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Sleep Architecture Parameters That Predict Postoperative Resolution of Nocturnal Enuresis in Children With Obstructive Sleep Apnea

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Objectives: We performed a prospective cohort study in a pediatric tertiary care center to determine whether preoperative sleep architecture is associated with complete resolution of nocturnal enuresis (NE) after adenotonsillectomy.

Methods: Thirty-seven pediatric patients with primary NE who underwent adenotonsillectomy for obstructive sleep apnea (OSA) were evaluated. Preoperative polysomnograms, as well as preoperative and postoperative reports of NE, were recorded. We performed χ^2 analysis, Fisher's exact test (for p values), and *t*-tests to evaluate the impact of multiple demographic characteristics on sleep architecture, comparing children with resolved NE to those with unresolved NE after adenotonsillectomy.

Results: The patients' mean age was 8.0 years (SD, 2.32 years). All children had presurgical primary NE. No age or gender differences were identified between children with resolved NE and those with unresolved NE. After surgery, more than half of the participants had resolution of NE. A higher percentage of boys had unresolved NE ($\chi^2 = 3.63$; $p = 0.06$). Improvement of NE was identified in children with a higher obstructive apnea-hypopnea index and more desaturation events. Eleven of the 12 children with prolonged stage 2 sleep reported resolution of NE ($p = 0.001$). Children with an obstructive apnea-hypopnea index of greater than 10 had a significantly greater rate of resolution of NE ($p = 0.01$). Logistic regression demonstrated that an elevated body mass index and the interaction of severe OSA and prolonged stage 2 sleep predicted resolution of NE. All 10 children with severe OSA and an abnormal total time spent in stage 2 sleep had resolution of NE.

Conclusions: Adenotonsillectomy is a treatment option for children with OSA and NE. Postoperative resolution of NE was seen in 51.4% of patients who underwent adenotonsillectomy. The children with both severe OSA and prolonged stage 2 sleep were 3.4 times as likely to have postoperative resolution of NE. These results suggest that there are significant differences in preoperative sleep architecture between children whose NE resolves after adenotonsillectomy and those whose NE does not resolve.

Key Words: adenotonsillectomy, enuresis, obstructive sleep apnea, pediatrics, polysomnogram, sleep architecture.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common ailment among the pediatric population and is believed to affect nearly 500,000 children in the United States alone.[1,2] The sequelae of untreated OSA include daytime somnolence, hyperactivity, behavioral problems, poor school performance, morning headaches, and parasomnias such as nocturnal enuresis (NE).[3] The most common cause of OSA in children is adenotonsillar hypertrophy, and adenotonsillectomy is the preferred surgical treatment performed by otolaryngologists to alleviate OSA-associated morbidity.[1]

Primary NE accounts for more than 75% of enuresis cases and is defined as the absence of nocturnal urinary continence for more than 6 months after formal toilet training.[4] Unlike secondary NE, primary NE is not commonly associated with other medical or psychological disorders and is caused by a disparity between bladder capacity and nocturnal urine production and an associated failure to awaken in response to a full bladder.[4]

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Nocturnal enuresis has been reported to affect 8% to 47% of children with a diagnosis of OSA resulting from adenotonsillar hypertrophy.[5] Reports have estimated that 31% to 76% of children with OSA and NE have complete resolution of NE within months after adenotonsillectomy.[5] The American Academy of Otolaryngology–Head and Neck Surgery defines OSA as sleep-disordered breathing symptoms accompanied by obstructive events documented by polysomnogram (PSG).[6] Currently, it is estimated that PSGs are obtained in only 10% of children referred for adenotonsillectomy, but their utility in the diagnosis of pediatric OSA is becoming accepted among medical practitioners.[7]

The objective of this study was to evaluate relationships between sleep architecture on preoperative PSGs and postoperative resolution of NE in children with OSA and primary NE. To our knowledge, this study is the first to identify unique characteristics in sleep architecture as possible predictors of resolution of NE after adenotonsillectomy.

MATERIALS AND METHODS

Forty-nine children (5 to 12 years of age) were recruited for this prospective cohort study from the pediatric otolaryngology, pulmonology, and urology departments at Children's Hospital of Michigan. All had formal toilet training and were reported as having incidents of primary NE more than 3 days per week in the absence of daytime enuresis. These children had symptoms of OSA as described by the American Academy of Otolaryngology–Head and Neck Surgery clinical practice guidelines.[6] They had PSGs indicating an obstructive apnea-hypopnea index (OAHI) of greater than 1. We excluded patients with secondary enuresis, severe asthma, purely central apneic events, morbid obesity (body mass index [BMI] greater than 40 kg/m^2), mental retardation, abnormal bladder function, psychological illnesses, sickle cell anemia, cerebral palsy, or cardiac, renal, or endocrine conditions. Of the 49 patients recruited, 12 did not undergo adenotonsillectomy, because of either parental refusal or an absence of obstructive disease according to the PSG.

The patient's age, gender, weight, BMI, and tonsil grade were recorded upon the initial visit. The presence of primary NE and OSA symptoms was also documented at this time. The preoperative PSGs of the 37 children who completed and met the criteria for the study were examined in detail. The sleep stages, OAHI, oxygen saturation, end-tidal carbon dioxide level, and total obstructive and hypopneic events were documented. All data were obtained from initial evaluations, PSGs, operating room records, and 6- to 8-week postoperative visits. Three pediatric otolaryngologists and one pediatric nephrologist made the final assessment of primary NE. Severe OSA was classified as an OAHI greater than 10.[6]

TABLE 1. SLEEP STAGES IN HEALTHY CHILDREN

Stage	*% of Total Sleep Time*
Stage 1 (N1)	4 to 7.7
Stage 2 (N2)	36 to 49
Stage 3 (N3)	14 to 32
Rapid eye movement	17.4 to 21.1

Data are from references 8-13.

The PSGs were obtained at Children's Hospital of Michigan Sleep Laboratories with the Alice 5 Diagnostic Sleep System (Philips, Amsterdam, Netherlands). Sleep stages and respiratory events were scored and interpreted by use of the Morpheus automated sleep-testing management platform (WideMed, Tel Aviv, Israel). Two physicians who were board-certified in sleep medicine interpreted all PSGs. The sleep physicians were blinded to the patient's postoperative NE status. Data from several publications that reported PSG values in healthy pediatric populations were used to establish normal ranges of sleep stages and cardiorespiratory parameters (Table 1).[8-13] These data, along with established OSA sleep parameters, were used to analyze and compare our study children's data to the sleep architecture accepted as normal in the pediatric population. Obstructive apnea and hypopnea were scored according to the American Academy of Sleep Medicine sleep scoring manual.[14]

This study was reviewed and approved by the Wayne State University Human Investigation Committee and was partially funded through a grant obtained from the Society of Pediatric Urology. Data analyses were performed by χ^2 analysis, Fisher's exact test, and *t*-tests to evaluate the impact of multiple demographic characteristics on sleep architecture, comparing children with resolved NE and those with unresolved NE after adenotonsillectomy. A p value of 0.05 was used to define statistical significance. Logistic regression was conducted on all variables identified as statistically significant on univariate analysis to identify those that uniquely predicted postoperative NE outcome. The SPSS V.20 statistics system (IBM, Armonk, New York) was used for all data analysis.

RESULTS

The patients' mean age was 8.0 years (SD, 2.32 years; range, 5 to 15 years); 23 (62.2%) were male and 14 (37.8%) were female. The mean BMI was

TABLE 2. PATIENT DATA BY GROUP

	Unresolved Nocturnal Enuresis (n = 18)	*Resolved Nocturnal Enuresis (n = 19)*	t	χ^2	*p*
Age (y)	7.28 ± 1.87	8.68 ± 2.77	−1.80		0.08
Girls/boys	28.6%/60.87%	71.4%/39.13%		3.63	0.06
Adenoid grade	3.00 ± 0.97	3.21 ± 0.92	−0.68		0.50
Tonsil grade	3.00 ± 0.84	2.73 ± 1.05	0.84		0.41
Body mass index (kg/m²)	20.89 ± 5.60	27.53 ± 6.09	−3.45		0.001

Data are mean ± SD except where noted.

24.3 kg/m² (SD, 5.9; range, 12 to 39). Of the 37 participants, 29 underwent adenotonsillectomy, 3 underwent tonsillectomy, and 5 underwent adenoidectomy. Of these children, 51.4% reported resolution of NE at 6 to 8 weeks after operation. As shown in Table 2, children with a high BMI demonstrated a significantly higher rate of resolved NE ($t = -3.45$; $p = 0.001$). In addition, girls (71.4%) had a marginally higher rate of resolved NE than did boys (39.1%; $\chi^2 = 3.63$; $p = 0.06$).

As illustrated in Table 3, significant improvement of NE was seen in children with higher OAHIs on the preoperative PSG (resolved NE mean, 27.43 ± 29.19; unresolved NE mean, 9.09 ± 12.48; $p = 0.02$). Children with resolved NE also demonstrated a greater total number of obstructive apnea events than did those with unresolved NE (resolved NE mean, 112.26 ± 166.62; unresolved NE mean, 20.40 ± 48.49; $p = 0.03$). They also had a greater total number of desaturation events (resolved NE mean, 138.53 ± 177.12; unresolved NE mean, 35.79 ± 60.28; $p = 0.03$).

Patients with resolved NE demonstrated unique patterns of total sleep time spent in particular sleep stages that differed from established normal ranges (Table 4[8-13]). Children with "normal" or "prolonged" stage 1 (N1) sleep had a higher rate of postsurgical resolution of NE than did those who spent less time in stage 1 sleep ($p = 0.020$). The fact that 11 of the 12 children with prolonged stage 2 sleep had resolved NE suggests that prolonged stage 2 (N2) sleep is a significant predictor of resolution of NE in this patient population ($p = 0.001$). Children with prolonged stage 3 (N3; delta) sleep were more likely to have persistent NE than were children with normal stage 3 sleep ($p = 0.049$). A difference in rapid eye movement sleep was not associated with resolution or persistence of NE (Table 4).

In addition to an examination of sleep stage by resolution of NE, χ^2 analyses were also performed to examine the relationship between OSA and NE resolution. The results suggest that children with severe OSA (OAHI of greater than 10) have a significantly higher rate of resolution of NE than those with an OAHI of less than 10 (7 of 21; $p = 0.014$).

A stage 2 sleep–by–OAHI interaction term was calculated to examine a possible association between apnea severity and prolonged stage 2 sleep as related to resolved NE. The results revealed that the stage 2 sleep–by–OAHI interaction term ($\beta = 1.23$; $p = 0.02$) and BMI ($\beta = 0.15$; $p = 0.04$) were the only variables that uniquely predicted NE resolution. Children with NE who had abnormally long stage 2 sleep and severe OSA were 3.4 times as likely to have NE resolution. All 10 children who had severe OSA and an abnormally long time spent in stage 2 sleep had resolution of NE.

DISCUSSION

Multiple studies have investigated the relationship between NE and OSA, but the association between these disorders remains controversial.[15,16] In one study, NE occurred in 9% of children more than 6 years of age who had an OAHI of greater than 1.[16] In our study, 51.4% of children had total resolution of NE after operation. This rate is comparable to previous findings in the literature and further suggests a possible association between NE and OSA

TABLE 3. SLEEP CHARACTERISTICS BY GROUP

	Unresolved Nocturnal Enuresis (n = 18)	*Resolved Nocturnal Enuresis (n = 19)*	t	*p*
Total No. of obstructive apnea events	20.40 ± 48.49	112.26 ± 166.62	−2.25	0.03
Total No. of hypopnea events	29.06 ± 38.01	47.53 ± 42.94	−1.39	0.18
Obstructive apnea-hypopnea index	9.09 ± 12.48	27.43 ± 29.19	−2.46	0.02
Lowest oxygen saturation level (%)	83.77 ± 11.22	79.35 ± 12.92	1.11	0.28
% Sleep time with end-tidal CO_2 level of >45 mm Hg	8.65 ± 18.31	6.26 ± 18.63	0.39	0.70

Data are mean ± SD.

TABLE 4. SLEEP STAGES BY GROUP

	Unresolved Nocturnal Enuresis (n = 18)	*Resolved Nocturnal Enuresis (n = 19)*	*p*
Stage 1 (N1)			0.020
Below normal	11	4	
Normal or above normal	7	15	
Stage 2 (N2)			0.001
Normal or below normal	17	8	
Above normal	1	11	
Stage 3 (N3)			0.049
Normal	7	14	
Above normal	11	5	
Rapid eye movement			0.517
Below normal	8	11	
Normal or above normal	10	8	

Normal values were from references 8-13.

in some patients.[5,17,18] The mechanisms of resolution of NE after upper airway surgery have not been elucidated. The predominant theory is that increased upper airway resistance causes a higher intrathoracic negative pressure, which leads to cardiac distention, increased natriuretic hormone, and increased atrial natriuretic peptide secretion.[18] This cascade in turn causes disruption of the renin-angiotensin-aldosterone system and fluid regulation, leading to nocturnal diuresis.[18,19] Thus, by adenotonsillectomy, the abnormal airway resistance is alleviated, and fluid regulation is restored to normal.

In previous studies, female gender was associated with a lower rate of preoperative NE, but reports of postoperative rates of resolution of NE have been conflicting and scarce.[5,20,21] Basha et al[20] examined 57 children with OSA and NE and noted that 41.1% were female. On postoperative evaluation, they noted a trend toward a higher rate of resolution of NE in girls.[20] We found a marginally higher rate of postoperative resolution of NE in girls.

The relationship between obesity, OSA, NE, and medical intervention has been investigated. Guven et al[22] reported no significant response to NE treatment in children with an elevated BMI. Mitchell and Boss[23] reported a lower rate of resolution of OSA in obese children after adenotonsillectomy. Contrary to these previous reports. our analysis demonstrated a high rate of resolution of NE after adenotonsillectomy in children with an elevated BMI. However, unlike previous studies, ours excluded children with a BMI of greater than 40. This difference in results supports the possibility that both adenotonsillar hypertrophy and nonmorbid obesity were contributing to these patients' OSA and associated NE. This connection may explain the resolution of NE after operation.

Several studies have examined the relationship of severity of OSA, sleep architecture, and resolution of NE. Dhondt et al[24] reported that more-frequent arousals and disturbed sleep in the lighter sleep stages were associated with NE. Others have found more obstructive events in non–rapid eye movement sleep in patients with NE.[24,25] In regard to sleep architecture and respiratory events in our study, certain characteristics appeared to correlate with postoperative resolution of NE. Only 4 of 16 patients with severe OSA (as compared to normal pediatric OAHI ranges) continued to have NE after the operation.

In our study, children with NE, severe OSA, and abnormally prolonged stage 2 sleep were 3.4 times as likely to have postoperative resolution of NE. With this information, it can be theorized that frequent obstructive events are preventing these children from reaching slow-wave sleep and prolonging light, non–rapid eye movement sleep stages such as stage 2, thereby eliciting sleep fragmentation and increased arousals.[25]

This study provides insight into the possibility of an association of certain demographic and preoperative sleep architecture patterns with postoperative resolution of NE. Clinically, this may assist the physician in determining which patients with OSA and NE may benefit from surgery in terms of resolution of NE.

Although the results of this study appear to be fairly robust, there are some limitations. As a result of the strict inclusion criteria, the sample size and study power were relatively low (37 patients). It is possible that many of the variables that were significant in the bivariate analysis (eg, abnormal stage 1 and stage 3 sleep) did not reach statistical significance because of this reduced study power. Nonetheless, in the relationship between OAHI, stage 2 sleep, and postoperative resolution of NE, a large effect size was demonstrated.

This investigation could potentially be strengthened by the addition of a control group without surgical treatment, as well as the inclusion of further quantification of enuretic episodes and postoperative PSGs. Postoperative PSGs would have allowed the assessment of possible residual sleep apnea both in patients with resolved NE and in those with unresolved NE, and demonstrated any changes in sleep architecture patterns. Unfortunately, funding limitations and concerns about obtaining repeat PSGs from children with resolved complaints prevented us from obtaining postoperative PSGs. Further studies should be conducted in the future with a larger sample size, control subjects, and postoperative PSGs.

CONCLUSIONS

In recent years, the usefulness of PSGs as a means of diagnosing and evaluating pediatric OSA has been emphasized in numerous articles. Unfortunately, there is very little literature on the relationship between sleep architecture, NE, and postoperative outcomes in children with OSA. Our study is of particular value because it demonstrates statistically significant correlations between patients' sleep architectural patterns and postoperative resolution of NE. More than half of patients with OSA and primary NE were reported to have postoperative resolution of NE. Additionally, multivariate analysis demonstrated a relationship between an OSA–stage 2 sleep interaction term and postoperative resolution of NE. Of note, all children with severe OSA and prolonged stage 2 sleep were reported to have postsurgical resolution of NE. To our knowledge, this is the first study to prospectively examine sleep architecture as a factor correlating to resolution of NE after adenotonsillectomy.

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