He suggest that routine PSG should be offered to all DS children from the ages of four to six years for early diagnosis of OSA.

Marcus et al [3] and Southall et al [27] reported the prevalence of OSA in children with DS to be 45% [12] and 50% [5], respectively. de Miguel-Diez et al [7,28,29] reported that the prevalence of OSA, defined as ≥2 per hour, in a community sample of children with DS, was 65% [13]. Dyken et al [17] reported that OSA, defined as obstructive apnoea index >1, affected 79% in a group of 19 American DS children (aged 3-18 years) recruited from the outpatient population.

Dahlqvist et al [28] recruited Swedish DS children at a younger age (2-10 years) from the community and reported a much lower prevalence of OSA (24%), defined as AHI>1[15]. Stebbens et al [1] reported a slightly higher prevalence (31%) in a group of community-based sample of younger DS children (0-5 years).

Uong et al [29] also found that DS children had a significantly smaller upper airway volume compared to non-DS children. They reported that the difference in upper airway volume was not likely to be mediated by tonsillar hypertrophy or adenoid hypertrophy as the adenoid and tonsil volumes in DS children were significantly smaller than non-DS children as shown by magnetic resonance imaging. The same study also demonstrated that DS children had a significantly smaller mid- and lower-facial skeleton, shorter mental spine-clivus distance, hard palate length and mandible volume compared to non-DS children. However, the size of tongue, soft-palate, pterygoid and parapharyngeal fat pads were similar in DS children and non-DS children [30]. Donnelly et al [30] found that 25% of OSA in DS children were caused by glossoptosis during sleep.

A review by Hatipoglu and Rubinstein [31] suggested that local, e.g. allergic rhinitis, or systemic inflammation might amplify upper airway narrowing, and thus worsen OSA.

Our study have similarly confirmed that AHI in patients with DS is high (83%) and has been missed by many physicians. The high percentage of AHI and of cardiac anomalies (70%) in our study is possibly due to a referral bias as a tertiary care center for difficult cases of DS and as a cardiac center. In addition to a higher percentage of morbidity with PHT that required vasodilator use is described for the first time compared to other studies mentioned earlier.

Pulmonary hypertension and EisenMenger syndrome are severe moribidity and may causes mortality form right heart failure (324-33). Vasodilator treatment is commonly used in such patients to improve their survival [34].

In summary: patients with DS with upper air way symptoms or sleep disturbance should be screened for sleep abnormalities early before advanced and irreversible complication develop and should be managed accordingly.

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