ORIGINAL RESEARCH

Sleep apnea in children with refractory monosymptomatic nocturnal enuresis

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Background: Children with nocturnal enuresis (NE) are believed to have deep sleep with high arousal threshold. Studies suggest that obstructive sleep apnea–hypopnea syndrome (OSAHS) and NE are common problems during childhood. We sought to assess the prevalence of OSAHS in children with refractory NE and whether its severity is associated with the frequency of bedwetting.

Methods: The study group comprised 43 children with refractory monosymptomatic NE and a control group of 30 children, both aged 6–12 years. All subjects underwent thorough neurological examination, one night of polysomnography only for the patient group, and a lumbosacral plain X-ray to exclude spina bifida.

Results: The groups were well matched. Two subjects of the control group had mild OSAHS. The mean age of the patients was (9.19±2.4 years), 26 were boys, and 67% showed frequent NE (>3 days bedwetting/week). Patients with NE had significantly higher rates of OSAHS ($P<0.0001$); three patients had mild, 12 had moderate, and eleven showed severe OSAHS. There was no significant statistical difference among patients having OSAHS in relation to age, sex, or family history of NE. The frequency of bedwetting was statistically significantly higher in patients with severe OSAHS ($P=0.003$).

Conclusion: Patients with refractory NE had a significantly higher prevalence of OSAHS with no sex difference. The frequency of bedwetting was higher in patients with severe OSAHS.

Keywords: nocturnal enuresis, refractory, OSA

Introduction

Nocturnal enuresis (NE) refers to the involuntary loss of urine during the night after the age of 5 years, when children are expected to have achieved full bladder control at night.[1] It is classified as primary when the child has never achieved nighttime dryness and secondary when bedwetting occurs after dryness for at least 6 months.[2] Moreover, NE is divided into monosymptomatic NE (MNE) with no daytime urinary symptoms and nonmonosymptomatic NE if accompanied by daytime urinary symptoms.[3] The prevalence of enuresis (at least 1 night per week) has been reported to be 1.6% to 13.7%, depending on the subject's age and ethnic and cultural characteristics.[2,4,5]

Enuretic children suffer from low self-esteem,[6] reduced fine motor coordination, visuomotor integration abnormalities,[7] attention deficit hyperactivity disorder,[8] reading difficulties,[9] and there may be an association with migraine.[10] Moreover the risk of psychosocial comorbidity is higher in therapy-resistant enuresis.[11] Refractory NE is defined as less than 50% improvement in symptoms with an adequate trial of treatment (3 months).[12]

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NE has been related to obstructive sleep-disordered breathing (SDB) in both adults[13,14] and children.[15,16] The association between the two conditions in pediatric subjects is supported by the decrease or complete resolution of bedwetting after successful treatment of SDB with adenotonsillectomy or intranasal corticosteroids.[16,17] Moreover, effective treatment of obstructive sleep apnea–hypopnea in adults by continuous positive airway pressure has improved enuresis.[13]

Studies have assessed NE in patients with upper airway obstruction.[18–23] Nonetheless, to our knowledge none has assessed obstructive sleep apnea (OSA) in patients with NE and whether the frequency of bedwetting is related to the severity of OSA. The aim of our study was to objectively assess the prevalence of OSA using polysomnography in patients with refractory MNE and whether the frequency of bedwetting is related to the severity of OSA.

Materials and methods
Patients
Included in the study were consecutive children with primary MNE, aged 6–12 years, and medication resistant, who were recruited from the neurology outpatient clinic in the Department of Neurology at Mansoura University Hospital in Mansoura, Egypt over a 3-year period (2010–2013). A control group of healthy children, not complaining of symptoms related to urinary tract or ear, nose, and throat conditions, were selected to be similar with respect to age and sex. They were recruited through the personnel of our hospital and their acquaintances. The study was approved by the medical ethics committee of Mansoura University, and informed consent was given by the parents of each child in both groups.

Inclusion criteria for the patient group were age from 6–12 years, presence of MNE (with no daytime urinary symptoms), and refractory MNE (either no response or less than 50% symptom improvement despite more than 3 months of continuous medication [compliance with medication had been assured by the parents]).

Exclusion criteria for the patient group were clinical, laboratory, or radiological signs suggestive of an underlying neurological disease other than MNE; psychological problems; diabetes mellitus and diabetes insipidus; ear, nose, and throat problems; daytime urinary symptoms such as incontinence, urgency, and frequency (defined as >10 voidings per day).

Inclusion criteria for the control group were age-, sex-, and body mass index-matched normal healthy children without NE.

Exclusion criteria for the control group were neurological disease; psychological problems; diabetes mellitus and diabetes insipidus; ear, nose, and throat problems; presence of urinary symptoms, either NE or daytime symptoms.

Methods
All patients were subjected to a thorough history taking, including the frequency of bedwetting per week, compliance with medication, snoring, seizures, perianal itching, vulvovaginitis, excessive thirst, nighttime drinking (diabetes mellitus and diabetes insipidus), and family history of NE. Patients underwent anteroposterior plain X-ray of the spine to detect and exclude individuals with spina bifida occulta.

A single night of attended polysomnography (Compumedics Limited, Melbourne, VIC, Australia) was performed on each subject at the sleep laboratory, and no drugs were used to induce sleep. Two channel electroencephalogram, electrooculogram, and tibialis and chin electromyogram were registered using standard methods. Oronasal airflow was recorded by thermistor, and thoracic and abdominal respiratory efforts were measured by impedance plethysmography. Body position was recorded using body position sensor. Oxygen saturation was measured by finger pulse oximetry (ResMed Model 305A; San Diego, CA, USA) and the electrocardiogram from a precardial lead. Sleep data were staged manually according to standard criteria.[24] An apnea was defined as cessation of airflow or reduction of thermistor signal to less than 10% of the normal flow, with a duration of at least 10 seconds and oxygen desaturation of >4%; and hypopnea was defined as a discernible reduction of airflow to between 50% and 75% of at least 10 seconds duration, followed by either an arousal or a desaturation of $\geq 4\%$.[25]

The data were coded and entered into a computer using Statistical Package for Social Sciences (SPSS), version 16.0 (IBM Corporation, Armonk, NY, USA). Data are expressed as mean ± standard deviation unless otherwise stated. Student's t-test was used to ascertain the significance of differences between mean values of two continuous variables, and the Mann–Whitney test was used for nonparametric distribution. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups. The level of $P < 0.05$ was considered as the cut-off value of significance.

Results
Between January 2010 and May 2013, a total of 43 children with primary monosymptomatic, pharmacologically-resistant NE and 30 age- and sex-matched children were enrolled in

our study. Thirty nine (90%) patients had been initially on imipramine (25–50 mg/night) for 1 to 4 months without improvement and eventually shifted to desmopressin while only four were already on desmopressin. A total of 22 patients (51%) continued on desmopressin (nasal: 20–40 μg/night or oral: 0.2–0.4 mg) alone while the remaining 21 patients have been on combined desmopressin and oxybutynin (5–10 mg/night) for 9.4±5.8 months.

There were no statistically significant differences in demographic characteristics between patients and controls (Table 1). Two subjects (6.6%) of the control group showed mild OSAHS. Sixty seven percent of the patients showed frequent NE (>3 days bedwetting/week). Twenty six (60%) out of the 43 patients showed OSAHS. Compared with controls, patients showed significantly higher rates of OSAHS (P<0.0001); three patients had mild, 12 had moderate, and eleven had severe OSAHS (Table 2). The frequency of bedwetting was statistically significantly higher in patients with severe OSAHS (P=0.03) (Table 3). There was no significant statistical difference among patients having OSAHS regarding the sex (12 females and 14 males; P=0.098) or the family history of NE (out of the 26 patients, eleven had a positive family history of NE; P=0.52).

Discussion

NE in children is generally benign but can cause emotional stress to children and their parents.[26] The pathogenesis of enuresis may be based on a mutual balance of three basic mechanisms: bladder capacity, nocturnal production of urine, and the threshold of arousability.[27,28] Among NE children, sleep could be strongly altered, thus helping to affirm the hypothesis that NE tends to alter sleep architecture, or it could itself be the consequence of an abnormal sleep structure.[29]

The prevalence of OSAHS in children ranges from 0.7% to 3% in different epidemiological studies.[30,31] The incidence peak was found in preschool children within the age in which tonsil hypertrophy and adenoid are more common.[32]

Table 2 Polysomnographic criteria of the studied groups

	Control	Patients	Significance
No OSA	28 (93.3%)	17 (39.5%)	χ^2=21.7,
Mild OSA (AHI 1 to <5)	2 (6%)	3 (7%)	P<0.0001*
Moderate OSA (AHI 5 to <10)	0	12 (27.9%)	
Severe OSA (AHI ≥10)	0	11 (25.6%)	
Apnea–hypopnea index	2.7	16	z=1.3, P=0.002*
Oxygen desaturation index (events/hour)	3.8	6.1	t=3.2, P=0.002*
Average saturation (%)	95.4	90.6	t=2.9, P=0.004*
Saturation nadir (%)	90.2	84.9	t=3.3, P=0.002*
Sleep stage distribution (% of time from the total sleep time)			
Stage 1	2	3	t=1.2, P=0.08
Stage 2	53	57	t=1.3, P=0.07
Slow wave sleep	20	18	t=1.7, P=0.045*
REM	25	22	t=2.5, P=0.01*
Arousal index (events/hour)	6.5	7.9	t=1.4, P=0.067

Note: *Represents statistical significance.
Abbreviations: AHI, apnea–hypopnea index; OSA, obstructive sleep apnea; REM, rapid eye movement.

In the present study, two subjects of the control group showed OSAHS; only one (3%) showed clinically significant OSA (AHI >1). The incidence of NE among the children with upper airway obstruction was 34.5%,[33] and the prevalence of NE in OSA patients is 47% compared to 17% for non-OSA children.[15] The frequency of NE in Chinese children with OSA was 51.6% compared to 15.8% in primary snorers.[34]

To the best of our knowledge, no study has evaluated the prevalence of OSA in patients with refractory NE. Our study showed significantly higher rates of OSAHS in patients with refractory NE compared with controls. Sixty percent of the patients showed OSAHS, which is still higher than prevalence of NE in patients with OSA; this may reflect the selection of a specific group of therapy-resistant patients or the reverse method used for assessment.

The current study showed no significant statistical difference among patients having OSAHS regarding the sex or the family history of NE. Some studies revealed a higher prevalence of SDB symptoms among boys,[35–39] and others

Table 1 Demographic characteristics of the studied groups

	Control (n=30)	Patients (n=43)	P
Age (mean ± SD)	9.6±2.7	9.19±2.4	0.4
Sex (boys)	18 (60%)	26 (60.5%)	0.6
Body mass index	22.9±3.5	22.7±3.6	0.8
Frequency of bedwetting/week			
>3/week	–	29 (67%)	–
<3/week	–	14 (33%)	–
Family history of nocturnal enuresis	–	16 (37%)	–

Abbreviation: SD, standard deviation.

Table 3 Relation between OSAHS and frequency of bedwetting

OSA severity	Infrequent	Frequent	Total	Significance
No apnea	10	7	17	χ^2=9.2,
Mild apnea	0	3	3	P=0.027*
Moderate apnea	2	10	12	
Severe apnea	2	9	11	
Total	14	29	43	

Note: *Represents statistical significance.
Abbreviations: OSA, obstructive sleep apnea; OSAHS, obstructive sleep apnea–hypopnea syndrome.

showed no difference by sex[40–48] while a single study reported a higher prevalence of snoring in girls.[49] Prevalence of NE was increased with increasing severity of OSA in girls.[50] In our study, 67% of the OSA patients showed frequent NE (>3 days bedwetting/week), and frequency of bedwetting was statistically significantly higher in patients with severe OSAHS.

The treatment protocol for NE recommended by the International Children's Continence Society is initially lifestyle modification, followed by alarm treatment, and pharmacotherapy.[51] Despite the high percentage of the adherence to enuresis treatment which is more than 70%,[52] a substantial number of enuretics do not become dry in response to desmopressin.[53] Moreover, tolterodine in monotherapy had no proven effect. Imipramine was better than placebo, but side effects were common.[54] Oxybutynin alone was not effective in management of NE[55] but in combination with desmopressin gave significantly faster and more cost-effective results.[56] Alarm therapy was effective for cases refractory to pharmacotherapy, and nonresponders to alarm therapy were also refractory to pharmacotherapy.[57] In patients with refractory MNE, a combined approach may improve enuresis,[58–60] and methods such as posterior tibial nerve stimulation,[61] interferential electrical stimulation therapy,[62] acupuncture treatment,[63] abdominal and pelvic floor muscle retraining,[64] and assumption of unusual posture during sleep, in particular legs retracting or crossing during sleep to enlarge the diaphragmatic excursion and promote alveolar gas exchanges,[65] have been tried in refractory primary MNE. The identification of SDB may open new therapeutic pathways, in terms of surgery for the upper obstructed airway for those patients with NE who do not respond to standard treatment.[66]

Patients with NE had significantly higher positive SDB than controls.[67] NE is associated with OSA and appears to improve or resolve following adenotonsillectomy.[15,16,67–69] In children diagnosed with SDB, the preoperative prevalence of enuresis was 31% and the postoperative was 16% in a review of 14 studies.[70] The acquisition of urinary continence seems to be complex and is probably not yet completely understood.[71] Increased brain natriuretic peptide levels may account for the increased prevalence of enuresis in the context of SDB;[67] children with refractory NE showed abnormal sleep architecture, high incidences of periodic limb movements in sleep, and increased cortical arousability, leading to awakening.[72]

The vast majority of the published studies have investigated NE among children with SDB, and to the best of our knowledge no study has investigated OSA and its severity in relation to the frequency of NE among children with pharmacologically-resistant NE. Our study shows higher frequency of OSA in children with refractory NE compared with the controls and a positive correlation between frequency of NE and the severity of OSA. In conclusion, patients with refractory NE had a significantly higher prevalence of OSAHS with no sex difference. The frequency of bedwetting was higher in patients with severe OSAHS. These finding may open up further investigative pathways and treatment modalities for patients with refractory NE with OSA.

Disclosure

The authors report no conflicts of interest in this work.

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