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CLINICAL STUDY

Abnormal circadian blood pressure regulation in children with nocturnal enuresis

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ABSTRACT

Introduction: To investigate autonomic nervous system function in enuretic children by performing ambulatory blood pressure monitor (ABPM) for 24 h. **Methods:** Twenty-eight children ranging in age from 6 to 15 years with primary nocturnal enuresis and 27 age-matched healthy controls were enrolled and they get 24 h ABPM. Hypertension was defined as standard deviation score (SDS) > 1.64 (i.e., >95th percentile) adjusted for gender and height. Urinalysis, urine electrolyte levels, urinary culture, and urinary system ultrasound were carried out in all children. They have also requested to have a diary about daily fluid intake and urine volume. **Results:** Although the mean 24-h and daytime diastolic blood pressure (BP) did not differ between the groups, systolic BP (SBP) was significantly higher in enuretic children ($p < 0.05$). The mean night-time SBP, DBP values, SDS and BP loads were found to be significantly higher than those in the controls ($p < 0.01$). A lack of nocturnal decrease was more prevalent in the enuretic children compared with the control subjects, the difference was statistically significant for DBP but not for SBP. Patients with elevated night-time BP load was found to have higher frequency of urinary incontinence per week as well as per night when compared with enuretic children with normal night-time BP load ($r = 0.72$, $r = 0.69$, $p < 0.01$, respectively). **Conclusion:** Subtle abnormalities of circadian BP regulation in enuretic children indicated by a selective elevation of nocturnal SBP, DBP, and MAP, and attenuated nocturnal dipping may reflect sympathetic hyper activation and its possible role in pathogenesis of enuresis.

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Introduction

Nocturnal enuresis (NE) is involuntary voiding on at least two nights per months at age when volitional control of micturition is expected in the absence of congenital or acquired defects of the urinary tract.^{1,2}

Children without dysfunctional voiding and without daytime incontinence but with urgency and enuresis are defined as having monosymptomatic nocturnal enuresis.^{1,3}

NE is a common problem in pediatric age group and also affects about 20% of children at the age of 5 years.^{4,5} Bed-wetting spontaneously ceases with increasing age, being present in 15% of 5-year-old children, 5% of 10-year-old children, and 1% of 15-year-old children.^{6,7} It should not only perceived as a voiding abnormality, but also as a real trouble for children and their families because of its negative effects on the self-image of children and possible comorbidities such as learning disability and visuomotor integration abnormalities.^{8,9}

The etiopathogenesis of NE is not yet fully understood due to the complexity of the processes involved. It can be attributable to one or more pathogenic

mechanisms, such as increased nocturnal urine production, decreased bladder capacity, bladder over activity, and inability of the child to wake up.^{10–12}

Actually, urine production and excretion is controlled by several hormones including arginine vasopressin (antidiuretic), renin/angiotensin (diuretic/antidiuretic and natriuretic/antinatriuretic), aldosterone (antinatriuretic), atrial natriuretic peptide (ANP, diuretic and antinatriuretic) and autonomic nervous system, which also show a circadian rhythm. Hence, urine production has also a circadian rhythm. Autonomic nervous system effects urine production by changing renal blood flow and glomerular filtration pressure in addition to its effect on hormonal circadian rhythm.^{13,14} Blood pressure (BP) changes are therefore thought to be associated with urine production. The regulation of BP also modulated by autonomic nervous system and its dysfunction is reflected in both urine production and BP. Consequently, the nocturnal decrease in urine production is expected to be due to the physiological drop in nocturnal BP. The correlation between nocturnal BP and nocturnal urine production has also been shown in

some studies.^{15,16} However, studies about autonomic nervous system dysfunction in enuretic patients are limited. In this study, we aimed to investigate autonomic nervous system function in enuretic children by performing ambulatory BP monitor (ABPM) for 24 h.

Materials and methods

The patient group consisted of 28 patients ranging in age from 6 to 15 years who were diagnosed mono-symptomatic NE in Baskent University Faculty of Medicine, Clinic of Pediatric Nephrology. The diagnosis of mono-symptomatic NE was in accordance with the International Children's Continence Society standardization.¹ The patients were composed of healthy children who were carefully matched for age, gender, and body mass index (BMI).

Patients were excluded if they had a current history of urinary tract infection, a diagnosis of diabetes insipidus, obesity, constipation and/or encopresis, current hypertension, anatomic abnormalities in the urinary system and/or a history of chronic disease. Also, any child with autonomic symptoms such as chronic fatigue, syncope, and postural hypotension was excluded from the study.

The detailed physical examination was performed in all children. The casual BP was measured in all participants after 5 min rest in a sitting position with a standard sphygmomanometer. Patients and their families completed a 3-day voiding diary with volume intake and output, as described and recommended by the International Children's Continence Society.¹

Parents were questioned about how many days a week their children woke up wet and the number of voids at night. They also were instructed to check their children's bed as often as possible on the day of monitoring.

Twenty-seven healthy children, carefully matched for age, gender and BMI, were recruited as the control group among the siblings of patients and the children who had presented to the healthcare unit for a routine control.

Complete blood count, renal function tests, fasting blood glucose, electrolyte levels, urinalysis, urine culture were evaluated in all participants. Thyroid function tests and plasma and urine osmolality were measured in the study group (enuretic patients). Glomerular filtration rate (GFR), fractional excretion of Na (FE-Na), and daily protein excretion rate were calculated from 12-h urine sample for each subject. Lumbar X-ray and urinary ultrasonography were also performed to the study group to exclude anatomic problems that could be the cause of enuresis.

The ethics committee of Baskent University Faculty of Medicine approved the study protocol. All participants and their parents were informed about the study. Signed informed consent was obtained from a parent of each child.

ABPM monitoring

Twenty-four hours ABPM was measured by the oscillometric method using a portable automatic monitor (Spacelabs ABPM Model no.: 90207; SpaceLabs Medical, Redmond, WA). An appropriate cuff, chosen out of three available sizes, was attached to the non-dominant arm. Measurements were performed every 20 min during daytime and every 30 min during the night. To rule out bias by different bed rest habits, the day was defined as the period from 08:00 to 20:00 and the night period from midnight to 06:00.¹⁷

Blood pressure load (BPL) is defined as a percentage of total BP measurements exceeding upper limit of normal for age, sex, and height, adjusted for periods of awakesness and sleep. BPL of 25% or more is considered as hypertension.¹⁸

To calculate the individual nocturnal BP decreases, the nocturnal mean (midnight to 06:00) was compared with the daytime mean (08:00 to 20:00) in each subject, and the difference was expressed as the percentage of the daytime mean. A dipper is a person with a BP decrement of at least 10% during sleep time.^{19,20}

Height, sex and age dependency of BP were corrected for using standard deviation score (SDS) values for systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP) and heart rate by using the European reference standards published by Wühl et al.²¹ We used the LMS method to calculate appropriate SDS values for ABPM. The LMS method describes the distribution of measurement (Y) by its median (M), the coefficient of variation (S), and a measure of skewness (L) required to transform the data normality.¹⁷ While casual hypertension (HT) was defined as office SBP and/or DBP greater than or equal to the 95th percentile based on gender, age, and height on at least three different occasions,²¹ according to the ABPM criteria, HT was defined as $SDS > 1.64$ (i.e., >95th percentile) adjusted for gender and height.¹⁷

Statistical methods

The ABPM profiles were analyzed using the ABPM-Fit program, which performs conventional linear analyses (calculation of BP mean, SD, load, highest and lowest readings) for user-defined day and night periods. Data are given as mean \pm standard deviation (SD).

The student *t* test, chi-square test and Mann–Whitney *U*-test were used to test the difference between the patient group and the control subjects. Possible correlations among frequency of urinary incontinence per week as well as per night and BP measurements were tested with “Pearson correlation analysis.” Statistical significance was defined as $p < 0.05$.

Results

A total of 28 (F/M: 9/19) enuretic patients and 27 (F/M: 13/14) age- and gender-matched healthy children aged 7.9 ± 2.2 and 8.77 ± 2.65 years, respectively ($p > 0.05$), were included in the study. No statistical difference was observed between the patients and controls in terms of age, sex, height, weight, and BMI ($p > 0.05$; Table 1). The patients had no additional complaints other than NE. Seventeen patients (60.7%) had family history of NE. All had normal physical examination. Routine laboratory tests as well as thyroid function tests, fasting glucose level and plasma osmolality were within the normal limits. Urinalysis, urinary culture, and urine osmolality were also normal (Table 2). Ultrasonographic examination of urinary system was normal.

The daily fluid intake/patient was 1060 ± 128 cc. Unfortunately, we could not calculate the daily urine output due to patients' noncompliance. Urinary incontinence frequency of patients was reported as

Table 1. Demographic features of the study group and the controls.

	Study group (mean \pm SD)	Control group (mean \pm SD)	<i>p</i>
Age (years)	7.9 ± 2.2	8.7 ± 2.6	NS
Height (cm)	128 ± 10.3	126 ± 13.6	NS
Weight (kg)	28.1 ± 8.7	29.5 ± 9.7	NS
Body mass index (kg/m ²)	16.7 ± 2.6	17.9 ± 2.6	NS

Notes: SD: Standard deviation; NS: not significant.

Table 2. Laboratory data of the study group.

	Mean \pm SD	Normal range
Fasting blood glucose (mg/dL)	85.2 ± 7.4	60–100
BUN (mg/dL)	11.2 ± 2.23	6–21
Creatinine (mg/dL)	0.53 ± 0.04	0.3–1
Uric acid(mg/dL)	2.61 ± 0.61	2–6.1
Na (mmol/L)	137.7 ± 2.03	132–145
K (mmol/L)	4.3 ± 0.35	3.5–5.2
Ca (mg/dL)	9.7 ± 0.34	8.8–10.8
Hb (g/dL)	12.9 ± 1.04	12–15
fT4 (ng/mL)	1.26 ± 0.19	0.8–1.76
TSH (uIU/mL)	1.96 ± 0.83	0.35–4.94
Plasma osmolality (mosm/kg)	288 ± 12.4	275–295
Urine osmolality (mosm/kg)	786 ± 167.3	300–900
Glomerular filtration rate (mL/1.73 m ² /min)	114.5 ± 31.6	100 \pm 25
Fe-Na excretion (%)	0.51 ± 0.23	0.63 ± 0.21
Urinary protein excretion (mg/m ² /h)	1.54 ± 1.19	<4

Notes: SD: standard deviation; BUN: blood urea nitrogen; Hb: hemoglobin; TSH: thyroid-stimulating hormone; fT4: free tetraiodothyronine.

1.28 ± 1.39 at night and 3.6 ± 2.82 per week by their parents.

Casual BP measurements of all patients were within the normal limits (mean \pm SD = 85.3 ± 7.8 mmHg). The average fraction of successful readings obtained at each monitoring session was at least $84\% \pm 13$. None of the patients were hypertensive according to age and height percentile values, but eight patients (28%) were found to be hypertensive according to SDS. The 7/8 had only systolic HT both during the daytime and night-time measurements. One of them was found to have SBP and DBP elevation. Specifically, a number of patients with high night-time SBP and DBP SDS and night-time mean arterial BP SDS were found to be significantly high ($p = 0.003$, $p = 0.004$ and $p = 0.008$, respectively).

Twenty-four-hour daytime and night-time systolic and diastolic mean BP values and SDS of the study and control groups are summarized in Table 3. The mean 24-h and daytime DBP values and SDS did not differ between the groups; however, the mean SBP values and SDS were significantly higher in the patient group ($p < 0.05$). The mean night-time SBP and DBP values and SDS of patients were significantly higher compared to those of the controls ($p < 0.01$).

The daytime BP load did not found to be elevated in both groups. Elevated night-time SBP load was observed in four patients and was not observed in the control group (14.2% vs. 0%; $p < 0.01$). The night-time DBP load was elevated in 7 of 28 patients, compared with 1 of 27 control subjects (25% vs. 3.7%; $p < 0.01$).

The nocturnal BP dip was significantly reduced in the patient group compared with the control group for DBP (11.5 ± 5.9 mmHg vs. 18.1 ± 7.3 mmHg, respectively; $p < 0.05$). Although the difference was not found to be statistically significant for systolic dipping (8.6 ± 6.1 mmHg vs. 9.3 ± 5.6 mmHg, respectively; $p > 0.05$), the percentage of systolic non-dipping was high in patient group when compared with the control group (71.4% vs. 40.7%, respectively; $p > 0.05$).

Patients with elevated night-time BPL were found to have higher frequency of urinary incontinence per week (number of days with incontinence/week) as well as per night (number of incontinence/night) while compared with enuretic children with normal night-time BPL ($r = 0.72$, $p < 0.01$; $r = 0.69$, $p < 0.01$, respectively) (Figure 1a and b).

The FE-Na was found to be higher, almost twice as much as controls, in patients with increased night-time SBP/DBP. However, the difference was not found to be statistically significant ($p > 0.05$).

The 24-h and daytime heart rate SDS was significantly higher in control subjects ($p < 0.05$). The nocturnal heart rate SDS tended to be higher in the control

Table 3. Mean 24-h, daytime, and night-time blood pressures of patient and control groups.

	24 h BP		Daytime BP		Night-time BP	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
mmHg						
Patient group	108.3 ± 7.02	65.7 ± 4.94	111.1 ± 7.64	69.1 ± 5.5	102.7 ± 6.9	59.6 ± 5.4
Control group	103 ± 6.13	64 ± 3.7	106.4 ± 7.53	68.4 ± 4.8	96.2 ± 5.7	56.1 ± 4.0
<i>p</i> -Values	0.005	0.15	0.025	0.6	<0.001	0.008
SDS						
Patient group	0.26 ± 0.95	-0.11 ± 0.87	-0.09 ± 0.97	-0.5 ± 0.89	0.86 ± 0.81	0.81 ± 0.93
Control group	-0.61 ± 0.82	-0.42 ± 0.67	-0.79 ± 1.02	-0.61 ± 0.76	-0.19 ± 0.78	0.07 ± 0.69
<i>p</i> -Values	0.001	0.14	0.012	0.63	<0.001	0.002

Notes: 24-h BP: 24 h blood pressure measurements; day time BP: daytime blood pressure measurement; night-time BP: night-time blood pressure measurement. *p*-Values <0.05 denote statistical significance and are indicated in bold.

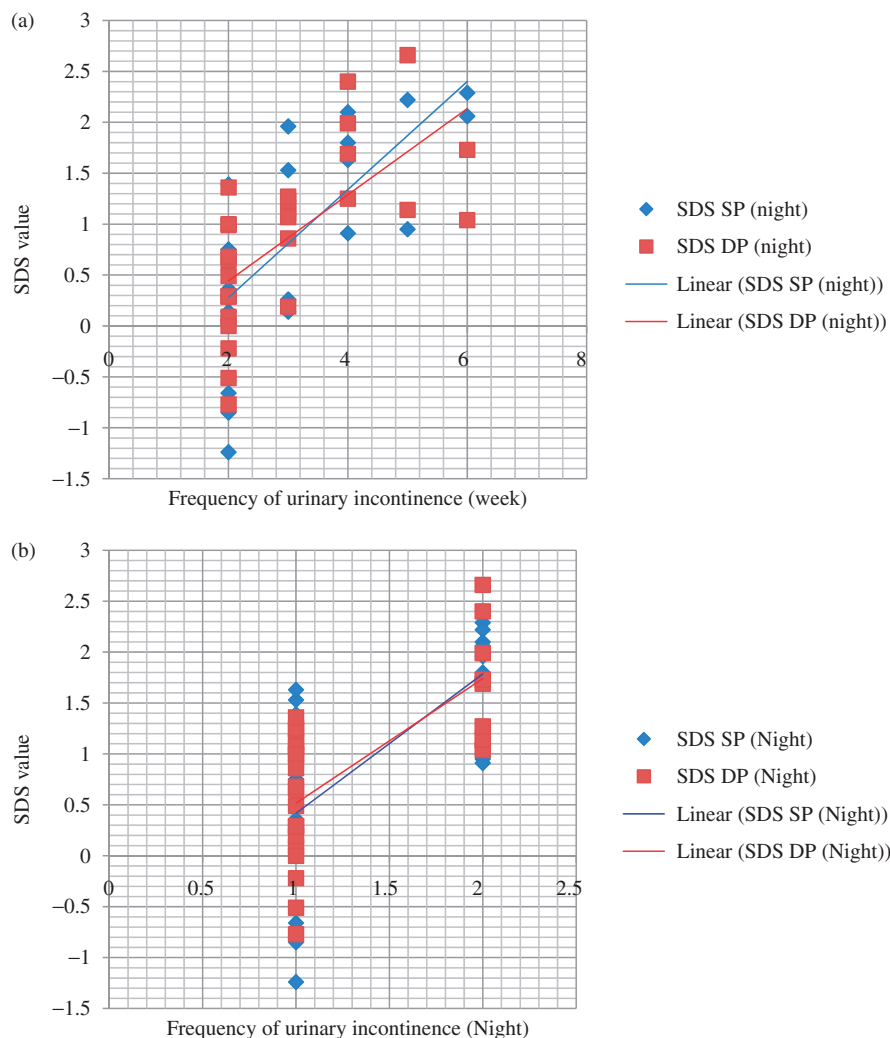


Figure 1. (a) SDS score of BP and urinary incontinence frequency per week. (b) SDS score of BP and nightly urinary incontinence number. SP: systolic pressure; DP: diastolic pressure; SDS: standard deviation score.

subjects, although statistical significance was not reached (0.33 ± 1.29 vs. -0.09 ± 1.12 ; $p=0.2$). There was no difference in nocturnal heart rate SDS between patients and control subjects who have elevated night-time BP SDS. Additionally, no correlation was observed between the night-time SBP/DBP SDS and nocturnal heart rate SDS ($r=0.21$, $p>0.05$; $r=0.13$, $p>0.05$).

Discussion

We assessed the role of autonomic activity in the pathogenesis of enuresis. For this purpose, the 24-h BP monitoring was performed in enuretic children due to easy applicability and low cost as well as being noninvasive. Our main findings indicated that enuretic patients have a selective nocturnal increase in nocturnal systolic,

diastolic and mean arterial BP, whereas none of them were hypertensive according to age and height percentile values. Furthermore, the prevalence of systolic and diastolic non-dipping was increased in the patient group. We also noticed that in our patients the frequency of urinary incontinence per week and urinary incontinence number per night were associated with elevated night-time BP. The observed results can be interpreted as a reflection of sympathetic nervous system hyperactivity.

The previous studies have yielded conflicting results about autonomic activity in enuretic patients. In fact, some researchers are believed that NE is the result of autonomic nervous system immaturity and/or delayed maturation.^{22,23} This view has been supported by “vegetative infantilism theory”.²⁴ Furthermore, the decrease in enuresis with advancing age was presented as an evidence of its developmental nature,^{25,26} although some researchers consider that this situation is more associated with autonomic nervous system dysfunction than with autonomic nervous system immaturity. Several studies have planned with using different methods for that purpose. In some of these studies, parasympathetic activity in enuretic patients has increased^{27–29}, while it has decreased in others.³⁰

Dundaröz et al. have reported the dominant activity of sympathetic nervous system in enuretic patients, which was consistent with our finding.³¹ They also speculated that their results could explain unresponsiveness of some enuretic patients to anticholinergic medications.

Sympathetic hyperactivity is not expected in terms of voiding physiology. However, the increased BP as a result of sympathetic hyperactivity leads to urinary output of both fluid volume and also of sodium. This phenomenon is called “pressure diuresis” and “pressure natriuresis”.³² Elevated BP has a direct effect on peritubular capillary hydrostatic pressure to increase urinary output. Besides this, the released ANP response to atrial wall tension is decreased afferent arteriolar resistance and increased efferent arteriolar resistance in the glomeruli. Glomerular capillary hydrostatic pressure therefore increases. Accordingly, the filtration fraction and GFR increase. The renin secretion rate, plasma renin activity, aldosterone levels reduce reversibly due to the increase in glomerular filtration.^{33–35}

The association between hormonal rhythm, urine production and BP changes has been evaluated in a few studies. The study conducted by Rittig et al. was the most comprehensive of them. They investigated the circadian rhythm of renin, angiotensin and aldosterone system in enuretic patients together with BP changes and urine production. An increase was found in the

aldosterone and angiotensin II levels during sleep in the control group and a significant difference was found between day and night for urine production and sodium excretion. This difference was not observed in the patient group and explained with impaired hormonal circadian rhythm. A significant circadian rhythm and a decrease in nocturnal mean BP were shown in the control group and the reduction in BP was found to be significantly higher in the control group and the non-polyuria patients than in polyuria patients.³⁶

Another study evaluating 24-h BP in enuretic patients showed that enuretic patients were non-dipper and had higher nocturnal SBP and DBP levels. However, no statistically significant correlation was observed between mean SBP, DBP, MAP and aldosterone/renin values.³⁷ All of these studies, consequently, have been showed that autonomic activity dysfunction in enuretic patients, which are consistent with our study. However, we were not able to measure the amount of nocturnal urine output and the hormone levels (renin/aldosterone, ANP, etc.) during sleep, which was the limitation of our study, in addition to the small number of patients. Though we expected to have a higher heart rate in enuretic patients, because of the sympathetic hyperactivity, the 24-h and daytime heart rate SDS was found to be significantly higher in control subjects. This, probably, could be explained by the arterial baroreceptor reflex response. Normally, increased arterial pressure stimulates the arterial baroreceptors located in the aortic arch and carotid sinus regions. This leads to reflex inhibition of sympathetic efferent nerve activity and excitation of parasympathetic efferent nerve activity resulting in a fall in the heart rate.³⁸

As such, these findings associated with over activity autonomic system can be well explained by the observation of potential therapeutic implications of sympatholytic agents in such patients. However, to date, no study has tested the use of sympatholytic agents' effects.

Conclusion

Subtle abnormalities of circadian BP regulation are apparent in enuretic patients. A selective elevation of nocturnal SBP, DBP, and MAP and attenuated nocturnal dipping may reflect sympathetic hyper-activation. From the results presented, we could speculate that autonomic activity dysfunction may have a possible role in the pathogenesis of enuresis. It could also be speculated that its influence on the regulation of hormonal activities by changing their circadian rhythm could be the key factor in pathogenesis. Further comprehensive studies with larger groups will be required to clarify the

causative relationship between the BP dysregulation, hormonal circadian rhythm and NE in children.

Disclosure statement

None of the authors has conflict of interest with the submission. No financial support was received for this submission.

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