ORIGINAL ARTICLE

Nocturnal enuresis in children is associated with differences in autonomic control

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Abstract

Study Objectives: To assess the relationship between urine osmolality, cardiovascular parameters, and nocturnal enuresis in a population of children undergoing polysomnographic assessment.

Methods: This prospective observational study included consecutive children aged 5–17 years presenting for overnight polysomnography. Children were evaluated using continuous ambulatory blood pressure monitoring to assess heart rate and blood pressure. Urine samples were collected throughout the night to determine urine sodium excretion and osmolality. Comparisons of results were made between children with and without a history of nocturnal enuresis.

Results: A total of 61 children were included for analysis; 13 had a history of nocturnal enuresis. Children with nocturnal enuresis had greater disruption in respiratory parameters including higher apnea–hypopnea index (mean difference 12.2 ± 8.8 events/h, $p < 0.05$), attributable to more central respiratory events (mean difference 5.4 ± 4.9, $p < 0.05$), and higher variability in both oxygen and carbon dioxide parameters compared to those without nocturnal enuresis. Sleep parameters, urine osmolality, and blood pressure did not differ between groups. Children with nocturnal enuresis showed an increase, rather than a decrease, in heart rate across the night (+5.4 ± 19.1 vs. −6.0 ± 14.8 beats/min, $p < 0.05$).

Conclusions: Children with a history of nocturnal enuresis have greater respiratory abnormalities, no differences in urine osmolality or blood pressure, and loss of normal heart rate decrease across the night. This pattern suggests that autonomic control, rather than renal or hemodynamic abnormalities, may contribute to the pathophysiology of nocturnal enuresis.

> **Statement of Significance**
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> Nocturnal enuresis and obstructive sleep apnea commonly co-occur in children; understanding the link between these conditions will shed light on their shared pathophysiology and potential for novel treatment strategies. Our results highlight autonomic disruption as a potential contributor to nocturnal enuresis and a plausible link between nocturnal enuresis and obstructive sleep apnea in children. Exploring pathways linked to autonomic function may lead to novel treatments for both nocturnal enuresis and obstructive sleep apnea.

Introduction

Nocturnal enuresis (NE), commonly referred to as bedwetting, is defined as inappropriate urine outflow during sleep and affects approximately 15% of 5-year-old and 5% of 10-year-old children [1]. Enuresis can have dramatic psychological and emotional impact on young children and severely affect their quality of life [2]. The most dominant theories with respect to proposed mechanisms for NE include maturational delay in bladder response, increased threshold for arousal from sleep, abnormal bladder dynamics, and impaired release of renin–angiotensin–aldosterone system hormones, atrial natriuretic peptide, or antidiuretic hormone (ADH) [3, 4]. With a strong relationship between obstructive sleep apnea (OSA) and NE in young children, understanding the mechanisms associated with NE in the context of OSA may shed new light on the mechanisms of NE overall.

OSA is defined by repetitive complete or partial airway closure that may disrupt breathing during sleep, sleep patterns, or both. Several retrospective studies have demonstrated a positive correlation between NE and OSA in children including resolution of NE after surgical management of OSA by adenotonsillectomy. A systematic review which included data from 3550 children reported a prevalence of 33% for NE in children with reported sleep disordered breathing (SDB), a broader term that includes OSA; the prevalence of NE dropped to 16% after adenotonsillectomy [5]. NE occurs more commonly in children with higher apnea–hypopnea index (AHI) [5, 6] and children with NE have a high rate of snoring and symptoms of SDB [7, 8], suggesting a common pathway contributing to both NE and SDB. Treatment for OSA with adenotonsillectomy leads to resolution or improvements of NE in 33%–74% and 23%–31% of children, respectively [1, 9–11], showing that OSA alone cannot explain NE in children with OSA. Pathways postulated to be involved in the association between NE and OSA include heightened sympathetic output leading to increased blood pressure and secondary natriuresis, heightened arousal threshold leading to a failure of arousal from sleep, and swings in intrathoracic pressure resulting in the release of cardiac hormones including brain-derived neurotropic factor leading to increased urine production [12, 13]. There is, however, a paucity of physiological data available to support these hypothesized mechanisms.

The objective of this study was to determine the association between polysomnography results, physiologic variables, including hemodynamics and urine osmolality, and NE in a population of children undergoing polysomnography. We hypothesize that children with NE will have greater respiratory disturbance resulting in increases in heart rate and blood pressure as well as higher urine volume throughout the night when compared to children without NE.

Methods

The study design was a prospective observational cohort study. Consecutive children aged 5–17 years under going overnight diagnostic polysomnography for the investigation of sleep-related symptoms were recruited through the pediatric sleep laboratory at a tertiary care children's hospital. The lower limit of 5 years of age for inclusion is consistent with international consensus guidelines on NE [14]. Exclusion criteria included children with known neurological disorders, significant congenital bladder anomalies, or conditions associated with alterations in cardiac or renal function. Written informed consent from parents/guardians and assent from children was obtained prior to participation. The study protocol was approved by the institutional health research ethics board (Pro00034514).

Patient demographics, including age, height, weight, body mass index, past medical history, reason for the polysomnography, and medications were collected from sleep laboratory records. Information about daily sodium and fluid intake was collected using a dietary recall sheet completed by the parents/guardians and analyzed using Food Processor Nutrition software (www.ehsa.com). Children and parents were asked about previous history of NE, defined for the purpose of this study as greater than three wet nights per month for the past 6 months.

Polysomnography was conducted in accordance with standard laboratory protocols and scored according to the criteria of the American Academy of Sleep Medicine [15] by an experienced polysomnography technologist. The AHI includes the total number of apneas and hypopneas per hour of total sleep time. The obstructive-mixed AHI and central AHI include obstructive/mixed and central apnea and hypopneas per hour of total sleep time, respectively. Oxygen desaturation index (ODI) was defined by the number of oxygen desaturation events ≥3% per hour of total sleep time.

During the polysomnography, children were monitored with an ambulatory blood pressure monitor (Spacelabs Medical Ambulatory Blood Pressure Cuff 90217-1Q). Heart rate and blood pressure were checked in the supine position when the child first went to bed. Additional readings were taken automatically throughout the night on an hourly basis and at the time of waking (between 0600 and 0700) while the child was in a supine position. Blood pressure and heart rate data were extracted from the analysis software (Spacelabs software On Track). Measurements were converted to z-scores using established reference equations and thresholds [16, 17].

Children were asked to provide urine samples overnight, collected using a toilet hat. Each sample was measured for volume and then divided into two separate containers: the first for urine osmolality, and the second for urine sodium. The first urine collection occurred just prior to going to bed and represented the pre-sleep urine collection. Further urine specimens from spontaneous voids were collected throughout the night. Children were then asked to fully empty their bladder in the morning after awakening. Enuresis overnight was documented by the parent or sleep technician. Urine samples were then deposited at the laboratory for analysis. Samples were kept refrigerated according to laboratory protocols. Urine sodium was assessed by the University of Alberta Hospital Laboratory, while urine osmolality was measured with an Advanced Osmometer (model 3D3, Advanced Instruments, Norwood, MA).

Children were grouped into those with and without a history of NE for the purpose of analysis. Non-parametric data were transformed, where possible, prior to analysis. Student t-tests and Mann–Whitney U were used to compare group results for continuous variables as appropriate. Chi-square was used to compare distribution of categorical variables. Spearman correlation was used to assess bivariate non-parametric relationships. Linear regression was used for multi-variable analysis of parametric data. A p-value of <0.05 indicated statistically significant group differences.

Results

Sixty-eight children agreed to participate in the study, of which 61 children completed the protocol and were included for analysis. Mean age for this sample of children was 9.9 ± 3.8 years (range 5–17 years) and 13 (21%) patients had a history of NE. Age was the only descriptive factor that differed between those with and without a history of NE where children with enuresis were younger (Table 1).

Polysomnography was consistent with OSA for 67% of children with no difference in the rate of OSA between children with (77%) and without a history of NE (65%, $\chi^2 = 0.70$, p = ns). There were no differences in sleep parameters between groups (Table 2); however, children with a history of NE had more respiratory events and greater variability in respiratory parameters compared to those without NE (Table 2). These included a greater number of central respiratory events accounting for a higher AHI and greater variance in both oxygen and carbon dioxide measures.

There were no between-group differences in daily fluid or sodium intake, or urine osmolality. Children with NE had lower overnight urine sodium excretion when compared to children without NE (Table 3); post hoc analysis showed that history of NE was not a significant independent predictor of overnight urine sodium after adjustment for age (history of NE $\beta = 0.022$, p = ns; age $\beta = 0.44$, $p < 0.05$). Average systolic and diastolic blood pressure z-scores, calculated from the average of all measurements within an individual, and rates of elevated blood pressure or hypertension did not differ between groups (Table 3). While the pattern of systolic and diastolic blood pressure across the night did not differ between groups, the heart rate pattern was different (Figure 1). From the start to the end of the study, children with NE showed a 5.4 ± 19.1 beats/min increase in heart rate while children without NE showed a drop in heart rate of 6.0 ± 14.8 beats/min with a mean difference of 11.4 ± 5.6 beats/min ($p < 0.05$) between groups. Post hoc analysis showed that the history of NE remains a significant independent predictor of change in heart rate after adjustment for age (history of NE: $\beta = -0.35$, $p < 0.05$; age: $\beta = -0.19$, p = ns). Change in heart rate was negatively correlated with arousal index (Spearman –2.88, $p < 0.5$), AHI (Spearman –0.29, $p < 0.05$), and ODI (Spearman –0.31, $p < 0.05$) such that as arousals and respiratory event rates increase, change in heart rate across the night decreases.

Table 1. Comparison of demographics between children with and without NE

	NE (*n*, %; mean ± SD)	No NE (*n*, %; mean ± SD)
n	13	48
Age (year)*	8.2 ± 3.2	10.5 ± 3.8
Male:female (% female)	5:8 (38%)	17:31 (35%)
Height z-score	−0.16 ± 1.43	0.13 ± 1.88
Weight z-score	0.39 ± 1.30	0.93 ± 1.55
BMI z-score	0.59 ± 1.34	1.04 ± 1.41
Reason for sleep study		
OSA/SDB	12 (92%)	43 (90%)
Excessive daytime sleepiness	1 (8%)	2 (4%)
Restless leg syndrome	0	3 (6%)
NE on the night of the study*	5 (38%)	0

BMI, body mass index.

*$p < 0.05$.

Discussion

This is the first study to measure multiple physiological parameters, including urine osmolality and blood pressure, in an unselected cohort of children undergoing polysomnography. Our results demonstrate that children with NE, when compared to children without NE, have greater abnormalities in their polysomnographic respiratory parameters, including more central respiratory events, and blunting of normal heart rate depression across the night despite similar incidence of OSA between groups. No differences were seen with respect to measures of sleep disruption, urine osmolality, or hemodynamics between groups. Greater disruption in respiratory parameters with higher variability in oxygen and carbon dioxide parameters as well as blunting of the decline in heart rate across the night are supportive of impairments in autonomic control in children with NE when compared to those without NE.

There is a clear association between OSA and NE though the mechanism of this association is still debated. One theory is that upper airway obstruction results in increased intrathoracic pressure swings with subsequent myocardial stretch and release of natriuretic peptides resulting in inhibition of the action of ADH. Levels of ADH are lower and 12-hour overnight urine volumes are higher in children with OSA when compared to control children; treatment with adenotonsillectomy normalizes ADH levels and reduces urine volume [18, 19]. The presence of NE with OSA further decreased pre-treatment ADH compared to OSA alone [19]. Brain natriuretic peptide (BNP) is elevated in children with OSA [20], children with OSA and NE [12, 19], and decreases after treatment with adenotonsillectomy [19, 20]. Adenotonsillectomy, however, does not correct NE in all children with approximately half of children continuing to have NE after surgery and changes in post-operative ADH and BNP levels do not differ in those with and without continued post-operative NE [9] suggesting that upper airway obstruction alone cannot explain the association between OSA and NE. In the present study, with similar levels of obstructive respiratory events between children with and without NE, we found no difference in urine osmolality overnight between groups. Looking at prior studies examining the pathway between increased intrathoracic pressure and NE, the majority report an index of total respiratory events without a separate index of obstructive respiratory events. Interestingly, the one study that did report an obstructive respiratory index showed a similar level of airway obstruction between children with and without NE [12] consistent to what we describe here. Together with our study results, the accumulated evidence suggests that airway obstruction leading to alterations in ADH and BNP, ADH inhibition, and subsequent increase in urine volume is insufficient to explain the association between OSA and NE.

Sleep disruption associated with OSA may explain the occurrence of NE for some children and the resolution of NE after adenotonsillectomy. Airway obstruction and the ensuing repetitive intermittent hypoxia lead to disruption of sleep though this is often harder to measure in children [21]. Acute sleep deprivation in healthy children leads to a suppression of ADH and aldosterone levels as well as a substantial increase in nocturnal diuresis, natriuresis, and urine volume [22]. Children with unresolved NE post-adenotonsillectomy have lower amounts of stage 2 sleep and higher amounts of slow-wave, or deep, sleep compared to those whose NE resolved post-operatively [11], a pattern of sleep stage changes that is

Table 2. Polysomnography characteristics in children with and without NE

	NE (mean ± SD)	No NE (mean ± SD)	Mean difference (95% confidence interval)
Total sleep time (min)	458 ± 49	419 ± 79	–8.8, 87.8
Sleep efficiency (%)	84.7 ± 8.7	79.2 ± 14.2	–2.8, 13.8
Wake after sleep onset (min)	58.3 ± 38.1	79.5 ± 67.5	–57.4, 21.0
% SWS	30.5 ± 7.3	27.0 ± 9.3	–2.1, 9.1
% REM	19.3 ± 5.7	18.4 ± 6.2	–2.9, 4.7
Total arousals (events/h)	12.1 ± 9.7	9.7 ± 10.3	–3.9, 8.8
AHI (events/h)	17.8 ± 31.1	5.7 ± 13.0	
logAHI*	0.80 ± 0.61	0.47 ± 0.44	0.031, 0.64
OMAHI (events/h)	11.2 ± 18.7	4.4 ± 11.8	
logOMAHI	0.52 ± 0.76	0.22 ± 0.57	–0.94, 0.68
CAHI (events/h)	6.7 ± 16.2	1.2 ± 1.5	
logCAHI*	0.29 ± 0.58	–0.066 ± 0.47	0.037, 0.67
Mean S_pO_2 (%)**	95.0 ± 4.8	96.1 ± 1.4	Non-parametric
Minimum S_pO_2 (%)	88.7 ± 3.9	88.6 ± 4.0	–2.5, 2.8
ODI (events/h)	25.4 ± 41.7	9.3 ± 14.3	Non-parametric
Mean E_TCO_2 (mm Hg)**	42.2 ± 7.1	42.3 ± 3.7	Non-parametric
Maximum E_TCO_2 (mm Hg)	51.6 ± 6.7	49.1 ± 8.2	–4.4, –1.4
% Time with E_TCO_2 > 50 mm Hg**	24.7 ± 6.8	1.6 ± 0.2	Non-parametric

CAHI, central AHI; E_TCO_2, end-tidal carbon dioxide; OMAHI, obstructive-mixed AHI; REM, rapid eye movement sleep; S_pO_2, pulse oxygen saturation; SWS, slow-wave sleep.
*$p < 0.05$.
**Ranges differ between children with and without NE, $p < 0.05$.

Table 3. Urine and blood pressure parameters in children with and without NE

	NE (mean ± SD; n, %)	No NE (mean ± SD; n, %)	Mean difference (95% confidence interval)
Fluid intake (L/24 h)	0.999 ± 0.442	1.325 ± 0.852	–0.064, 0.716
Sodium intake (mmol)	117 ± 59	300 ± 822	–320, 685
Osmolality pre-sleep (mOsm/L)	782 ± 268	843 ± 279	–137, 259
Osmolality post-sleep (mOsm/L)	929 ± 153	860 ± 234	–185, 47
Change in osmolality (mOsm/L)	130 ± 217	28 ± 219	–55, 258
Overnight volume voided (L)[a]	0.409 ± 0.181	0.591 ± 293	–0.067, 0.431
Overnight sodium excretion (mmol)*	60.3 ± 29.8	89.4 ± 50.9	4.2, 53.9
Average systolic z-score	0.025 ± 0.83	0.065 ± 0.90	–0.562, 0.641
Average diastolic z-score	–0.052 ± 0.66	–0.16 ± 0.61	–0.530, 0.322
Blood pressure category			
Normal blood pressure	10 (77%)	34 (71%)	
Elevated blood pressure	0	5 (10%)	
Hypertension – stage 1	3 (23%)	7 (15%)	
Hypertension – stage 2	0	2 (4%)	

[a]Data are included only for children with NE who did not have an episode of NE ($n = 6$) on the study; given the imbalance in subject numbers, statistical comparison may not be valid.
*$p < 0.05$, post hoc multivariate analysis shows that history of NE is not a significant predictor of overnight sodium excretion after adjustment for age.

associated with sleep deprivation, suggesting that resolution of NE is related to resolution of sleep deprivation. In addition to effects on urine parameters, sleep deprivation in healthy children leads to blunting of normal nighttime dipping for heart rate and blood pressure [22]. Not surprisingly, we failed to show a difference in sleep parameters between children with and without NE; that may be because we had similar incidence of OSA between groups or because standard measures of sleep deprivation are insensitive to detecting differences in children.

An alternative mechanism to explain the association between NE and OSA is a common pathway that contributes to the occurrence of both conditions independently with mechanisms related to sleep continuity being clear candidates.

NE is a predictor of residual OSA post-adenotonsillectomy [23], supporting a shared factor between OSA and NE that is not improved by adenotonsillectomy. Inherent differences in arousal threshold, or the level of stimuli required to cause arousal from sleep, likely contributes to NE as arousal to bladder stimuli is the main difference between NE and nocturia [24]. Differences in arousal threshold are also seen between children with and without OSA whereby children with OSA, when compared to children without OSA, arouse at a higher inspiratory resistance load and have blunted arousal response to hypercapnia [25, 26]. Corticotropin-releasing factor (CRF), a neuropeptide with a major role in regulating the hypothalamic–pituitary–adrenocortical axis and autonomic function in
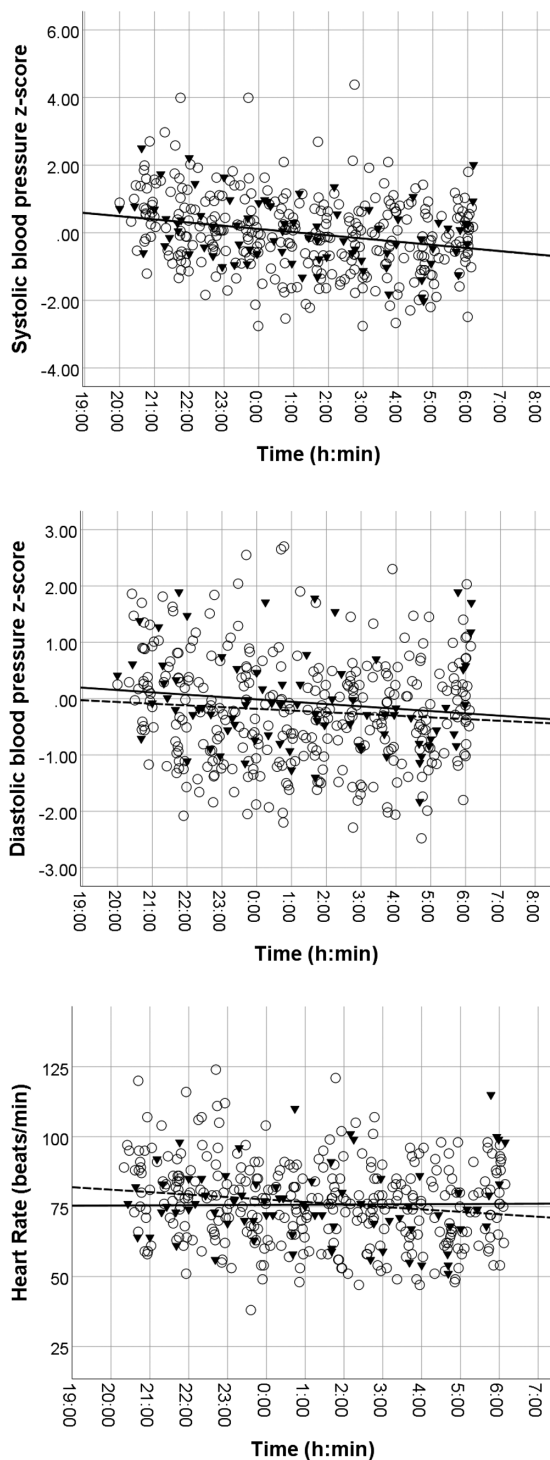
Figure 1. Blood pressure and heart measurements across the night in children with (triangles) and without (circles) a history of NE. Lines represent mean values across the night (solid – NE; dashed – no NE). While blood pressure changes across the night did not differ between groups, there was a mean difference in heart rate across the night of 11.4 ± 5.6 beats/min ($p < 0.05$) between groups.

response to stress, plays a role in regulating sleep and arousal whereby higher levels of CRF promote wake and arousal from sleep [27, 28]. A recent study examining CRF levels in children with and without NE demonstrated lower CRF levels in children with NE in both the evening and morning sample [29],

suggesting that lower levels of CRF may contribute to differences in arousal threshold in children with NE. Urocortins, members of the CRF family of peptides, were identified as a strong candidate biomarker for the discrimination of OSA from primary snoring in children [30]. CRF-related peptides are implicated in the regulation of autonomic cardiovascular and respiratory control [31], so could explain the differences in the blunting of nocturnal heart rate dipping and increase in central respiratory events seen in association with NE in our study. While further work is needed to characterize the CRF pathway in NE and OSA, its relationship to sleep continuity, autonomic function, and cardiorespiratory control makes it a highly plausible candidate to explain the association between NE and OSA as well as explaining each disorder independently.

Aspects of our methodology may impact interpretation of our results. We characterized children as having a history of NE but did not differentiate primary from secondary NE; it is possible that mechanisms responsible for NE differ between primary and secondary NE. Our subject sample included a high proportion of children undergoing polysomnography for OSA which may limit the application of our results to a more general population of children with NE. OSA is a known risk factor for NE but mechanisms responsible for NE in the context of OSA may differ from those in children without OSA. Our measurements were taken on a single night in an environment with inherent variability and challenges to a child's normal sleep routine; this alone could alter physiologic parameters unrelated to NE. We did, however, see that a higher proportion of children with NE had enuresis on the study night, suggesting that the laboratory setting maintained relevant differences between the groups. We also limited our measurements to those that could be conducted during the time of the polysomnography. This meant that we used 12-hour urine sodium output as a substitute for a 24-hour collection and only recorded nocturnal blood pressure. To reduce the likelihood of missing important differences between groups, we included multiple measures and compared both average parameters as well as examining the pattern of change of these parameters across the night.

Our results raise the possibility that autonomic disruption is an important contributor to NE and a plausible link between NE and OSA in children. Other than blunting of normal heart rate dipping, we failed to find defects in urine concentrating ability or hemodynamic parameters between children with and without NE. Further work is needed to understand the mechanisms responsible for NE; the CRF pathway appears to be a good candidate to explain the strong association between NE and OSA. Understanding the link between these conditions will not only shed light on their shared pathophysiology but also has the potential to lead to novel treatment strategies

Acknowledgments

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