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ARTICLE

Increased Morning Brain Natriuretic Peptide Levels in Children With Nocturnal Enuresis and Sleep-Disordered Breathing: A Community-Based Study

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What's Known on This Subject

An increased frequency of bed-wetting has been noted in children at risk for obstructive sleep apnea who seem to have elevated levels of BNP. However, it remains unclear whether enuresis occurs in a severity-dependent fashion among snoring children and whether BNP accounts for the increased enuretic symptoms.

What This Study Adds

The risk for bed-wetting is markedly increased by the presence of habitual snoring among a large community cohort of young school-aged children but does not seem to be determined by the severity of sleep-disordered breathing. BNP levels are higher in enuretic children and are further elevated in the presence of obstructive sleep apnea.

ABSTRACT

INTRODUCTION. Habitual snoring and obstructive sleep apnea have been associated with bed-wetting in children, and effective obstructive sleep apnea treatment may improve enuresis.

OBJECTIVES. The purpose of this work was to assess whether habitual snoring is associated with increased incidence of enuresis and whether severity of obstructive sleep apnea correlates with enuretic frequency and to evaluate brain natriuretic peptide levels.

METHODS. Parental surveys of 5- to 7-year-old children were reviewed for habitual snoring and enuresis. Enuresis was also assessed in a cohort of 378 children with habitual snoring undergoing overnight polysomnographic evaluation, and brain natriuretic peptide plasma levels were determined in 20 children with obstructive sleep apnea, 20 with habitual snoring without obstructive sleep apnea, and 20 nonsnoring children, matched for enuresis.

RESULTS. There were 17 646 surveys completed (50.6% boys; 18.3% black). A total of 1976 (11.2%) of these children were habitual snoring (53% boys; 25.2% black). A total of 531 habitual snoring children also had enuresis (26.9%), with a predominant representation of boys (472 boys [87.5%]). Among the 15 670 nonsnoring children, enuresis was reported in 1821 children (11.6%), of whom 88.8% were boys. However, enuresis among 378 children with habitual snoring did not correlate with the magnitude of sleep respiratory disturbances. Indeed, enuresis was reported in 33 of 149 children with obstructive sleep apnea (obstructive apnea hypopnea index: >2 per hour of total sleep time; 53% boys) as compared with 36 habitual snoring children with enuresis (62% boys) and obstructive apnea hypopnea index <2 per hour of total sleep time. Brain natriuretic peptide levels were elevated among children with enuresis and were marginally increased among children with obstructive sleep apnea.

CONCLUSIONS. Habitual snoring is associated with increased prevalence of enuresis, and brain natriuretic peptide levels are increased in enuretic children with further increases with obstructive sleep apnea. However, the prevalence of enuresis is not modified by severity of sleep disturbance. Even mild increases in sleep pressure because of habitual snoring may raise the arousal threshold and promote enuresis, particularly among prone children, that is, those with elevated brain natriuretic peptide levels.

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Key Words
enuresis, sleep apnea, brain natriuretic peptide

Abbreviations
OSA— obstructive sleep apnea
HS— habitual snoring
SDB—sleep-disordered breathing
BNP— brain natriuretic peptide
TST—total sleep time
AHI— obstructive apnea hypopnea index
REM—rapid eye movement

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NOCTURIA AND BED-wetting are common symptoms among adult patients with obstructive sleep apnea (OSA),[1] and bed-wetting during sleep may also be associated with the presence of OSA in children.[2] Habitual snoring (HS) is the most common clinical manifestation of sleep-disordered breathing (SDB) in children, a condition that ranges from primary snoring to severe OSA syndrome.[2] The association between enuresis and SDB in children is supported by documented decreases in the frequency of enuretic complaints or even by the complete resolution of enuresis after successful treatment of SDB.[3–5] In addition, ≥2 surveys have reported the presence of a significant correlation between HS and enuresis.[6,7] The most recent study, which consisted of a questionnaire-based survey of

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a community sample of children in Greece, found that those children with HS reported more often the concurrent presence of primary nocturnal enuresis than did those without HS.[7]

One of the potential mechanisms accounting for the increased prevalence of enuresis in the context of SDB may be related to the release of both atrial and brain natriuretic peptides (BNPs) from cardiac myocytes after cardiac wall distension, as induced by the increased negative intrathoracic pressure swings that accompany the increased upper airway resistance in HS. Release of this cardiac hormone will, in turn, increase sodium and water excretion and will also inhibit other hormones that regulate fluid homeostasis, such as vasopressin and the renin-angiotensin-aldosterone pathway.[8] Indeed, in a very recent study by Kaditis et al,[9] BNP was increased among snoring children and seemed to correlate with severity of respiratory disturbance during sleep. Thus, based on the cumulative evidence presented heretofore, it is possible that SDB may increase the frequency of enuresis in children through BNP-dependent mechanisms.

Based on aforementioned considerations, the aims of the present study were to (1) determine the prevalence of enuresis in a large survey of young school-age community children, (2) assess whether the presence of HS would be associated with increased reports of enuretic symptoms, (3) determine whether the degree of severity of SDB would be accompanied by a corresponding increase in the frequency of enuresis, and (4) determine whether higher morning BNP levels are present in SDB, particularly when enuresis is present.

METHODS

Survey Questionnaire

The study was approved by the University of Louisville Human Research Committee and the Jefferson County Public Schools board. A previously validated questionnaire was used.[10,11] Parents of all children 5 to 7 years of age enrolling into the Jefferson County Public Schools system were invited to complete a detailed questionnaire about their child's sleeping habits. The information gathered through the questionnaire included gender, age, ethnic background, questions on whether the child had difficulty breathing during sleep, mouth breathing, witnessed apnea, daytime sleepiness, and enuresis and its frequency. Snoring and the severity of the snoring were also included. For the question on snoring, the responses were graded as "never," "rarely" (once per week), "occasionally" (twice per week), "frequently" (3–4 times per week), and "almost always" (>4 times per week). The responses on the frequency of enuresis, were graded as "never," "rarely" (once per month), "occasionally" (twice per month), "frequently" (2–6 times per month), and "almost always" (>3 times per week). Returned questionnaires were scanned into a computerized database and were subdivided according to their snoring patterns into nonsnoring children (responses of never or rarely on snore and not applicable on loudness of snore in questionnaire) or HS children (responses of almost always [>3 nights per week] or always on snoring frequency and medium loud to loud on loudness of snoring). Enuresis was considered to be present when responses were in the frequently or almost always range. Subjects were excluded if they had any known genetic or craniofacial syndromes.

To determine whether the severity of SDB is associated with a corresponding change in the frequency of enuresis, the presence of enuresis was also assessed in a subset of 378 children with HS who underwent overnight polysomnographic evaluation. Twenty nonsnoring, otherwise healthy children with (n = 12) and without enuresis (n = 8) were also studied in the sleep laboratory.

Overnight Polysomnographic Evaluation

Children were studied for ≤12 hours in a quiet, darkened room with an ambient temperature of 24°C in the company of 1 of their parents. No drugs were used to induce sleep. The following parameters were measured: chest and abdominal wall movement by inductance plethysmography and heart rate by ECG. Air flow was triply monitored with a sidestream end-tidal capnograph, which also provided breath-by-breath assessment of end-tidal carbon dioxide levels (P_{ETCO_2}; BCI SC-300, Menomonee Falls, WI), a nasal pressure cannula, and an oronasal thermistor. Arterial oxygen saturation was assessed by pulse oximetry (Nellcor N 100, Nellcor Inc, Hayward, CA), with simultaneous recording of the pulse wave form. The bilateral electro-oculogram, 8 channels of electroencephalogram (2 frontal, 2 occipital, 2 temporal, and 2 central leads), chin and anterior tibial electromyograms, and analog output from a body position sensor were also monitored. All of the measures were digitized using a commercially available system (Rembrandt, MedCare Diagnostics, Amsterdam, Netherlands). Tracheal sound was monitored with a microphone sensor, and a digital time-synchronized video recording was performed. The sleep technician followed patient behavior and confirmed sleep position by the infrared camera inside the room. All of the studies were initially scored by a certified technician and were then blindly reviewed by 2 physicians experienced in pediatric polysomnography, who underwent training in an accredited fellowship program.

Sleep architecture was assessed by standard techniques.[12] The proportion of time spent in each sleep stage was expressed as a percentage of total sleep time (TST). Central, obstructive, and mixed apneic events were counted. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for a duration of ≥2 breaths.[13,14] Hypopneas were defined as a decrease in oronasal flow of ≥50% with a corresponding decrease in arterial oxygen saturation of ≥4% and/or arousal.[14] The obstructive apnea hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of TST. Arousals were defined as recommended by the American Sleep Disorders Association Task Force report[15] and included respiratory-related (occurring immediately after an apnea, hypopnea, or snore), technician-induced, and spontane-

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ous arousals. Arousals were expressed as the total number of arousals per hour of sleep time. Periodic leg movements during sleep were scored if there were ≥4 movements of 0.5 to 5.0 seconds in duration and if they were between 5 and 90 seconds apart.[16] A periodic leg movements during sleep index of ≥5 per hour of sleep is generally considered as exceeding the reference range in children.[14,16]

The diagnostic criteria for OSA included an obstructive apnea index >1 per hour of TST and/or an AHI >2 per hour of TST with a nadir oxygen saturation value of ≥92%.[14] Correspondingly, children were considered to have HS if their obstructive apnea index and/or AHI were <1 or < 2 per hour TST, respectively. Control children were defined as nonsnoring children with an obstructive AHI ≤1 hour per TST.

Plasma BNP Levels

From the 378 habitually snoring children and from 127 nonsnoring healthy children, we matched 20 children with OSA, 20 children with HS, and 20 control children for age, gender, BMI, and enuresis, and obtained fasting blood samples by venipuncture in the morning immediately after the initial diagnostic sleep study into EDTA-containing tubes. Blood samples were immediately centrifuged and frozen at −80°C until assay. Plasma BNP levels were then measured in triplicate using a commercially available ELISA kit (Phoenix Pharmaceuticals, Burlingame, CA). The assay has a sensitivity of 0.15 pg/mL and exhibits a linearity range of 93% to 97%. The intraassay and interassay coefficients of variability were 5.8% and 8.2%, respectively.

Data Analysis

The presence or absence of enuresis was the main outcome variables, and HS was the independent variable of interest. Comparison of habitual snorers with nonhabitual snorers for continuous variables was conducted using Student's *t* tests and for categorical characteristics using the χ^2 test (Yates' correction).

The odds ratios and corresponding 95% confidence intervals for enuresis in children with HS as compared with those without HS were calculated using univariate logistic regression analysis. Multiple logistic regression analysis was then performed to adjust the odds ratio for age, gender, and ethnicity (SPSS 11.5 [SPPS Inc, Chicago, IL]). A *P* value of <.05 was considered statistically significant.

RESULTS

Population Survey

During the years 2000–2006, a total of 58 117 questionnaires were mailed, and 17 646 surveys with complete data sets were returned. In addition, 2498 questionnaires were returned but had data missing regarding either enuresis or snoring. An additional 523 questionnaires were returned with a signed statement that the parents refused to participate in the survey, and 867 questionnaires were returned because of a wrong address. Finally, 329 questionnaires were excluded because of the presence of known genetic or craniofacial syndromes. Thus, the overall response rate was 37.6%.

Of the 17 646 complete surveys, 50.6% were boys and 18.3% were black. HS was reported in 1976 (11.2%) of these children, of whom 53% were boys, and 25.2% were black. Enuresis among HS children was present in 531 responders (26.9%), with a predominant representation of boys (472 boys [87.5%]). Among the 15 670 nonsnoring children, enuresis was reported in 1821 children (11.6%; $P < .00001$; odds ratio: 2.79 [95% confidence interval: 2.50–3.13]), of whom 88.8% were boys. Thus, as in previous published studies,[5,6] enuresis was more frequently reported among children who are at risk for SDB.

Overnight Polysomnography

To assess the potential effect of SDB severity on the frequency of enuresis, 378 habitually snoring children who were randomly selected from the pool of questionnaire responders underwent overnight polysomnographic evaluation in the sleep laboratory. OSA was present in 149 of these children, and among the latter, enuresis was reported in 33 children (53% boys). Among the 229 children with HS but no evidence of OSA, enuresis was reported in 36 children (62% boys; *P* value for OSA versus HS was not significant). There were no significant correlations between the categorical frequency of enuresis and the magnitude of respiratory disturbances during sleep, as derived from the obstructive AHI, lowest arterial oxygen saturation, or the respiratory arousal index.

To examine the possibility that sleep macroarchitecture might differ in enuretic children, sleep structure and respiratory patterns were also compared between the 69 children with enuresis and those without enuresis ($n = 309$). As shown in Table 1, no major differences emerged in sleep characteristics among these 2 groups, except for nonrapid eye movement (REM) sleep stage 4 and sleep efficiency, which were increased in enuretic children.

Morning Plasma BNP Levels

BNP concentrations were slightly, albeit significantly, higher among 20 children with OSA compared with 20 control subjects ($P < .02$; Fig 1). Although there was a trend for higher BNP levels among 20 HS children compared with control subjects, the differences did not achieve statistical significance ($P = .13$). In contrast, a prominent correlation emerged between enuresis and increased BNP levels. Indeed, among the 12 otherwise healthy children with enuresis, BNP levels were significantly higher (1037.3 ± 115.5 pg/mL) when compared with the 8 control children who did not have enuresis (181.0 ± 19.8 pg/mL; $P < .00001$). Moreover, BNP levels were markedly greater among all 36 of the children with enuresis independent of whether they had SDB or not when compared with 24 without reported enuresis (Fig 1).

DISCUSSION

This study show that the prevalence of nocturnal enuretic symptoms is increased among children with HS

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TABLE 1 **Demographic and Polysomnographic Characteristics in HS Children With Nocturnal Enuresis and in Children Without Nocturnal Enuresis**

Characteristic	Enuresis ($n = 69$)	No Enuresis ($n = 309$)
Age (range), y	6.5 ± 1.2 (5.5–7.8)	6.7 ± 0.7 (5.5–7.8)
Male, %	65	44
BMI, kg/m^2	18.8 ± 3.6	19.2 ± 4.0
Sleep latency, min	14.5 ± 24	11.3 ± 23.6
REM latency, min	131.5 ± 65.7	143.1 ± 64.2
TST, h	8.0 ± 1.6	7.9 ± 1
Sleep efficiency, %	93.9 ± 1.5[a]	88.7 ± 1.6
No. of awakenings	3.1 ± 2.7	4.7 ± 2.6
Stage 1, %	4.4 ± 4.6	5.7 ± 3.7
Stage 2, %	43.1 ± 4.3	46.8 ± 6.6
Stage 3, %	7.5 ± 2.5	7.6 ± 4.4
Stage 4, %	26.1 ± 4.8[a]	20.3 ± 6.1
REM sleep, %	18.9 ± 12.33	20.4 ± 9.2
Respiratory arousal index, per h of TST	0.6 ± 3.5	0.5 ± 4.1
Total arousal index, per h of TST	6.3 ± 4.5	7.3 ± 5.2
PLM index with arousal, per h of TST	0.0 ± 0.4	0.0 ± 0.3
PLM index in sleep, per h of TST	1.6 ± 1.8	1.3 ± 1.8
AHI, per h of TST	0.9 ± 1.5	0.8 ± 2.2
OAI, per h of TST	0.3 ± 1.6	0.3 ± 1.7
Mean pulse oxygen saturation	97.4 ± 1.8	97.5 ± 0.9
Pulse oxygen saturation nadir	92.3 ± 5.1	91.4 ± 6.4

PLM indicates periodic leg movement; OAI, obstructive apnea index.
[a] *P* value is <.01.

but that the severity of SDB does not seem to impact on the frequency of enuresis. Furthermore, we show that sleep architecture in habitually snoring children with enuresis is not markedly different from that of habitually snoring children without enuresis, although some subtle increases in sleep efficiency and delta-wave sleep are present. In addition, we not only confirm that BNP levels are increased in the presence of OSA but further show that enuretic children have markedly higher BNP levels compared with nonenuretic children at any degree of SDB severity.

Nocturnal enuresis refers to the involuntary loss of urine after the age of 5 years, when children are expected to have achieved full bladder control at night.[17] In most cases, enuresis is ultimately categorized as primary monosymptomatic, as documented by the absence of overt urogenital pathology or daytime voiding problems. In addition, enuresis is also classified as primary when the child has never achieved nighttime dryness and secondary when bedwetting occurs after being dry for ≥6 months.[18] The minimal frequency of nocturnal urine loss required to diagnose the condition has varied in different studies from once in the previous year[17] to at least twice a week.[19] Primary nocturnal enuresis is exceedingly more common in boys, with a 3:1 gender ratio.[20] In the present study, children presenting with bed-wetting episodes ≥3 nights per week were considered as being enuretic, and the overall frequency in this large, population-based study of young school-aged children was similar to the prevalence reported in previous studies from all over the world.[6,7,21–26] Similarly, as in previous reports, the overrepresentation of the male gender among enuretic children was clearly present.

However, most of these studies did not examine potential links between HS, as an indicator of risk for SDB, and the presence of enuresis. Among those surveys that included HS as part of their questionnaires, an increased frequency of enuresis was generally reported among HS children.[6,7,21] For example, Yeung et al[25] reported that 46% of children with OSA diagnosed by polysomnography had nocturnal enuresis, whereas Alexopoulos et al[7] found that 23.3% of children with nocturnal enuresis were habitual snorers. Taken together, it would seem that increased upper airway resistance during sleep, manifesting either as HS or as polygraphically documented OSA, is indeed associated with an increased probability for enuresis, and our current findings further confirm this assumption. Indeed, 26.9% of habitually

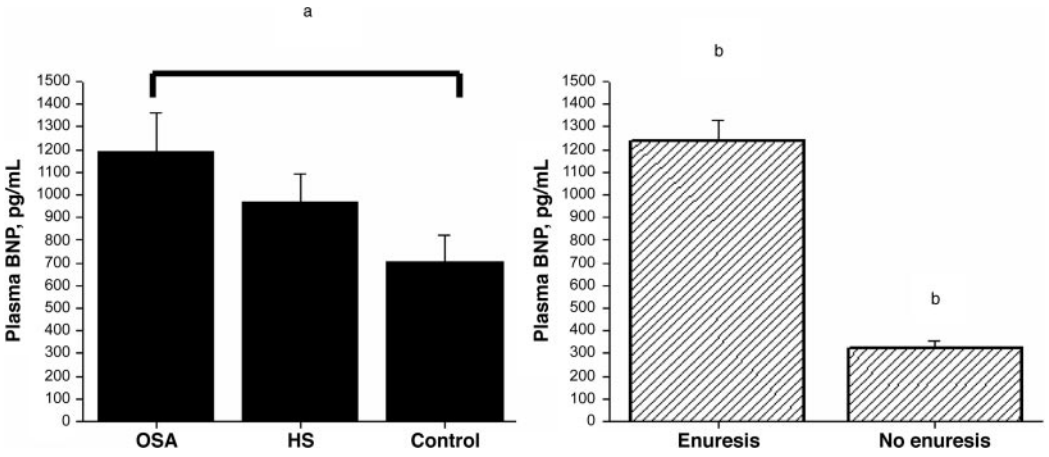

FIGURE 1
Plasma BNP levels in 60 children. Left, Plasma BNP levels in 20 children with OSA, 20 children with HS, and 20 control children matched for age, gender, and for the presence of enuresis. [a] OSA versus control subjects: *P* value is <.02. Right, Plasma BNP levels in 36 children with enuresis and 24 children without enuresis. [b] *P* value is <.00001.

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snoring children reported enuresis as compared with 11.6% among nonsnoring children. Surprisingly, and in contradiction with our initial hypothesis, we did not find any differences in the frequency of enuresis among HS children with or without OSA. Our findings are similar to those of Brooks and Topol,[27] who did not find any differences in the prevalence of enuresis among children with OSA when the latter were subdivided into respiratory disturbance severity categories.[27] It is possible that the presence of HS alone is sufficient to saturate the effect of sleep-disordered breathing on enuretic-prone children (see below).

Notwithstanding such considerations, decreases in the frequency or complete resolution of bed-wetting will occur after successful treatment of the breathing disorder during sleep. Indeed, Weider et al[3] showed resolution or decreased frequency of primary nocturnal enuresis after relief of upper airway obstruction by adenotonsillectomy. Similar results were reported by Cinar et al[28] and by Weissbach et al[29] in enuretic children who underwent adenotonsillectomy.[27,29] Furthermore, resolution of enuresis was also noted in children with HS and nasal obstruction who received treatment with intranasal corticosteroids.[4]

Several different pathophysiological mechanisms have been proposed to explain the association between increased upper airway resistance during sleep and nocturnal enuresis. Of the 3 major mechanisms that have been implicated in uncomplicated nocturnal enuresis in children, namely, hyperactive detrusor activity, polyuria, and deep sleep with reduced arousability,[30] the latter 2 mechanisms seem particularly propitious in the context of HS. Although a deficiency in antidiuretic hormone is highly unlikely,[31] increased natriuresis has been reported in enuretic children.[32] HS could lead to increased urinary output and natriuresis by promoting the release of atrial and BNPs through increased venous blood return and atrial distension in the context of the increased intrathoracic pressure swings associated with upper airway obstruction. However, supportive evidence for such an assumption is somewhat conflictive. For example, Patwardhann et al[33] did not find an association between natriuretic peptides and OSA in adult patients. Similarly, Pepperell et al[34] reported the absence of any significant changes in BNP among adult patients with OSA after treatment with continuous positive airway pressure. Conversely, Tasci et al[35] reported that, although no differences existed in BNP levels among OSA patients and control subjects, treatment with continuous positive airway pressure induced marked decreases in BNP levels in the OSA patients. Furthermore, Kaditis et al[9] have shown recently that increased BNP levels are much more likely to occur among children with HS and AHI $\geq$5. Our current findings confirm this latter report and add additional insights into this particular issue. Indeed, in the present study we controlled for both the presence of enuresis and the degree of upper airway obstruction during sleep. Under these circumstances, the major determinant for increased morning BNP levels was the presence of enuresis, with lesser, albeit significant, contributions by the degree of respiratory disturbance during sleep. Thus, in children with a preexisting propensity for enuresis, the already heightened BNP levels may be further enhanced by HS or OSA and, therefore, tip the balance in favor of more pronounced enuretic symptoms.

As mentioned above, increased arousal threshold despite the presence of micturition signaling may also contribute to the onset and maintenance of enuresis.[30] Several studies have attempted to examine whether sleep characteristics may differ among children with and without enuresis. In general, most of these studies have reported normal polysomnographic findings and have failed to identify a specific sleep phenotype that may explain the occurrence of enuresis.[36–40] In the present study, which examined a large cohort of enuretic children, we found only subtle changes in their sleep architecture, namely, increased sleep efficiency and stage 4 non-REM sleep. Although such differences in sleep macrostructure cannot explain the putative increases in the arousal threshold of enuretic children,[41–43] the increased density of delta frequency in the electroencephalograms of enuretic children, which is supportive of decreased arousability,[44] could be further compounded by the increases in sleep propensity associated with SDB.[45] Thus, it would be anticipated that, in children with already preexisting elevations in arousal thresholds from sleep, as seen with primary monosymptomatic nocturnal enuresis, further increases in such a threshold, as dictated by the increased sleep fragmentation associated with either HS or OSA, might either promote the appearance or worsen existing enuresis in children.

The association among nocturnal enuresis, nocturnal polyuria, and increased urinary levels of aquaporin 2 has been noted previously in children,[46] although these findings have not been consistently corroborated.[47] Nevertheless, the possible association between natriuretic factors and induction of aquaporins to increase urinary excretion[48] merits additional study in both enuretic children and those with OSA.

CONCLUSIONS

In summary, we have found in a large population-based cohort that the presence of HS is associated with marked increases in the prevalence of enuresis and that the latter does not seem to be affected by the severity of SDB. Furthermore, only minor increases in stage 4 non-REM sleep and in sleep efficiency emerge among enuretic children and are unlikely to account for the presence of enuresis. However, BNP morning levels are markedly elevated in children with enuresis, and the presence of SDB leads to further, albeit small, increases in BNP plasma levels. Taken together, these findings suggest that sleep fragmentation and, to a lesser extent, increased release of BNP in the context of increased upper airway resistance during sleep may contribute to the higher prevalence of enuresis in habitually snoring children.

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