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Enuretic children with obstructive sleep apnea syndrome: Should they see otolaryngology first?

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Abstract *Objectives:* To study: (1) the prevalence of diurnal urinary incontinence (DI) and nocturnal enuresis (NE) in children with obstructive sleep apnea syndrome (OSAS) who underwent surgery for their upper airway symptoms, (2) the postoperative rate of enuresis resolution, and (3) factors that may predict lack of improvement post surgery.
Patients and Methods: An observational, pilot study of children 5—18 years of age with OSAS and NE who underwent tonsillectomy and/or adenoidectomy (T&A) between 2008 and 2010 was performed. Study consisted of a phone interview and chart review. Severity of NE and DI, frequency, arousal and sleeping disturbances were assessed pre and post T&A. Factors associated with failure to respond were analyzed using a logistic regression model.
Results: Among the 417 children who underwent T&A, 101 (24%) had NE (61 males, mean age 7.8 ± 2.5 years), and of these 24 had associated DI (6%). Mean postoperative follow-up was 11.7 months. Of the 49 whose NE responded to T&A (49%), 30 resolved within 1 month postoperatively. DI resolved in 4 children (17%). There was a statistically significant difference between responders and non-responders regarding the presence of prematurity, obesity, family history of NE, type of enuresis, enuresis severity, and ability to be easily aroused.
Conclusion: NE was present in about one fourth of children with OSAS undergoing surgery, and resolved in about half. Lower response rate was associated with prematurity, obesity, family

Abbreviations: DI, diurnal urinary incontinence; NE, nocturnal enuresis; OSAS, obstructive sleep apnea syndrome; T&A, adenotonsillectomy; HIC, Human Investigation Committee; ENT, ear—nose—throat; BMI, body mass index; ICCS, International Children's Continence Society; ADHD, attention deficit hyperactivity disorder; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; Non-MNE, non-monosymptomatic NE; MNE, monosymptomatic NE; PNE, primary nocturnal enuresis; ANP, atrial natriuretic peptide.

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history of NE, presence of non-monosymptomatic NE, severe NE preoperatively, and arousal difficulties.

Background

Nocturnal enuresis (NE) is a common childhood condition, present in about 5–7 million children in the United States. It occurs more commonly in boys, and in children with a family history of enuresis, lower socioeconomic status, and black ethnicity. The prevalence of NE decreases but the severity increases with age. [1]. It is reported in about 15–20% of 5 year olds, 5–7% of 10 year olds, and 1–2% of 15 year olds, reaching a plateau of approximately 0.5–1% in adulthood.

There is ongoing debate regarding the relationship between obstructive sleep apnea syndrome (OSAS) and NE. While NE has been reported in 8–47% of children with OSAS caused by adenotonsillar hypertrophy [2–4], the prevalence of OSAS in children with NE is unknown. Consequently, the role of OSAS in causing or maintaining enuresis is not clear. Release of upper airway obstruction by tonsillectomy and/or adenoidectomy (T&A) has been associated with complete resolution of NE in 31–76% of children within months of surgical intervention [5–8]. If airway obstruction is the possible etiology for NE in these children, it is not clear why enuresis persists post T&A in some, since the postoperative release of upper airway obstruction is demonstrated in almost all patients. To our knowledge no study has addressed this question. Others have found no association between tonsillar hypertrophy and urinary incontinence before or after T&A [9]. Due to the existing controversies, we sought to analyze the prevalence of NE in children with OSAS and the response to T&A in a large cohort. The study also identified factors associated with lack of response after T&A.

Patients and methods

Children 5–18 years of age who underwent T&A for relief of their upper airway obstruction due to adenoid and/or tonsillar hypertrophy between September 2008 and September 2010 at our medical center, were screened for the presence of NE by the use of a phone questionnaire that has not yet been validated. All patients were seen in the Ear, Nose and Throat (ENT) Department and did not undergo a urological evaluation at our institution. Parents of enuretic children completed the phone interview, and their charts were reviewed in detail.

The study protocol was approved by the Human Investigation Committee. Initially, an Institutional Review Board approved informative letter and a copy of the phone questionnaire were mailed to the parents of all children who had T&A done for upper airway obstruction release. Telephone consent was obtained by the urology staff from parents of the participating children. Parents were given the opportunity to opt-out.

Parents were queried regarding their child's birth, past medical and family history, current medical conditions and medications. Also identified were age at toilet training, presence of daytime urinary symptoms (such as urgency, increased urinary frequency, etc.), past or current use of an alarm and/or medications to treat NE, and fluid restriction at bedtime. Symptoms suggestive of OSAS (such as snoring, mouth breathing/drooling, apnea), as well as the ability to wake up at night were assessed pre and post T&A. The number of weekly wet days and nights, and daily voids were compared pre and post T&A. Parents were also asked whether their child had ever experienced a dry period of at least 6 months.

Only patients with NE before T&A were selected for chart review to obtain the following information: gender, race, growth (height, weight) at the time of T&A, perinatal history (prematurity), past medical history (chronic conditions, medication), presenting symptoms prior to surgery, degree of tonsillar and adenoid hypertrophy (assessed by the ENT surgeon during the clinic visit), indication for surgery, age at the time of surgery, and sleep study results. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). A child was considered overweight if the BMI exceeded the 85th percentile on curves generated by age and sex. [10]. BMI values were compared to parental assessment of weight. NE was defined in accordance with the International Children's Continence Society (ICCS) standardized terminology [11]. OSAS was defined as abnormal breathing during sleep causing sleep disruption, and identified by the presence of snoring, intermittent pauses, snorts, and/or gasps.

Patients were grouped by age (Group 1, 5–8 years; Group 2, 9–18 years), NE severity prior to T&A (mild 1–2 nights/week, moderate 3–4 nights/week, and severe 5–7 nights/week), and degree of tonsil or adenoid hypertrophy (mild $\leq$ 50% obstruction, moderate 50–75%, severe $\geq$ 75%). Patients were divided into two categories based on their enuresis response after T&A: responders had complete resolution or decreased enuresis episodes to less than 2 nights a week, and non-responders had no change or 3 or more wet nights a week.

Statistical significance of comparisons of continuous and categorical variables was assessed by Student's *t*-test and Fisher's exact test, respectively. Analysis of covariance was used to examine mean differences in the number of weekly wet nights pre and post T&A between responders and non-responders. Postoperative mean number of weekly wet nights was the dependent variable, study group was held as the factor variable, and pre-surgery mean number of weekly wet nights represented the covariate. Normality and homogeneity of variance were checked using Levene's test. A Bonferroni post-hoc correction was used to control Type I error.

Variables found to be significantly associated with failure to respond in a univariate fashion were then examined using logistic regression. Estimated odds ratios and their 95% confidence interval (CI) are reported. All tests were two-tailed, and statistical significance was considered

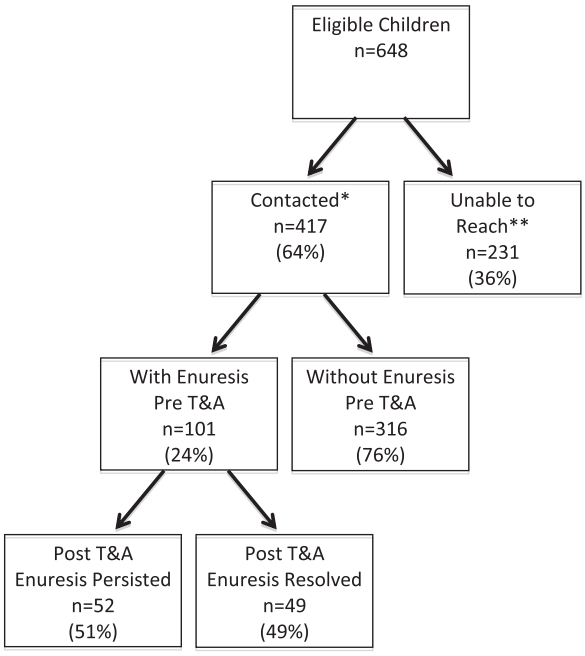

Figure 1 Study flowchart. *All patients who were contacted agreed to participate in the study. **Patients were not reached due to disconnected or incorrect telephone numbers.

at a p-value ≤ 0.05. SPSS Version 18.0 was used for the analyses. We adhered to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [12] for reporting this study.

Results

Population characteristics

Study flow is presented in Fig. 1. Mean time from surgery to postoperative follow-up phone interview was 11.7 months (range = 2—24 months; median = 13 months). Demographic and clinical characteristics of the study sample based on response of NE to T&A are presented in Table 1A and 1B. The groups did not differ on any demographic characteristics, but did significantly differ on some clinical variables. BMI values (available in 87/101 children with enuresis pre T&A) and parental perception were used to define obesity, and when compared concordance was found in 94% of cases. Therefore, we used parental information with regard to weight in our analysis.

Thirty-two children (32%) presented with additional medical problems such as attention deficit hyperactivity disorder (ADHD, 9), asthma (22), seasonal allergies (11), and seizure (1). None had neuromuscular disorders, or craniofacial or urologic abnormalities.

Preoperative Data

All children had a history of upper airway obstruction including snoring (94), apnea (88), and mouth drooling (92). Data regarding tonsil and adenoid size were available in 63 and 70 patients, respectively. Moderate to severe airway obstruction was reported in 49 out of 63 with tonsillar hypertrophy (77%) and 44 out of 70 with adenoid enlargement (63%). Forty children (40%) were reported to be easily aroused from sleep. Sleep study was done in 15 children and showed OSAS in 12 and snoring in 3.

Preoperatively, the average number of weekly wet nights was 4.9 (range 1—7). Seventy-eight (77%) had moderate to severe enuresis. Twenty-four out of 101 children with NE (24%) had also diurnal incontinence (DI). Twenty-seven percent of children reported associated daytime urinary symptoms such as urgency and increased urinary frequency. Pre T&A, NE alarm was attempted in 13 patients (with some improvement seen in 3), while NE medication was given to 19 patients (desmopressin in 9 with improvement in 1, ditropan in 5, imipramine in 1, not identified in 4). None of the children were on NE medication or fluid restriction at the time of surgery or post T&A.

Adenoidectomy was performed in 12 children (12%), T&A in 87 (86%), and tonsillectomy in 2 (2%).

Postoperative response

Snoring, apnea and mouth drooling resolved in all but 10 children, 7 of whom also had persistent NE. Improved arousal was reported in 46 children (46%), and of these 33

Table 1A Demographic characteristics of the sample in relation to response of nocturnal enuresis to T&A.

	All patients (N=101)	Responders (N=49)	Non-responders (N=52)	*P-value*
Gender				0.07
Male (%)	61 (60%)	25 (41%)	36 (59%)	
Female (%)	40 (40%)	24 (60%)	16 (40%)	
Age Groups				0.83
Age 5—8 years (%)	70 (70%)	33 (47%)	37 (53%)	
Age 9—18 years (%)	31 (30%)	16 (52%)	15 (48%)	
Race				0.42
White	29 (30%)	11 (38%)	18 (62%)	
African American	51 (53%)	27 (53%)	24 (47%)	
Other	16 (17%)	7 (44%)	9 (56%)	

Table 1B Clinical characteristics of the sample in relation to response of nocturnal enuresis to T&A.

	All patients (N=101)	Responders (N=49)	Non-responders (N=52)	*P-value*
BMI in kg/m^2, (mean ± SD)	20.5 ± 6.50	19 ± 5.39	21.3 ± 7.52	0.017*
Obesity	35 (35%)	11 (31%)	24 (69%)	0.021*
Prematurity	22 (22%)	6 (27%)	16 (73%)	0.029*
Family history	44 (44%)	16 (36%)	28 (64%)	0.029*
Enuresis severity pre T&A				
Mild	23 (23%)	15 (65%)	8 (35%)	0.076
Moderate	21 (21%)	14 (67%)	7 (33%)	0.068
Severe	56 (56%)	20 (36%)	36 (64%)	0.003**
MNE	74 (74%)	42 (86%)	32 (62%)	0.007**
Arousal				
Pre T&A	41 (40%)	26 (63%)	15 (37%)	0.016*
Post T&A	46 (46%)	33 (72%)	13 (28%)	0.001**

BMI, body mass index; MNE, monosymptomatic nocturnal enuresis. *$p \leq 0.05$; **$p \leq 0.01$.

(71.7%) also had resolution of their NE. This is in contrast to the resolution of NE in only 16 (29.1%) of the 55 patients (54%) whose arousal did not improve post T&A ($p < 0.0001$).

Following T&A, NE significantly improved in 49%, with complete resolution in 39 (39%), of whom 31(79%) experienced resolution within 1 month of surgery. Of the 12 children with OSAS proved by sleep study, 4 showed complete resolution, 2 showed improvement, and 6 had no change in their NE. NE persisted in 8 out of 9 (89%) with ADHD, and in 13 out of 22 (59%) with asthma. When patients with ADHD, other comorbid medical conditions (e.g. asthma, allergies, seizures), and/or non-monosymptomatic nocturnal enuresis (MNE) were excluded from analyses, 51 patients remained with 'pure' NE. Of these, NE significantly improved in 62.7% ($N = 32$), with complete resolution in 49.0% ($N = 25$). Of the 12 children with secondary NE, 8 became dry. The sample was categorized based on the length of time between T&A surgery and the follow-up phone interview (i.e. 0–6 months, 7–12 months, 13–17 and 18–24 months). Due to the small number of patients with follow-up between 19 and 24 months, the last two groups were combined so that a Chi-square analysis could be conducted. Results revealed no significant differences between the groups in regard to resolution of NE ($p = 0.18$).

DI resolved in 4 children, improved in 5, and remained unchanged in 15. All of the children whose DI resolved ($n = 4$; 100%) also showed resolution of their enuresis. In contrast, all 15 (100%) of the children whose DI remained unchanged continued to have enuresis postoperatively.

Although parents had difficulty specifying the number of daily voids pre and post T&A, a decrease was reported in the majority of children.

The total number of weekly wet nights in the whole cohort significantly decreased post surgery (mean ± SD = 2.33 ± 0.83, $p < 0.001$) (see Fig. 2). There was a significant difference in the mean number of weekly wet nights between responders (0.2 ± 0.41) and non-responders (4.84 ± 2.24) postoperatively. When the preoperative mean number of weekly wet nights was held as covariate, responders showed a significantly smaller mean number of weekly wet nights (0.44 ± 0.21) in comparison to non-responders (4.61 ± 0.2). The mean difference of 4.17 was statistically significant at a p-value < 0.001 (95% CI 3.59–4.75). Thirty-three responders (72%) and 13 non-responders (28%) were easy aroused postoperatively ($p < 0.001$).

Factors associated with poor response

Significant differences between responders and non-responders were observed. Children who were born premature, were obese, or had a positive family history of NE, non-MNE, severe NE pre T&A, or arousal difficulties pre

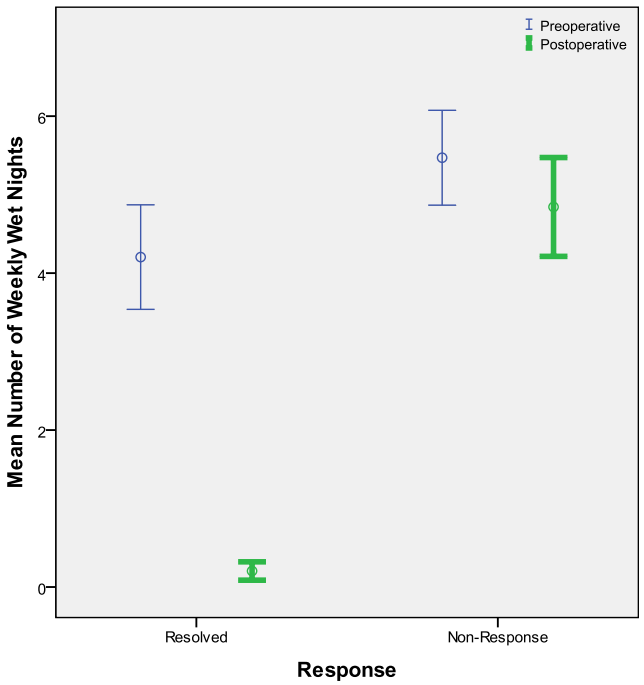

Figure 2 Mean and 95% confidence interval of the number of weekly wet nights between responders and non-responders pre and post T&A (ANCOVA p-value < 0.001).

and post T&A exhibited a poorer response (Table 1B). All these factors except non-MNE independently correlated with a lack of response after T&A (Table 2).

Sixteen out of 31 children (52%) whose NE resolved in less than 1 month had none of the identified risk factors (i.e. were born at term, had normal weight, presented with mild and monosymptomatic NE pre T&A, and denied family history of NE and arousal difficulties). There were no differences between responders and non-responders in terms of age, gender, race, degree of adenotonsillar obstruction, and type of NE (primary vs secondary).

Discussion

The prevalence of NE, as well as the ratio of MNE to non-MNE and preponderance of primary NE, in our study was similar to that reported in the literature [6,13]. NE was more frequent in boys and younger children. A slight male predominance in OSAS children with enuresis was also reported by Brooks and Topol [4] (51%) and Basha et al. [5] (58.9%), and may reflect the overall predisposition of boys to NE (about 60%).

The resolution of NE following T&A has been previously reported in a small number of children. In contrast to these studies, we followed a large cohort and included only children who were 5 years of age or older. This strict inclusion criteria is important as NE may be considered physiological in children younger than 5 years. Our results indicate a good response rate of NE to T&A. More than one third of the children with OSAS in this study showed complete resolution of their NE following surgical release of upper airway obstruction. This is comparable to the rate reported by others and provides additional evidence on the role of OSAS in NE. About two thirds of the patients responded in the first month after surgery, an effect that cannot be solely attributed to spontaneous remission reported at the annual rate of 14%.

Our study is unique in identifying several factors associated with the lack of response of NE to T&A in a group of children with OSAS. Children with persistent NE were born premature, had comorbid conditions (including obesity, ADHD and asthma), a strong family history of NE, severe enuresis, and arousal difficulties. Boys appeared to have a poorer response compared to girls, although the difference did not reach statistical significance. Also, younger children 5—8 years of age were less likely to respond.

Table 2 Results of logistic regression analysis for factors associated with lack of response after T&A.

Variable	Odds Ratio[a]	95% CI
Prematurity	5.76	(1.51, 21.8)
Obesity	4.15	(1.33, 12.94)
Family history	3.22	(1.1, 9.4)
Preoperative mild vs severe enuresis	0.31	(0.10, 0.92)
Preoperative moderate vs severe enuresis	0.47	(0.06, 3.87)
Postoperative arousal difficulties	10.66	(3.47, 32.78)

[a] Odds ratio of NE failure to respond to T&A when controlling for other risk factors in the model.

Treatment failure of NE in overweight children has been reported by others. Guven et al. found a strong correlation between BMI and response to treatment in children with NE. [14]. Children with BMI above the 85th percentile showed no improvement in NE frequency following treatment compared to normal weight children at 6 and12 months follow-up. Obese children do often suffer from sleep-disordered breathing which may cause NE. [15]. Indeed, persistence of breathing problems post T&A may explain why two obese patients in our study did not show resolution of their NE. However, the remaining overweight children reported no change in their NE even though their obstruction symptoms resolved post T&A. Weight reduction prior to attempting T&A may be a reasonable recommendation that could lead to cessation of sleep apnea symptoms and NE.

The relationship between prematurity and NE has been reported in the past. Ohlweiler et al. noticed that NE was more prevalent in 51 children aged 7 years with a history of prematurity compared to 44 born at term [16]. This could be explained by maturational delay, a recognized contributing factor in NE. Based on our results, a conservative approach may be justified in young children with NE born premature.

Positive family history of NE was an indicator of failure to respond to T&A in this study, possibly due to genetic factors involved in the pathogenesis of enuresis [17]. Strong family history of NE has been reported in 50—65% of enuretic children. It is likely that, when present, a family history of NE contributes to resistance to treatment. Moreover, children with non-MNE in our study were less likely to respond. A different pathogenesis of NE in this particular group may be responsible for treatment failure. ADHD, as well as asthma, was also associated with a poorer NE resolution after T&A. These children may represent a separate, and more difficult to treat, entity.

We found that the resolution of NE paralleled improvement in arousal in a small number of children. Easier awakening may be responsible at least in part for the effect of T&A on enuresis. In addition, as hypothesized by others [12], T&A may have caused a decrease in atrial natriuretic peptide secretion leading to reduction of sodium excretion and urinary volume at night. This explanation remains speculative since to date no studies have explored the possible mechanism responsible for this effect.

There are some limitations to our study. The use of phone interview follow-up at varying times postoperatively may have resulted in a recall bias regarding the severity of the child's NE. However, the significant burden of NE on families suggests it should be remembered by parents. In spite of its observational design, we believe that our results are helpful in counseling parents regarding the probability of their child's NE responding to T&A. Due to the inclusion of only children older than 5 years of age, the number of patients with NE in our study was small, but greater than in previous studies, and still relevant to clinical practice. The small number of children with secondary enuresis and associated daytime incontinence makes the interpretation of these results difficult in regard to those conditions. The

diagnosis of OSAS was made clinically by the ENT surgeon based on the presence of intermittent pauses, snorts, and/or gasps, snoring, and mouth breathing, which is common practice. Sleep studies to confirm the diagnosis were only performed in a few patients.

Conclusions

NE was present in about one fourth of children with OSAS who underwent T&A for the relief of their upper airway obstruction. T&A had a favorable therapeutic effect on enuresis in these children, which was mostly seen in the first month after surgery. Children with OSAS and NE should be referred to an ENT surgeon for possible T&A evaluation. Parents can be counseled that there is a 50% probability of the child becoming dry at night post T&A. This decreases if the child was born premature, is obese, has a family history of NE and associated comorbidities such as ADHD and asthma, severe NE, and arousal difficulties. Weight control should be attempted as the initial step in obese children with OSAS and NE. Easier arousal may be partly responsible for the effect of T&A on NE in children with OSAS. Prospective controlled studies are needed to further clarify these issues.

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Conflict of interest/funding

None.

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