

# Why does Adenotonsillectomy Not Correct Enuresis in All Children with Sleep Disordered Breathing?

Larisa Kovacevic,\* Cortney Wolfe-Christensen, Hong Lu, Monika Toton, Jelena Mirkovic, Prasad J. Thottam, Ibrahim Abdulhamid, David Madgy and Yegappan Lakshmanan

From the Departments of Pediatric Urology (LK, CW-C, HL, MT, JM, YL), Otolaryngology (PJT, DM), and Pulmonology and Sleep Medicine (IA), Children's Hospital of Michigan, Detroit, Michigan

## Abbreviations and Acronyms

ADH = antidiuretic hormone  
BMI = body mass index  
BNP = brain natriuretic peptide  
MPNE = monosymptomatic primary NE  
NE = nocturnal enuresis  
O-AHI = obstructive apnea-hypopnea index  
OSAS = obstructive sleep apnea syndrome  
PSG = polysomnography  
SDB = sleep disordered breathing  
T&A = tonsillectomy and/or adenoidectomy  
TST = total sleep time

Accepted for publication October 7, 2013.

Study received institutional review board approval.

Supported by the Society for Pediatric Urology (2012) and Children's Research Center of Michigan R2-2011-43.

\* Correspondence: Department of Pediatric Urology, Children's Hospital of Michigan, 3901 Beaubien, Detroit, Michigan 48201 (telephone: 313-745-5588; FAX: 313-993-8738).

**Purpose:** We analyzed the outcome of nocturnal enuresis after adenotonsillectomy in children with sleep disordered breathing. We also evaluated differences in demographic, clinical, laboratory and polysomnography parameters between responders and nonresponders after adenotonsillectomy.

**Materials and Methods:** We prospectively evaluated children 5 to 18 years old diagnosed with sleep disordered breathing (snoring or obstructive sleep apnea syndrome) on polysomnography and monosymptomatic primary nocturnal enuresis requiring adenotonsillectomy to release upper airway obstruction. Plasma antidiuretic hormone and brain natriuretic peptide were measured preoperatively and 1 month postoperatively.

**Results:** Sleep studies were done in 46 children and 32 also underwent blood testing preoperatively and postoperatively. Mean  $\pm$  SD patient age was  $8.79 \pm 2.41$  years and the mean number of wet nights weekly was  $6.39 \pm 1.26$ . Polysomnography revealed obstructive sleep apnea syndrome in 71.7% of patients and snoring in 28.3%. After adenotonsillectomy 43.5% of patients became dry. Preoperative polysomnography findings indicated that responders, who were dry, had significantly more arousals and obstructive apnea episodes but fewer awakenings than nonresponders, who were wet. Significant increases in plasma antidiuretic hormone and significant decreases in plasma brain natriuretic peptide were seen in all children with no difference between responders and nonresponders. No difference between the groups was noted in age, gender, race, body mass index, constipation, preoperative number of wet nights weekly or type of sleep disordered breathing.

**Conclusions:** Nocturnal enuresis resolved after adenotonsillectomy in almost half of the children with sleep disordered breathing. Those who became dry had more frequent arousal episodes caused by apnea events than those who remained wet.

**Key Words:** bladder, enuresis, sleep apnea syndromes, tonsillectomy, adenoidectomy

NOCTURNAL enuresis caused by adenotonsillar hypertrophy has been reported in 8% to 47% of children with SDB.<sup>1-3</sup> Release of upper airway obstruction by T&A, which is

potentially curative for the whole spectrum of SDB, is associated with complete resolution of NE in 31% to 76% of children within months of surgical intervention.<sup>4-8</sup> This



association indicates a possible causative role of SDB in children with enuresis with T&A as curative treatment.

To our knowledge the mechanism by which T&A resolves enuresis remains unknown. It was suggested that upper airway obstruction in SDB causes negative intrathoracic pressure, leading to cardiac wall distension, which results in the release of atrial natriuretic peptide and BNP from cardiac myocytes. These hormones cause increased water and sodium excretion, which in turn inhibit vasopressin secretion.

Based on this theory we hypothesized that by releasing upper airway obstruction T&A may lead to the normalization of urinary volume and urinary sodium excretion by BNP and ADH dependent mechanisms, ie by decreasing BNP secretion and/or increasing ADH secretion. If airway obstruction is a possible etiology of NE in these children, it is not clear why enuresis persists after T&A in some of them since postoperative release of upper airway obstruction occurs in almost all patients. We studied 1) the outcome of NE after T&A in children with SDB and 2) differences between responders and nonresponders after T&A.

## METHODS

We performed a multidisciplinary prospective study of children 5 to 18 years old diagnosed with SDB (snoring and OSAS) on PSG and untreated MPNE requiring T&A to release upper airway obstruction. Children with non-MPNE, chronic diseases, abnormal urinalysis and/or renal ultrasound, extreme obesity (BMI greater than 95% for age and gender) and mental retardation were excluded from study.

Participants were identified based on presentation to the pediatric urology clinic with a diagnosis of MPNE. Those who reported SDB (eg snoring or gasping in sleep) during the clinical interview were referred to the ear, nose and throat service. PSG was performed in patients identified as possible candidates for T&A based on ear, nose and throat evaluation. Those with positive sleep studies confirming an SDB diagnosis of snoring or apnea also underwent blood testing to establish baseline ADH and BNP before T&A. Repeat blood testing and a urology clinic visit to assess bedwetting frequency were done 1 month postoperatively, as described. Unfortunately, PSG was not performed postoperatively due to cost limitations.

Patients were asked to keep a log of bedwetting frequency for 1 month postoperatively. Logs were returned at the followup visit to the urology department and confirmed during the history taken by the physician. As recommended by ICCS (International Children's Continence Society) criteria, clinical resolution of NE was defined as a 90% or greater decrease in the number of weekly wet nights.<sup>9</sup> Demographic and clinical characteristics were compared in responders (those dry after T&A)

and nonresponders (those wet after T&A), including age, gender, BMI, preoperative number of wet nights weekly, constipation, SDB type (snoring or OSAS), plasma ADH and BNP concentrations, and PSG parameters. BMI was calculated as weight in kg divided by height in m<sup>2</sup>.

## Sleep Study Parameter Definitions

The proportion of time spent in each sleep stage is shown as a percent of TST. O-AHI was defined as the number of obstructive mixed apneas and hypopneas per hour of TST. OSAS was defined as an O-AHI of at least 1 per hour. In accordance with the ASDA (American Sleep Disorders Association) an arousal represented an increase in electroencephalography frequency at least 3 seconds in duration.<sup>10</sup> Awakening and arousal indexes are shown as the number of events (awakenings and arousals) per hour of TST.

## Blood Collection

Based on reported studies of ADH and BNP secretion in patients with enuresis<sup>11,12</sup> blood specimens were collected between 6 and 7 a.m. after the sleep study but before and 1 month after T&A. A topical anesthetic cream was applied 30 minutes before venous puncture to decrease pain. Blood samples were drawn into 2 chilled ethylenediaminetetraacetic acid tubes and centrifuged at 1,000 × gravity for 20 minutes at 4°C, as recommended by the manufacturer. Samples were stored at -70°C until analysis.

## ADH and BNP Measurement

ADH was measured in plasma using a radioimmunoassay kit. The assay uses a rabbit anti-vasopressin antibody and a radioiodinated vasopressin (<sup>125</sup>I) tracer. Bound and free phases are separated by a second antibody bound to solid phase particles, followed by a centrifugation step. Radioactivity in the bound fraction is measured and a typical standard curve is generated. Values of extracted samples are corrected for extraction recovery. The detection range is 2.05 to 65 pg/ml. Intra-assay and interassay coefficients of variation are 6.5% and 6.9%, respectively, with a lower detectable assay limit of 0.5 pg/ml.

BNP was measured in serum according to the manufacturer using a sandwich enzyme immunoassay kit (No. E90541Hu, USCN Life Science, Wuhan, People's Republic of China). Absorbance was measured at 450 nm. The detection range is 31.2 to 2,000 pg/ml. Intra-assay and interassay coefficients of variation are 10% and 8.5%, respectively, with a lower detectable assay limit of 8 pg/ml.

## Statistical Analysis

Descriptive statistics were calculated to elucidate the nature of the sample. We used the independent t-test and chi-square analysis to compare demographic variables and clinical characteristics in the wet and dry groups. The Mann-Whitney U test was applied to compare sleep study parameters between the groups. Finally, we used multivariate, mixed design ANOVA to compare changes in plasma ADH and BNP levels between the groups. All analysis was done with SPSS®, version 20.



## RESULTS

The study was performed in 46 children (26 males) with a mean  $\pm$  SD age of  $8.79 \pm 2.41$  years who had MPNE and a mean of  $6.22 \pm 1.58$  wet nights weekly. PSG revealed OSAS in 33 patients (71.7%) and snoring in 13 (28.3%). After T&A 17 patients with OSAS and 3 with snoring (overall 43.5%) became dry. There was no difference in demographic (gender, age or race) or clinical characteristics (BMI, preoperative number of weekly wet nights, constipation or SDB type) between responders and nonresponders (each  $p > 0.05$ , table 1).

Table 1 lists preoperative PSG results. There was no difference in the percent of time spent in the 4 sleep stages between responders and nonresponders (each  $p > 0.05$ ). Mann-Whitney U test results revealed that responders had significantly more cortical arousal events per hour ( $U = 159.5$ ,  $Z = -2.07$ ,  $p = 0.039$ ), more arousals associated with respiratory events ( $U = 156.0$ ,  $Z = -2.31$ ,  $p = 0.021$ ), significantly higher O-AHI ( $U = 162.0$ ,  $Z = -2.2$ ,  $p = 0.030$ ) and fewer awakenings per hour ( $U = 152.0$ ,  $Z = 342.0$ ,  $p = 0.043$ ) than nonresponders. Also, responders showed a trend toward lower oxygen saturation ( $U = 173.5$ ,  $Z = -1.9$ ,  $p = 0.055$ , table 1).

Table 2 shows preoperative and postoperative plasma ADH and BNP levels. Multivariate, mixed design ANOVA revealed a main effect for ADH, indicating that plasma ADH significantly increased

**Table 2. Multivariate analysis of estimated marginal group/hormone interaction**

	No. Pts	Mean $\pm$ SD ADH (pg/ml)	Mean $\pm$ SD BNP (ng/ml)
Wet:	18		
Before T&A		$7.19 \pm 1.61$	$32.49 \pm 13.17$
After T&A		$44.62 \pm 17.58$	$19.32 \pm 6.41$
Dry:	14		
Before T&A		$7.36 \pm 1.71$	$47.33 \pm 14.01$
After T&A		$67.42 \pm 18.70$	$27.45 \pm 6.82$
p Value		0.385	0.673

in all children ( $F[1,30] = 14.39$ ,  $p = 0.001$ ). We noted no difference between those who became dry and those who remained wet. Similarly, a main effect for BNP was also found ( $F[1,30] = 4.43$ ,  $p = 0.044$ ), indicating that plasma BNP decreased significantly in all children with no difference between responders and nonresponders.

## DISCUSSION

This comparison of demographic, clinical, laboratory and PSG characteristics between children with MPNE who were dry after T&A and those who remained wet addresses important gaps in the current literature. We found no difference between responders and nonresponders in demographic variables, including gender, age and race. Also, the groups did not differ in clinical characteristics, including SDB type, BMI, constipation or number of wet nights preoperatively. Laboratory findings revealed a significant increase in plasma ADH and a significant decrease in plasma BNP in all children with no difference between those who became dry and those who remained wet. Sleep study results indicated that before surgery children who ultimately became dry had more obstructive events, ie more severe apnea, which caused a significantly higher number of arousal episodes than in children who remained wet.

More severe hypoxia detected in dry vs wet children appears to be a strong arousal stimulus causing sleep disruption. As such, it appears that in children with more fragmented sleep as a result of frequent apneas, the release of upper airway obstruction contributes to NE resolution. However, in other children NE must be influenced by factors other than those studied.

In the current study T&A led to NE resolution in 43% of children with SDB irrespective of SDB type (snoring or OSAS). Compared to the 15% annual rate of spontaneous resolution this 1-month resolution rate of 43% is significantly higher than would be expected.<sup>13,14</sup> This finding is consistent with the rate of MPNE resolution in other series

**Table 1. Demographic, clinical and sleep stage characteristics, sleep study results**

	Wet	Dry	p Value
No. male	15	11	
No. female	11	9	0.86
Mean $\pm$ SD age	$9.33 \pm 2.14$	$8.11 \pm 2.60$	0.10
No. race:			0.12
White	4	4	
Black	17	16	
Other	5	0	
Mean $\pm$ SD BMI (kg/m <sup>2</sup> )	$23.46 \pm 6.68$	$24.60 \pm 7.80$	0.60
Mean $\pm$ SD preop No. wet nights/wk	$5.90 \pm 1.92$	$6.46 \pm 1.24$	0.24
No. first visit constipation (%)	7/19 (36.8)	9/26 (34.6)	0.96
No. SDB type:			0.08
Snoring	10	3	
OSAS	16	17	
Mean $\pm$ SD No. sleep stage (%):			
1 (N1)	$7.04 \pm 6.67$	$6.35 \pm 3.35$	0.67
2 (N2)	$43.39 \pm 9.16$	$46.65 \pm 10.27$	0.26
3 (N3)	$32.75 \pm 7.76$	$30.47 \pm 9.85$	0.38
Rapid eye movement	$16.73 \pm 6.18$	$16.53 \pm 4.99$	0.90
Median sleep study results:			
Arousal index/hr	4.8	6.7	0.039
Arousal associated with respiratory events	5.0	12.0	0.021
Awakening index/hr	2.6	1.7	0.043
O-AHI/hr	1.5	11.3	0.030
% Lowest oxygen saturation	89.6	87.1	0.055



and it provides additional support for a relationship between SDB and NE.

However, previous studies of the association between SDB and NE showed contradictory results. When interpreting those data, caution is needed due to study limitations, including retrospective design, patient recollection bias, small number of children with enuresis who underwent T&A, inclusion of children younger than 5 years in whom enuresis may have been physiological and in whom spontaneous remission may have been possible even without intervention, inclusion of children with nonmonosymptomatic enuresis in whom a secondary cause of enuresis was more likely and a lack of confirmatory PSG necessary for OSAS diagnosis.<sup>4-8</sup> In contrast, Kalorin et al reported no difference in preoperative and postoperative diurnal enuresis and NE in children who underwent tonsillectomy and those treated with surgery unrelated to airway or urinary tract problems.<sup>15</sup> However, that study also has several flaws since children younger than 5 years were included, there was a small number of children with enuresis and followup was brief.<sup>16</sup>

Sleep disturbance represents a major mechanism of NE, in addition to nocturnal polyuria and detrusor overactivity.<sup>17,18</sup> The latter 2 conditions do not cause enuresis unless the child cannot awaken in response to a full bladder. Contradictory data exist in the literature on the arousal threshold in children with enuresis. Some groups noted that children with NE sleep deeply, which prevents arousal when the bladder is full.<sup>19,20</sup> In contrast, Yeung et al recently reported that children with enuresis experience light sleep associated with frequent cortical arousals but fewer actual awakenings.<sup>21</sup> Our findings are consistent with those reported by Yeung et al, although the lack of postoperative PSG and a control group limited our ability to identify a causal relationship between arousal and NE resolution. However, these findings are important and suggest an association between the variables.

ADH and BNP induced natriuresis and diuresis were reported in cases of SDB and NE.<sup>22-25</sup> However, to our knowledge whether changes in ADH and BNP contribute to NE resolution has yet to be examined. ADH, also known as vasopressin, is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. It is secreted in response to blood pressure or plasma volume changes. ADH induces vasoconstriction of the systemic vasculature and contributes to osmoregulation and the maintenance of normovolemia. It increases water permeability in collecting tubules, promoting water resorption. BNP is a non-glycosylated peptide that belongs to the natriuretic

peptide family. It is secreted mainly by the left ventricle in response to myocyte stretch due to volume expansion and pressure load. BNP has natriuretic and diuretic effects.<sup>26</sup> BNP has a slow clearance rate and a long plasma half-life, making it easier to detect.<sup>26</sup>

Children with enuresis have a lower ADH level<sup>27,28</sup> and a higher BNP level<sup>12</sup> than healthy children. When these children also have SDB, they show a greater increase in BNP,<sup>12</sup> which correlates with SDB severity,<sup>29</sup> and normalizes after T&A.<sup>23</sup> Our findings are consistent with previous research since we found that low plasma ADH and high plasma BNP in children with enuresis and SDB normalized after SDB treatment.

In contrast to our expectations, changes in ADH and BNP did not explain NE resolution. Importantly, these findings are preliminary and our small sample size resulted in underpowered analysis. As such, it is possible that a relationship between these hormones and NE resolution exists and might emerge in a larger sample.

The current study has many strengths since it was developed to address flaws in previous research to evaluate a homogeneous group of children with MPNE. The prospective design, strict inclusion criteria (exclusion of children younger than 5 years and those with nonMPNE) and PSG to confirm SDB diagnoses are critical to strengthen the external validity of the results. However, our results are preliminary and should be interpreted in light of several limitations. We acknowledge our small sample, lack of a control group and inability to perform PSG postoperatively.

## CONCLUSIONS

NE resolved after T&A in almost half of the children and it was unrelated to the type of SDB diagnosed on PSG. Significant changes in plasma ADH and BNP were seen in all children after T&A but these changes did not predict NE resolution. Preoperatively PSG revealed more frequent arousal episodes due to more severe apneas but significantly fewer actual awakenings in children who became dry postoperatively than in those who remained wet. The current findings suggest a relationship between arousal-awakening episodes and NE resolution, although to our knowledge the causal link between these variables has yet to be determined.

## ACKNOWLEDGMENTS

Joseph Kierzkowski provided comments on sleep study results.



## REFERENCES

1. Stone J, Malone PS, Atwill D et al: Symptoms of sleep-disordered breathing in children with nocturnal enuresis. *J Pediatr Urol* 2008; **4**: 197.
2. Brooks LJ and Topol H: Enuresis in children with sleep apnea. *J Pediatr* 2003; **142**: 515.
3. Basha S, Bialowas C, Ende K et al: Effectiveness of adenotonsillectomy in the resolution of nocturnal enuresis secondary to obstructive sleep apnea. *Laryngoscope* 2005; **115**: 1101.
4. Firoozi F, Batniji R, Aslan AR et al: Resolution of diurnal incontinence and nocturnal enuresis after adenotonsillectomy in children. *J Urol* 2006; **175**: 1885.
5. Weissbach A, Leiberman A, Tarasiuk A et al: Adenotonsillectomy improves enuresis in children with obstructive sleep apnea syndrome. *Int J Pediatr Otorhinolaryngol* 2006; **70**: 1351.
6. Leiberman A, Stiller-Timor L, Tarasiuk A et al: The effect of adenotonsillectomy on children suffering from obstructive sleep apnea syndrome (OSAS): the Negev perspective. *Int J Pediatr Otorhinolaryngol* 2006; **70**: 1675.
7. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K et al: Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med* 2010; **182**: 676.
8. Kovacevic L, Jurewicz M, Dabaja A et al: Enuretic children with obstructive sleep apnea syndrome: should they see otolaryngology first? *J Pediatr Urol* 2012; **9**: 145.
9. Neveus T, von Gontard A, Hoebeke P et al: The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. *J Urol* 2006; **176**: 314.
10. American Sleep Disorders Association: EEG arousals: scoring rules and examples. *Sleep* 1992; **15**: 173.
11. Rittig S, Knudsen UB, Jønler M et al: Adult enuresis. The role of vasopressin and atrial natriuretic peptide. *Scand J Urol Nephrol Suppl* 1989; **125**: 79.
12. Capdevila OS, Crabtree VM, Kheirandish-Gozal L et al: Increased morning brain natriuretic peptide levels in children with nocturnal enuresis and sleep-disordered breathing: a community-based study. *Pediatrics* 2008; **121**: 1208.
13. Forsythe WI and Redmond A: Enuresis and spontaneous cure rate. Study of 1129 enuretics. *Arch Dis Child* 1974; **49**: 259.
14. Klackenberg GSD: Nocturnal enuresis in a longitudinal perspective. A primary problem of maturity and/or a secondary environmental reaction? *Acta Paediatr Scand* 1981; **70**: 453.
15. Kalorin CM, Mouzakes J, Gavin JP et al: Tonsillectomy does not improve bedwetting: results of a prospective controlled trial. *J Urol* 2010; **184**: 2527.
16. Kovacevic L and Lakshmanan Y: Re: tonsillectomy does not improve bedwetting: results of a prospective controlled trial. C. M. Kalorin, J. Mouzakes, J. P. Gavin, T. D. Davis, P. Feustel and B. A. Kogan. *J Urol* 2010; **184**: 2527.
17. Neveus T: Enuretic sleep: deep, disturbed or just wet? *Pediatr Nephrol* 2008; **23**: 1201.
18. Neveus T: The role of sleep and arousal in nocturnal enuresis. *Acta Paediatr* 2003; **92**: 1118.
19. Dhondt K, Raes A, Hoebeke P et al: Abnormal sleep architecture and refractory nocturnal enuresis. *J Urol* 2009; **182**: 1961.
20. Wolfish NM, Pivik RT and Busby KA: Elevated sleep arousal thresholds in enuretic boys: clinical implications. *Acta Paediatr* 1997; **86**: 381.
21. Yeung CK, Diao M and Sreedhar B: Cortical arousal in children with severe enuresis. *N Engl J Med* 2008; **358**: 2414.
22. Ichioka M, Hirata Y, Inase N et al: Changes of circulating atrial natriuretic peptide and anti-diuretic hormone in obstructive sleep apnea syndrome. *Respiration* 1992; **59**: 164.
23. Yue Z, Wang M, Xu W et al: Secretion of anti-diuretic hormone in children with obstructive sleep apnea-hypopnea syndrome. *Acta Otolaryngol* 2009; **129**: 867.
24. Ljunggren M, Lindahl B, Theorell-Haglöw J et al: Association between obstructive sleep apnea and elevated levels of type B natriuretic peptide in a community-based sample of women. *Sleep* 2012; **35**: 1521.
25. Eggert P and Kuhn B: Antidiuretic hormone regulation in patients with primary nocturnal enuresis. *Arch Dis Child* 1995; **73**: 508.
26. Kimura K, Yamaguchi Y, Horii M et al: ANP is cleared much faster than BNP in patients with congestive heart failure. *Eur J Clin Pharmacol* 2007; **63**: 699.
27. Wille S, Aili M, Harris A et al: Plasma and urinary levels of vasopressin in enuretic and non-enuretic children. *Scand J Urol Nephrol* 1994; **28**: 119.
28. Aikawa T, Kasahara T and Uchiyama M: The arginine vasopressin secretion profile of children with primary nocturnal enuresis. *Eur Urol* 1998; **33**: 41.
29. Kaditis AG, Alexopoulos EI, Hatzi F et al: Overnight change in brain natriuretic peptide levels in children with sleep-disordered breathing. *Chest* 2006; **130**: 1377.