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Comparison of Laboratory Data Between Pediatric Patients with Enuresis Nocturna and Healthy Children: A Prospective Clinical Study

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Abstract

Background: To investigate whether there is a difference in the parameters of blood and urine tests of pediatric patients with and without Monosymptomatic Enuresis Nocturna (MEN).

Methods: Pediatric patients aged 5 to 18 years who applied to the urology outpatient clinic with primary MEN between January 2022 and November 2022 and were started on desmopressin were prospectively included in the study. Age-matched pediatric patients who applied for right flank pain without detectable pathology were included in the control group. Urine density, pH, leukocyte (WBC), erythrocyte (RBC) and bacterial counts, Leukocyte Esterase (LES) positivity, and nitrite positivity of the patients were recorded at the time of admission. Sublingual desmopressin was started in all enuretic patients. Serum sodium, potassium and chlorine values, and results of complete urinalysis of the enuretic patients were recorded within 3 to 7 days after desmopressin treatment, and control groups at admission. Complete urinalysis and blood electrolytes of both groups were compared.

Results: A total of 267 patients were included in the study. The mean age of the patients was 9.48 ± 3.27 years, the mean urine pH was 6.0 ± 0.6, and the mean urine density was 1018.1 ± 9.1. The patients were allocated to enuretic (Group 1, n:122) and non-enuretic control (Group 2, n:145) group. There was no statistically significant difference between the two groups in terms of age, sodium and chlorine values in blood, nitrite positivity in urine test, bacterial count and pH values. Gender, LES positivity, RBC, WBC counts, potassium values in urine and urine density were significantly different between both groups.

According to the ROC analysis, the cut-off value for urine density, which was different between the enuretic and non-enuretic group, was 1019.5 with the 54.5% sensitivity, 61.5% specificity and 0.578 of AUC value (95% CI = 0.509-0.642, p=0.029).

Conclusion: Urine density was found lower in children with MEN than those without.

Keywords: Nocturnal enuresis; Osmolar concentration; Polyuria

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Introduction

Monosymptomatic enuresis nocturna is the involuntary leakage of urine that develops during sleep in children older than 5 years of age, without daytime and other accompanying symptoms [1,2]. It is seen in 5% to 10% of the cases around the age of 7 years. Annual spontaneous recovery rate of 15% is observed in all age groups, but its incidence decreases to 1% to 2% in adolescence [1]. However, it continues to be a source of serious stress, especially for children studying in boarding schools and their families. Children with primary enuresis do not stay dry for at least 6 months after toilet training, while those with secondary enuresis remain dry for at least six months but later on bedwetting reoccurs.

Enuresis nocturna consists of 3 components according to the widely accepted view. These components can be listed as nocturnal polyuria, decreased bladder capacity at night, and nocturnal detrusor hyperactivity. Presumably, it develops by the combined effect of one or more of these 3 components. Nocturnal polyuria develops as a result of a decrease in the diurnal variation in Arginine-Vasopressin (AVP) levels [3]. AVP is synthesized in the hypothalamus in response to

extracellular fluid osmolality. In healthy children, the level of AVP increases during the night, which prevents enuresis. Measurement of serum level of AVP is difficult due to its instability.

AVP plays a significantly greater role in the excretion of water from the kidneys. At low AVP levels, few changes in AVP lead to high changes in urine volume [4]. According to a study, AVP levels increase 9-fold in normal children, and reach its peak level at 04:00 AM in the morning. In enuretic children, its levels increased 2.5 times of its normal values [5]. It is thought that the relative lack of AVP in enuretic children may cause urinary concentration defect and increase renal excretion of water, resulting in low urine density [6,7].

In our study, we aimed to investigate whether there is a difference between the parameters in urine tests of children with primary MEN and non-enuretic children.

Material and Method

Ethics committee approval for our study was obtained from Mardin Artuklu University (Approval no. 2022/12-3). Pediatric patients aged 5 to 18 years who applied to the Urology outpatient clinic of Nusaybin State Hospital with the diagnosis of primary MEN between January 2022 and November 2022 were prospectively included in the study. According to the criteria of the International Child Continence Society, at least one attack per month during at least three months is required for the establishment of diagnosis. We made the diagnosis of primary MEN based on this definition [8]. Patients in this patient group, who were thought to have nocturnal polyuria according to their voiding diaries, and started on desmopressin were included in the study. Urine density and pH values measured in the first morning urine sample of these patients at their applications to the outpatient clinic, and WBC, RBC counts, bacteria, leukocyte esterase and nitrite positivity in the urine were recorded. A second urine sample was obtained at a different time on the same day only for the measurement of urine density and pH values, and the average of these two measurements was taken into consideration. Urine density was measured by refractometry method (ATAGO digital urine refractometer- Tokyo-Japan).

Education on behavior modification, lifestyle changes, regulation of fluid intake and bladder training was provided for all children. All children received 120 mcg sublingual desmopressin treatment. After an average of 3 to 7 days, serum sodium, potassium and chlorine values were recorded.

In the enuretic group, patients with urinary tract infection findings, history of neurological disease, endocrine disorders (diabetes mellitus, diabetes insipidus, etc.), psychiatric diseases (psychogenic polydipsia, etc.), urological surgery, cases considered to have non-monosymptomatic enuresis nocturna, and MEN administered some other treatments such as alarm therapy or imipramine, but without desmopressin therapy were excluded from the study.

As the control group, healthy children in the same age range (5 to 18) who applied for flank pain but without any detectable pathology were prospectively included in the study. Patients who had stones, hydronephrosis, congenital kidney and ureteral anomaly detected in urinary ultrasonography performed for flank pain, those with findings of urinary tract infection and history of enuresis were excluded from the study. First morning urine, serum electrolytes and second urine samples taken at different times in the same day were also analyzed in the control group patients. Average of density and pH measurements of two urine samples was taken into consideration.

Density and pH values measured in spot urine and serum electrolytes were compared between control and enuretic groups. The entire study process was carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

Statistical methods

Statistical analysis was performed using IBM SPSS version 21 (IBM Corp., Armonk, NY, USA). Variables were expressed as mean and standard deviation. Kolmogorov-Smirnov test was used to test the normality of distribution. Student-t test was employed to compare the parametric data between the groups. Categorical variables were given as numbers (percentages) and compared with the Pearson chi-square test. The ROC curve analysis was used to examine the role of urine density in the differentiation of enuresis. The sample size of the study was calculated using the G-Power 3.1.9.4 statistical power analysis program. A p value <0.05 was considered statistically significant.

Results

According to the result of the power analysis calculation (two-way correlation, type 1 error rate (α) =0.05, power of the study (1-β) =0.90 and effect size =0.42), at least 121 patients for each group were deemed to be sufficient for the statistical analysis. A total of 267 patients were included in the study. The male/female ratio was 114/153. The mean age of the patients was 9.48 ± 3.27 years, the mean urine pH was 6.0 ± 0.6, and the mean urine density was 1018.1 ± 9.1. The patients were allocated to enuretic (Group 1, n:122) and non-enuretic control (Group 2, n:145) group. There was no statistically significant difference between the two groups in terms of age, serum sodium and chloride values nitrite positivity, number of bacteria in complete urinalysis and urine pH values. When analyzed according to gender, statistically significantly higher number of girls were found in the control group (p<0.001). Statistically significantly increased LES positivity, greater number of RBC and WBC in urine were observed in the control group (p<0.001 for each). The mean potassium value of the enuretic group was significantly higher than the control group (p=0.048).

The mean urine density of the enuretic group (1016.7 ± 9.2) was comparable to the control group (1019.3 ± 9). The mean urine density was found to be statistically significantly lower in the enuretic group than in the control group (p<0.001) (Table 1).

According to the ROC analysis, the cut-off value for urine density, which was different between the enuretic and non-enuretic groups, was 1019.5, while its sensitivity (54.5%), specificity (61.5%), and the AUC value (0.578) were as indicated (95% CI = 0.509-0.642, p=0.029) (Table 2 and Figure 1).

Discussion

Arginine-vasopressin is a nano-peptide synthesized from the hypothalamus, which has vital importance in body osmotic and sodium balance, blood pressure regulation and kidney functions. AVP whose synthesis is induced in hypovolemia and hypernatremia binds to V2 receptors in the distal tubule and collecting ducts of the kidneys, and activates the cAMP pathway and aquaporin-2 water channels. Water is absorbed from the activated channels [9]. Thus, concentrated and hyperosmotic urine is formed with the effect of AVP [10].

Nocturnal polyuria is defined as nighttime urine output greater

Table 1: Comparison of the results obtained from the enuretic, and non-enuretic control groups.

Parameters (mean ± SD)	All patients (n=267)	Enuretic group (n=122)	Control group (n=145)	p value
Age (years)	9.48 ± 3.27	9.8 ± 3	9.2 ± 3.4	0.129
Gender, n (%)				<0.001
Male	114 (42.7)	79 (64.7)	35 (24.1)	
Female	153 (57.3)	43 (35.3)	110 (75.9)	
LES, n (%)				<0.001
Negative	238 (89.1)	119 (97.5)	119 (82)	
Positive	29 (10.9)	3 (2.5)	26 (18)	
Nitrite, n (%)				0.788
Negative	253 (94.8)	115 (94.2)	138 (95.1)	
Positive	14 (5.2)	7 (5.8)	7 (4.9)	
Sodium (mEq/L)	138.5 ± 3.4	139 ± 2.6	138.3 ± 3.8	0.05
Potassium (mEq/L)	4.3 ± 0.4	4.3 ± 0.3	4.2 ± 0.4	0.048
Chloride (mmol/ L)	101.9 ± 2.8	101.7 ± 2.3	102.1 ± 3.2	0.291
WBC (hpf)	1.7 ± 4.7	0.5 ± 1.8	2.7 ± 6	<0.001
RBC (hpf)	1.7 ± 3.6	0.8 ± 1.7	2.5 ± 4.6	<0.001
Bacteria (hpf)	0.7 ± 3.9	0.6 ± 3.9	0.9 ± 3.9	0.538
pH	6.0 ± 0.6	6 ± 0.5	6.1 ± 0.6	0.223
Density	1018.1 ± 9.1	1016.7 ± 9.2	1019.3 ± 9	0.017

SD: Standard Deviation; LES: Leukocyte Esterase; WBC: White Blood Cell counts in complete urinalysis; RBC: Red Blood Cell counts in complete urinalysis; hpf: high power field

Table 2: Predictive value of urine density in the evaluation of enuresis.

Urine density Cut-off value	Sensivity	Specificity	95 CI%	p value
1019.5	54.5	61.5	0.509-0.642	0.029

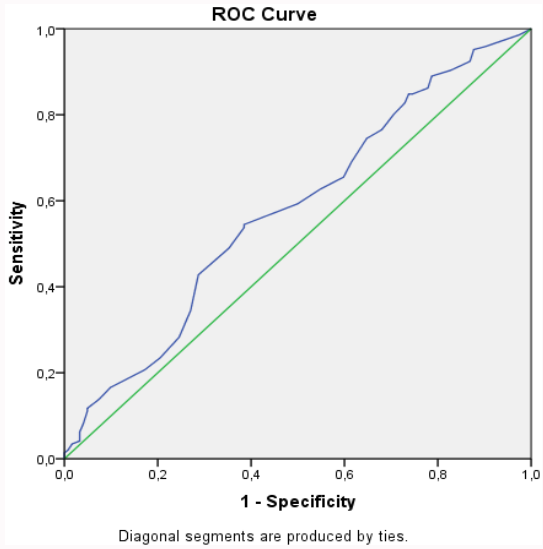

Figure 1: ROC analysis curve of the relationship between urine density and enuresis.

than 130% of expected bladder capacity in children. Nocturnal polyuria leads to involuntary bedwetting with the addition of sleep disorders in children whose neurological maturation of their bladders is not yet complete. Although it is thought that the main factor causing this situation is insufficient AVP secretion at night, the relevant evidence somewhat fails to support this assumption [11]. Studies conducted on this subject have intended to reveal whether changes in urine osmolality occur as a result of polyuria and AVP insufficiency [12,13]. In our study, we compared the enuretic patient group with the non-enuretic control group in terms of urine densities and showed that the urine density was statistically significantly lower in enuretic children.

There are studies in the literature that are compatible and contradictory with our data. Pomeranz et al. analyzed first-morning urine samples from all patients in their study, which included 52 enuretic and 15 non-enuretic control groups. In addition, urine samples were taken at 19.00, 22.00, 01.00, 04.00 and 07.00 o'clock. All enuretic children were given intranasal desmopressin for 6 months. There was no difference in morning urine osmolality between the two groups. Urine osmolality at 04:00 AM was significantly lower in the AVP- negative group compared to the AVP-positive group [13]. In their study, Abdelfatah et al. found urine osmolality to be significantly different between the control and the enuretic group, and between the patients in the enuretic group with and without nocturnal polyuria [6]. Conversely, Kawauchi et al. found no difference in urine osmolality between enuretic children and the control group [12].

Studies have investigated whether urine osmolality has an effect on predicting the desmopressin response. Abdovic et al. analyzed the data of 418 MEN patients retrospectively. In their study, patients were divided into 3 groups according to their desmopressin response as no response, partial response and complete response. The initial urine osmolality of the patients in the complete responder group was found to be statistically significantly lower than in the other groups [14]. They emphasized that non-desmopressin treatments should be considered in patients with pre-treatment urine osmolality of >814 mosm/kg, since desmopressin response would decrease in these patients. On the contrary, Ünüvar et al. indicated that neither daytime nor nighttime urine osmolality was predictive of desmopressin response [15]. In a study on 41 children with enuresis, Akagava et al. gave desmopressin to all children, and allocated them according to their morning urine

densities to low (<800 mosm/L) and high osmolality (>800 mosm/L) groups. They concluded that the desmopressin response of both groups was similar [16].

Presumably, nocturnal natriuria and hypercalciuria independent of AVP deficiency may play a role in the pathogenesis of nocturnal polyuria. Aceto et al. concluded in their study that nocturnal fractional sodium excretion was correlated with nocturnal diuresis. They stated that MEN patients who do not respond to desmopressin may benefit from a medical treatment approach tailored to the urinary excretion of electrolytes [17].

Urine osmolality is the gold standard criterion to be used to reveal the concentration capacity of the kidney. In clinical practice, it is usually measured with an osmometer. In some studies, it has been concluded that urine density and osmolality are not compatible [18,19]. However, in their study encompassing 205 patients, Mayo et al. stated that no difference was observed between the urine density measured by refractometry and urine osmolality. In this study, highly positive and significant linear correlation was found between urine osmolality and density [20]. In line with the above study, we also measured urine density using the refractometry method to determine the concentration capacity of urine. Similarly, Aydogdu et al. retrospectively analyzed the data of 45,558 pediatric patients, and evaluated the concentration capacity of urine by measuring urine densities. As a result, they found that the urine density and pH of the enuretic group were significantly lower relative to the control group [21].

One of the limitations of our study is that it was conducted with a small number of patients. The second limitation is that only daytime urine samples were taken from the patients. In studies, the average of the measurements of the first morning urine or nightly intermittent urine samples was generally taken into consideration. On the other hand, we included the first morning urine samples taken from the patients at the time of admission to the outpatient clinic and the average of two urine samples taken at different times on the same day were considered in the analysis. Because of the diurnal rhythm of AVP, averaging measurements of several overnight samples could be more accurate.

Conclusion

According to the results of our study, urine density was found to be lower than the control group in children with primary MEN, whose etiology is thought to be related to insufficient AVP secretion at night, consistent with the diagnosis of AVP insufficiency. If supported by large series of studies, urine density may assist clinicians in choosing the optimal treatment.

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