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ORIGINAL ARTICLE

Non-dipping phenomenon in children with monosymptomatic nocturnal enuresis

Aydin Kahraman · Hasan Dursun · Sami Hatipoglu · Bahar Kural · Mustafa Sahin · Korhan Birgul · Mehmet Bedir Akyol

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Abstract
Purpose Monosymptomatic nocturnal enuresis is a common disorder seen in childhood, and many factors play a role in its etiopathology to varying degrees. The aim of our study was to investigate the possible association between nocturnal enuresis and 24-h blood pressure profiles of enuretic children.
Methods A total of 45 children ranging in age from 6 to 15 years with monosymptomatic nocturnal enuresis and 22 age-matched healthy controls were enrolled in our study. The blood pressure measurement was made at 30-min intervals during a 24-h period via an ambulatory blood pressure measurement device. Both groups underwent medical tests that included a complete blood count, blood biochemistry profile, urinalysis and blood renin–aldosterone levels, and all study subjects received an abdominal ultrasound.
Results Statistically significant high nocturnal blood pressure levels were observed in our patients with monosymptomatic nocturnal enuresis compared with the control group ($p<0.05$). The mean values of the day-to-night difference (dipping) in the systolic and diastolic blood pressure of the patients were significantly lower than those of control group ($p<0.05$).
Conclusion Nocturnal enuresis should not only be accepted as a urinary system disorder. Possible systemic causative factors have to be examined, especially in patients that are resistant to first-line therapy. Based on the results of our study, we deduce that one of the factors that plays a role in the pathogenesis of enuresis nocturna is a non-dipping blood pressure profile (the "non-dipping" phenomenon).

Keywords Nocturnal enuresis · Children · Blood pressure · Non-dipping phenomenon

A. Kahraman · S. Hatipoglu · B. Kural · M. Sahin · K. Birgul
Division of Pediatrics, Dr Sadi Konuk Teaching and Medical Research Hospital, Istanbul, Turkey

H. Dursun (✉)
Unit of Pediatric Nephrology, Dr Sadi Konuk Teaching and Medical Research Hospital, Tevfik Saglam cad No 13, Bakirkoy, Istanbul, Turkey
e-mail: dursunhs@yahoo.com

M. B. Akyol
Division of Pediatric Cardiology, Dr Sadi Konuk Teaching and Medical Research Hospital, Istanbul, Turkey

Introduction

Enuresis is a common health problem worldwide, and it is estimated that there are over 50 million children with enuresis throughout the world. In the absence of accompanying symptoms of the lower urinary tract, such as urgency, daytime incontinence, urinary flow anomalies, among others, enuresis is defined as "mono-symptomatic nocturnal enuresis" [1–4]. In pediatric patients, it is mostly diagnosed between the ages of 5 and 7 years [5, 6]. It has recently been reported that 10–20% of all 5-year-old children suffer from enuresis and that the prevalence of enuresis decreases by about 15% each year, with 5 and 1–2 % of children being enuretic at 10 and 15 years of age, respectively [2, 7–9].

Similar to many other body functions, urine production has a circadian rhythm and, consequently, urine production decreases during sleep. This nocturnal decrease in urine production is accompanied by a decrease in arterial blood pressure (BP) [10, 11]. Even small changes in arterial BP may lead to profound variations in the urinary excretion of sodium and water. This phenomenon is called "pressure natriuresis" and "pressure diuresis". Increased arterial BP causes an increase in peritubular capillary hydrostatic pressure. Therefore an increase in renal parenchymal interstitial

hydrostatic pressure ultimately results in increased urine production. The third mechanism of natriuresis and diuresis secondary to increased arterial pressure is "decreased angiotensin II secretion" [12, 13].

There are significant variations in the BP during the 24-h circadian rhythm, with a significant decrease in arterial BP during sleep at night. Although this decrease may vary from person to person, the nighttime arterial BP in healthy individuals is about 10% that of the daytime mean arterial BP. In a study of 123 volunteers, which was performed using ambulatory blood pressure monitoring (ABPM), 83% of subjects showed a significant decrease in nocturnal BP values. This is defined as the "dipping" phenomenon [14, 15] and is thought to occur as a result of a downward shift of the baroreflex threshold that plays an important role in BP regulation. This threshold value defines the inhibitory or activator action of sympathetic nerve activity. Although the mechanism of circadian changes in this threshold value is not yet well understood, it is well known that particularly neuroendocrine factors, among many others, play a role in BP changes [15, 16]. In this study, we investigated the effect of the dipping phenomenon on enuresis using 24-h ABPM in pediatric patients with mono-symptomatic nocturnal enuresis.

Material and methods

A total of 45 patients ranging in aged from 6 to 15 years who were diagnosed with mono-symptomatic nocturnal enuresis between May 2010 and April 2011 in the Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Clinic of Pediatric Nephrology, were enrolled in our study. The diagnosis of mono-symptomatic nocturnal enuresis was in accordance with the International Children's Continence Society standardization [1]. Twenty-two age-matched healthy volunteers without nocturnal enuresis were included in the study as controls. Of the 45 patients, 18 were girls and 27 were boys; of the 22 controls, 13 were girls and nine were boys. Patients with a current history of urinary tract infection, a diagnosis of diabetes insipidus, obesity, constipation and/or encopresis, current hypertension, the presence of major abnormalities, and/or a history of chronic disease were not included in the study. The study protocol was approved by the ethics committee of our hospital. Parents of the patients and controls were informed about the study and informed consent was obtained.

In all subjects, ABPM was performed over 24 h using the SpaceLabs 90217 oscillometric device (SpaceLabs Inc, Redmond, WA). The appropriately sized cuff, chosen based on arm width, was placed on the non-dominant arm. The study participants and their parents were informed about the function of the device and were instructed to sleep from 2200 to 0800 hours (nighttime) and to perform their normal daily activities between 0800 and 2200 (daytime). The device was set to measure BP every 30 min. Values measured between the end of the nighttime to the end of daytime were grouped as "daytime values"; values measured between falling to sleep and waking up were grouped as "nocturnal values". Diurnal mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP), mean arterial pressure (MAP), mean nocturnal SBP, DBP, and MAP values and 24-h SBP, DBP, MAP values were compared. The 24-h SBP and DBP peak and trough values were defined as the highest and lowest SBP and DBP values recorded during the 24-h period. The SBP and DBP peak and trough values for daytime and nighttime were entered independently in the analysis. MAP was calculated for a specified time (daytime, nighttime, and 24 h) according to the formula: $MAP=DBP+[1/3\times(SBP - DBP)]$. The nocturnal BP reduction was calculated as: [(diurnal averaged MAP − nocturnal lowest MAP)/diurnal averaged MAP]×100 [17, 18].

Blood and first morning urine samples were also obtained from patients and controls on the morning of the day when the ABPM was performed. Medical reports on urine culture, urinalysis, spot urine biochemistry profile, complete blood count, blood biochemistry profile, blood rennin and aldosterone levels, lumbar X-ray and abdominal ultrasound scan were studied.

Statistical analysis was performed with the NCSS 2007 software package (NCSS, Kaysville, UT). The statistical analyses used were descriptive statistical methods [mean, standard deviation (SD), the *t* test for comparing two independent groups, the chi-square test for comparing qualitative data, and Pearson's correlation test to determine the relationships between the variables. The results were considered to be significant at $p < 0.05$.

Results

The mean age of the patients was 9.47±2.27 (range 6–15) years, and 18 (40 %) were girls and 27 (60 %) were boys. The mean age of the controls was 8.78±3.49 years, and 13 (59.1 %) were girls and nine (40.9 %) were boys. No statistically significant mismatch was observed between the patients and controls in terms of age, sex, height and weight distribution ($p>0.05$), nor in terms of gender distribution, mean height and weight values.

The distribution of BP, heart rates and dipping rates of the study subjects are summarized in Table 1. No statistically significant difference was observed between the patients and controls for the daytime and 24-h mean SBP and DBP values obtained by ABPM device ($p>0.05$). However, the nocturnal mean SBP and DBP values of patients were significantly higher than those of the controls ($p<0.05$).

Table 1 Blood pressure measurements, heart rates and dipping rates of study subjects

Blood pressures, heart rate and dipping rates	Time period	Enuretic patients (n=45)	Healthy controls (n=22)	p
SBP (mmHg)	Daytime	110±9	108±7	0.320
	Nocturnal	104±9	99±7	0.017
	24-hours	107±9	105±7	0.332
DBP (mmHg)	Daytime	69±6	67±4	0.219
	Nocturnal	62±6	58±4	0.001
	24-hours	66±6	63±4	0.074
MAP (mmHg)	Daytime	82±6	81±5	0.297
	Nocturnal	76±6	74±5	0.065
	24-hours	79±6	78±4	0.375
Heart rate (beats/min)	Daytime	95±2	97±2	0.603
	Nocturnal	83±2	83±2	0.846
	24-hours	92±2	91±2	0.731
Systolic dipping (%)		6.6±4.6	9±4	0.047
Diastolic dipping (%)		6.9±4.3	15±6	0.001

SBP Systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure

No statistically significant difference was observed between patients and controls with respect to the mean values of their daytime, nocturnal and 24-h MAP and heart rates (p>0.05). The differences between daytime and nocturnal mean SBP (systolic dipping), DBP (diastolic dipping) and MAP (mean dipping) values were evaluated. The mean values of systolic dipping and diastolic dipping of patients were significantly lower than those of control group (p = 0.047 and p = 0.001, respectively). However, no significant difference was observed between the mean values of mean dipping (p>0.05).

The day-to-night change (difference) in SBP values (expressed in percentage) based on a change of "< 10%" was found to be significantly higher in patients than controls [37 (82.2 %) vs. 13 (59.10 %), respectively; p<0.05]. The day-to-night percentage change in DBP values in patients based on a change of "<10%" was also higher in patients than in controls [21 (46.7 %) vs. 4 (18.2 %), respectively; p<0.05]. However, no statistically significant difference was observed in the day-to-night percentage change of MAP values between patients and controls (p>0.05) (Table 2).

Aldosterone and renin values were compared according to mean SBP, DBP and MAP values; no statistically significant correlation was observed (p>0,05). We also found no statistically significant correlation between the levels of spot urine urea, sodium, potassium, calcium, protein and the mean SBP, DBP and MAP in patients (p>0.05). No statistically significant correlation was found between the levels of spot urine creatinine and mean DBP and MAP values (p>0.05); however, we did find a statistically significantly negative correlation between spot urine creatinine and SBP (r = 0.409, p = 0,012). In addition, we observed a positive correlation between serum sodium levels (138.33±2.65) and SBP (r = 0.308 p = 0.039), DBP (r = 0.321 p = 0.032) and MAP (r = 0.311, p = 0.038) values. No significant correlation was observed between urine density and SBP (p>0.05); however we found a statistically significant negative correlation between urine density and DBP and MAP values (r = −0.338, p = 0.023 and r = −0.325, p = 0.029, respectively).

Discussion

Nocturnal enuresis is more common in boys than girls (60:40 %, respectively) [19–21], which was also the case in

Table 2 Comparison of day-to-night change (dipping) rates based on the "10%" rule

Dipping	Magnitude of dipping	Enuretic patients, n (%)	Healthy controls, n (%)	Significance according to chi-square test
Systolic dipping	>10%	8 (17.8)	9 (40.9)	χ^2:4.17*
	<10%	37 (82.2)	13 (59.1)	p=0.041*
Diastolic dipping	>10%	24 (53.3)	18 (81.8)	χ^2:5.12*
	<10%	21 (46.7)	4 (18.2)	p=0.017*
Mean dipping	>10%	13 (28.9)	11 (50.0)	χ^2:2.86
	<10%	32 (71.1)	11 (50.0)	p= 0.091

*Significant at p < 0.05

our patient group in which there was an overrepresentation of the male gender among enuretic children. Normally, the nocturnal decrease in urine production is accompanied by decreased BP during sleep. In otherwise healthy adolescents who are sleep-deprived, the nocturnal decrease in BP is less pronounced and nocturnal urine production is remarkably increased. The nocturnal decrease in BP in normal subjects has been reported to be about 10% of the daytime values [15, 16]. None of the patients included in our study were hypertensive according to age and height percentile values, but the nocturnal SBP and DBP values of these patients were higher compared to controls. The results we obtained are compatible with those reported in similar published studies, and they support the notion that the regulating mechanisms of the circadian rhythm of BP may play a role in the pathophysiology of nocturnal enuresis. Based on these data, we propose that enuretic children have a higher nocturnal BP compared to non-enuretics and thus the BP is an effective factor in the occurrence of enuresis in these children.

Nocturnal dipping of the arterial BP is a part of the normal circadian pattern, and its absence is called the "non-dipping" phenomenon. Although the underlying mechanisms of the nocturnal BP decrease are not yet fully understood, there is some evidence to suggest that non-dippers show some impairment in the autonomic system that includes abnormal parasympathetic and increased sympathetic nervous system activity. In order to investigate the possible mechanisms of the non–dipping phenomenon in enuretic patients, we performed 24-h ABPM in both enuretic participants and normal subjects. In our study, the mean values of systolic dipping and diastolic dipping of patients were significantly lower than those of control group, suggesting that the non–dipping phenomenon is linked to enuresis in patients. Our main finding was the alteration in absolute nocturnal BP—and not the dipping—indicating that daytime BP does not influence nocturnal urine output. It is possible that these patients have an increased sympathetic nervous system activity. Furthermore, our results may indicate that increased nocturnal diuresis is mediated directly by the renal effects of the increased arterial BP, such as, for example, by increasing the glomerular filtration rate and sodium excretion.

We found a negative correlation between SBP and urinary creatinine levels. We did not find similar findings in the literature on this subject, but the negative relationship between spot urine creatinine and SBP values were supported by other data obtained in our study. In our patients, the higher nocturnal BP and its insufficient nocturnal decrease versus the expected decrease may be associated with an inadequate excretion of creatinine in the urine. Further investigations are needed on this subject.

In recent studies, investigators observed increased nocturnal fractional sodium excretion in enuretic patients with polyuria, suggesting that sodium excretion is correlated with nocturnal polyuria and nocturnal enuresis [22–24]. In our study, we observed higher serum sodium concentrations in enuretic patients that had a lower day-to-night difference with respect to mean BP values. We also observed a positive correlation between serum sodium concentrations and BP in the patients. We were not able to measure the amount of nocturnal urine output and sodium excretion of patients. However, we do suggest that the lower nocturnal decrease in BP observed in this group of patients is associated with nocturnal polyuria and that their relative diurnal higher serum sodium concentrations (retention) might be a result of a feedback mechanism to compensate the nocturnal sodium and water loss.

In summary, nocturnal systolic and diastolic BP levels were observed to be significantly higher in enuretic patients compared to controls. Both systolic and diastolic dipping were significantly lower in enuretic patients compared to controls. Thus, based on our findings, which are consistent with those reported in the literature, it can be concluded that a disorder in the circadian rhythm of BP may play a role in the pathophysiology of nocturnal enuresis. This is the first study to show the relationship between the non–dipping phenomenon and enuresis in children. Further studies will be necessary to clarify the causative relationship between the non–dipping phenomenon and nocturnal enuresis in children.

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