0022-5347/04/1716-2567/0
THE JOURNAL OF UROLOGY®
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Vol. 171, 2567–2570, June 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000108420.89313.0f

SODIUM FRACTION EXCRETION RATE IN NOCTURNAL ENURESIS CORRELATES WITH NOCTURNAL POLYURIA AND OSMOLALITY

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ABSTRACT

Purpose: We verify the sodium fraction excretion rate (FE Na) and potassium fraction excretion (FE K) rates in monosymptomatic nocturnal enuresis. We also correlate FE Na and FE K to urinary osmolality, nocturnal polyuria and vasopressin in the same population.

Materials and Methods: A total of 438 children 6 to 15 years old (mean age 9.7) presenting with monosymptomatic nocturnal enuresis were recruited from different centers. Inclusion criteria were 3 or greater wet nights a week, no daytime incontinence and no treatment in the previous 2 months. Exclusion criteria were cardiopathy, endocrinopathy, psychiatric problems and urinary tract abnormalities. Micturition chart, diurnal (8 am to 8 pm) and nocturnal (8 pm to 8 am) urine collection, including separate diuresis volumes, (Na, K and Ca) electrolytes and osmolality were evaluated, as well as serum electrolytes, creatinine and nocturnal (4 am) vasopressin. Diurnal and nocturnal FE K and FE Na were calculated. ANOVA test, chi-square test, Student's t test and Pearson correlation test were used for statistical analysis.

Results: Nocturnal polyuria (diurnal to nocturnal diuresis ratio less than 1) was found in 273 children (62.3%, group 1 and nocturnal urine volumes were normal in 165 with enuresis (37.7%, group 2). Nocturnal FE Na was abnormal in 179 children (40.8%), including 118 in group 1 (43.2%) and 61 in group 2 (36.9%) (chi-square not significant). FE Na was also increased in nocturnal versus daytime diuresis (Student's t test $p < 0.001$). In group 1 nocturnal FE Na correlated with nocturnal diuresis (Pearson correlation $p = 0.003$, $r = +0.175$), while daytime FE Na and nocturnal FE Na correlated with diurnal diuresis (Pearson correlation $p = 0.001$, $r = +0.225$ and Pearson correlation $p = 0.001$, $r = +0.209$, respectively). In group 2 nocturnal FE Na did not correlate with diuresis (Pearson correlation $p = 0.103$, $r = +0.128$) but correlated with vasopressin values (Pearson correlation $p = 0.042$, $r = -0.205$). Urine osmolality was reduced in 140 children (31.9%) and correlated with nocturnal diuresis (Pearson correlation $p = 0.003$, $r = -0.321$). Vasopressin was decreased in 332 children (75.8%, 62.6% in group 1 and 13.2% in group 2). No significant difference was found between sexes and age of enuretic subgroups.

Conclusions: Nocturnal FE Na correlates with nocturnal diuresis, whereas daytime FE Na does not. FE K in daytime and nighttime diuresis does not statistically differ in nocturnal polyuric and nonpolyuric enuretic groups. Osmolality correlates with nocturnal diuresis, and vasopressin at 4 am was lower in the nocturnal polyuric group. The hypothesis of a subset of enuretic patients presenting with nocturnal polyuria associated with high nocturnal natriuria and low vasopressin values has been confirmed.

KEY WORDS: enuresis, polyuria, vasopressins, electrolytes, desmopressin

Pathogenesis of monosymptomatic nocturnal enuresis (MNE) is still debated as different etiopathogenetic hypotheses have been proposed, accepted or rejected during the last century. More recently, MNE has been differentiated from bedwetting associated with daytime urinary symptoms, such as urgency, frequency and urge incontinence.[1,2] Nocturnal polyuria has been demonstrated frequently in MNE[3] and has been related to nocturnal vasopressin deficiency.[4] Desmopressin administration has been proposed and widely adopted for MNE treatment,[5] and enuretic patients have been differentiated into responders (65%) and nonresponders (35%).[6]

Supported by the Club Italiano Enuresi Notturna.
Study received Ethical Committee approval.
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Urinary electrolyte excretion has recently been studied in MNE. Nocturnal polyuria seems to be correlated with increased salt excretion from the renal tubuli.[7] Moreover, nocturnal hypercalciuria has been demonstrated in 46% of MNE cases. Increased calcium excretion during the night has frequently been associated with nocturnal polyuria.[8] It is possible to argue that nocturnal natriuria and hypercalciuria could have significant roles in the pathogenesis of MNE that does not respond to desmopressin, reducing tubular concentrating activity and increasing nocturnal diuresis independently from vasopressin control.

The hypothesis of a subset of subjects with MNE presenting with nocturnal polyuria associated with high urinary sodium and low vasopressin levels has been postulated. We verified the urinary sodium fraction excretion rate (FE Na) and potassium fraction excretion rate (FE K) during the day and night in a population of patients with MNE. FE Na and

FE K were correlated with urinary osmolality, nocturnal/diurnal diuresis and plasma vasopressin levels.

MATERIALS AND METHODS

The study population consisted of 270 boys (61.8%) and 168 girls (38.2%) 6 to 15 years old (mean age 9.7 years) presenting with MNE. The inclusion criteria were 3 or greater wet nights a week, no daytime urgency, frequency or urge incontinence and no pharmacological treatment for bedwetting in the previous 2 months. All subjects were on unrestricted diet and fluid intake regimens during the 4 weeks preceding the study. Presence or history of cardiovascular diseases, endocrine disorders, psychiatric problems and urinary tract abnormalities were exclusion criteria. Specific informed consent from the parents of each recruited child and approval from the Ethical Committees were obtained.

Evaluation consisted of a 72-hour micturition chart of diurnal (8 am to 8 pm) and nocturnal (8 pm to 8 am) urine collection obtained using urine bags at night and including the morning void at 8:00 am. The 12-hour diurnal and nocturnal diuresis was determined, and Na, K and Ca electrolytes with osmolality were separately measured in nighttime and daytime urine output. Diurnal and nocturnal FE K and FE Na were then calculated. Serum electrolytes, creatinine and plasma vasopressin were measured at 4 am using the validated radioimmunological method.[9]

According to our control group of nonenuretic healthy children,[7] normal values were FE Na less than 1, FE K 7–23 (15 ± 8), urinary osmolality 700 mOsm/l or greater and plasma vasopressin 3.5 pg/ml or greater. FE Na was considered abnormal when 1 or greater, and FE K were defined as low if less than 7 and high if greater than 7. Nocturnal polyuria was defined when diurnal vs nocturnal urine output ratio was less than 1.[1,7,8]

Statistical analysis was performed using SPSS software (SPSS, Inc., Chicago, Illinois) and the results are expressed as percent or mean ± standard deviation (SD). Analysis of variance (ANOVA), chi-square test and Student's t test for paired data were used. The Pearson test was used to analyze correlations with 2-tailed $p < 0.05$ (95% significance level) considered statistically significant.

RESULTS

Nocturnal polyuria was present in 273 children (62.3%, group 1) and diurnal to nocturnal ratio was normal in 165 (37.7%, group 2). Diurnal and nocturnal FE Na and FE K, diurnal and nocturnal urine volumes, nocturnal urine osmolality and nocturnal (4 am) vasopressin values are shown in table 1. Both patient groups were comparable for age, sex and body weight.

The distribution of normal nocturnal FE K and FE Na between groups 1 and 2 was not significant (see figure). Nocturnal FE K was normal in 220 children, low in 207 and high in 11, and was significantly reduced in nighttime vs daytime urine output (Student's t test $p < 0.001$). Nocturnal FE Na was normal in 259 enuretic patients and abnormal in 179, and significantly increased in nocturnal vs diurnal diuresis (Student's t test $p < 0.001$).

The examined parameter values, distributed according to normal/abnormal nocturnal FE Na rate, are summarized in table 2. Nocturnal FE K, diurnal FE Na and nocturnal urine output volumes varied significantly between normal/abnormal nocturnal FE Na. No significant difference was found in FE Na, considering sex and age subgroups of the study population.

Urine osmolality was reduced in 140 subjects of the study population (31.9%) and correlated with nocturnal diuresis volumes (Pearson correlation $p = 0.003$, $r = -0.321$). Creatinine clearance was normal (greater than 90 ml per minute in all subjects. Vasopressin was reduced in 332 children (75.8%) and normal in 4.6% of group 1 and 19.6% of group 2, which was statistically different (table 3, ANOVA $p < 0.001$). Nocturnal FE Na correlated with nocturnal diuresis in the entire study population (Pearson correlation $p = 0.008$, $r = +0.127$). In group 1, nocturnal FE Na was more strongly correlated with nocturnal diuresis (Pearson correlation $p = 0.003$, $r = +0.175$) as were daytime and nighttime FE Na (Pearson correlation $p = 0.001$, $r + 0.225$ and Pearson correlation $p = 0.001$, $r + 0.209$, respectively). In group 2, nocturnal FE Na did not correlate with diuresis (Pearson correlation $p = 0.103$, $r + 0.128$) but it significantly correlated with vasopressin levels at 4 am (Pearson correlation $p = 0.042$, $r = -0.205$).

DISCUSSION

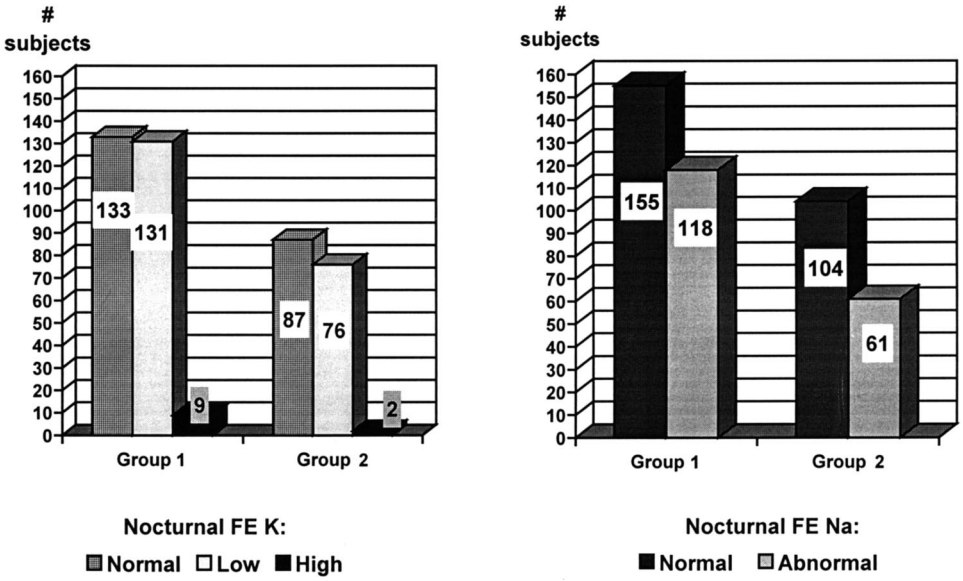
Bedwetting is a common problem in children and persists in about 1% of adolescents and young adults.[10] Despite the large amount of research published in the last 2 decades, the pathogenesis is not yet fully understood. Many factors (genetic, family history, and hormonal, biochemical, psychological and arousal disorders) have been proposed. Relative vasopressin deficiency during the night was demonstrated almost 20 years ago[11] and confirmed in a subset of MNE cases.[4,12] Nocturnal polyuria is present in about 2 of 3 enuretic patients, and it has been related to nocturnal vasopressin deficiency.[12,13] The MNE population has been divided into polyuric and nonpolyuric with the latter considered detrusor-dependent with small functional bladder capacity[1,6,14] or minor bladder dysfunction, which is common in daytime symptomatic enuretic patients.[15] In the polyuric group of MNE vasopressin has been advocated, with an overall positive response rate ranging from 50% to 75%.[13,14]

Not all polyuric bedwetters are vasopressin responders, and so other factors have been suggested as being responsible for nocturnal bedwetting. Pathogenetic factors of MNE remain to be defined in nonresponders and their identification may be of threshold relevance for identifying the appropriate treatment. Low functional bladder capacity and bladder dysfunction have been demonstrated in refractory MNE[15] but these urodynamic findings should be properly considered as associated with daytime symptoms of overactive bladder.

A significant pathogenetic factor may be solute diuresis,

TABLE 1. *Diurnal and nocturnal FE Na, FE K, diuresis, osmolality and plasma vasopressin*

	Mean ± SD		p Value (ANOVA)
	Group 1	Group 2	
% Diurnal FE Na	0.78 ± 0.36	0.78 ± 0.33	Not significant
% Nocturnal FE Na	0.96 ± 0.44	0.99 ± 0.55	Not significant
% Diurnal FE K	11.49 ± 5.54	11.29 ± 5.12	Not significant
% Nocturnal FE K	9.00 ± 5.93	8.87 ± 5.02	Not significant
Nocturnal diuresis (ml)	518.02 ± 193.80	346.94 ± 131.48	<0.001
Diurnal diuresis (ml)	401.15 ± 134.72	624.22 ± 305.01	<0.001
Osmolality (mOsm/l)	839.35 ± 304.49	857.33 ± 267.48	Not significant
Vasopressin (pg/ml)	2.02 ± 1.10	3.52 ± 1.50	<0.001



Nocturnal FE K and FE Na in nocturnal polyuric (group 1) and nonpolyuric (group 2) enuretic patients

TABLE 2. *Examined parameters in abnormal (high) and normal FE Na enuretic patients*

	Mean ± SD		p Value (ANOVA)
	% Abnormal FE Na (265 pts)	% Normal FE Na (185 pts)	
% Diurnal FE K	12.03 ± 6.06	14.04 ± 5.03	Not significant
% Nocturnal FE K	10.55 ± 6.77	7.76 ± 4.28	<0.001
% Diurnal FE Na	0.91 ± 0.36	0.69 ± 0.32	<0.001
Nocturnal diuresis (ml)	479.44 ± 220.87	435.69 ± 166.76	<0.001
Diurnal diuresis (ml)	497.54 ± 246.01	476.81 ± 237.05	Not significant
Osmolality (mOsm/l)	832.08 ± 267.41	873.00 ± 266.92	Not significant
Vasopressin (pg/ml)	2.47 ± 1.27	2.54 ± 1.55	Not significant

TABLE 3. *Plasma vasopressin in polyuric and nonpolyuric patients*

	Normal Vasopressin	Low Vasopressin	Overall
% Group 1	4.6	62.6	67.2
% Group 2	19.6	13.2	32.8
% Overall	24.2	75.8	

which leads to nocturnal polyuria in responders and nonresponders. Natochin and Kuznetsova recommended treatment of MNE by modifying tubular activity with desmopressin and diclofenac, suggesting a leading role decreased reabsorption of osmotically active solutes in enuretic patients.[16] Sodium and potassium urinary output has also been studied in the enuretic population.[17] Calciuria has recently been demonstrated as significantly increased in nocturnal diuresis of MNE, mostly associated with nocturnal polyuria.[7,8,18] Hypercalciuria could have a pivotal role in MNE, and has been associated with nocturnal polyuria in 43% of bedwetters without diurnal symptoms. Daytime calciuria has not been significantly modified in polyuric and nonpolyuric patients. Vasopressin level significantly correlated with hypercalciuria and nocturnal polyuria, and its correlation with FE Na was demonstrated in our study.

Recently, Nevéus et al reported no difference in urine osmolality and calcium excretion in 43 monosymptomatic, diuresis dependent and nondiuresis dependent enuretic patients, compared to a control group of dry age and sex matched children.[19] The authors found that the diuresis dependent group was polyuric and concluded that not all enuretic children with nocturnal polyuria have vasopressin deficiency.

The observation that not all polyuric enuretic patients have low vasopressin levels[3,8,19] led us to look for other pathogenetic factors that may cause increased urine output, especially during the night. Our study demonstrated that osmotically active electrolytes may modify nighttime urine production. Natriuria was increased in 118 of 273 enuretic patients presenting nocturnal polyuria (43.2%). We also demonstrated that nocturnal FE Na correlated with nocturnal diuresis (Pearson correlation $p = 0.008$, $r = 0.127$), whereas daytime FE Na did not. Conversely, FE K of daytime and nighttime diuresis was not statistically different in nocturnal polyuric or nonpolyuric enuretic patients. Nocturnal urine osmolality also correlated with nocturnal diuresis (Pearson correlation $p = 0.003$, $r = -0.321$), and vasopressin levels at 4 am were lower in the nocturnal polyuric group (ANOVA $p < 0.001$).

We are dealing with a heterogeneous group of bedwetters with or without nocturnal polyuria. In a subset of 60% of nocturnal polyuric MNE cases, nighttime urine overproduction depended on reduced overnight vasopressin secretion and responded to desmopressin. A second subset of almost 40% of bedwetters with nocturnal polyuria responded poorly or not at all to desmopressin, as the urine overproduction during the night was mostly electrolyte dependent. These subjects present with increased sodium urinary excretion and could benefit from a dietary regimen that reduces sodium and calcium intake during the afternoon, combined with desmopressin administration before bedtime if needed.[8]

CONCLUSIONS

Abnormal water and sodium excretion is present in nighttime urine production by a group of monosymptomatic bedwetters. Nocturnal polyuria and natriuria may interfere with vasopressin levels during the night. Nocturnal hypercalci-

uria seems to correlate with sodium excretion. These findings are not observed in all enuretic patients and, thus, multifactorial etiopathogenesis must be considered for MNE.

We can assume that Henle's loop of the renal tubuli has a significant role in MNE pathogenesis through the sodium and calcium excretion rate. A nonvasopressin dependent mechanism of osmotically activated diuresis seems to be involved in conjunction with the well documented vasopressin dependent diuresis, arising from the distal renal tubule. Desmopressin nonresponders should benefit from a different therapeutic approach based on calcium and electrolyte urinary excretion. Our study has shown the existence of a subset of bedwetters presenting with nocturnal polyuria associated with high nocturnal natriuria. Dietary sodium restriction, reduction of calcium excretion and desmopressin administration may be effective in such a subset of MNE. However, FE Na, urine osmolality and calcium excretion values of nocturnal urine output should be carefully considered to properly address treatment.

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