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Urinary risk factors for calcium oxalate urolithiasis in children with monosymptomatic enuresis

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ABSTRACT

Introduction: A disturbed calcium-phosphate balance is an important issue for kidney stone formation in nephrolithiasis. Hypercalciuria (HC) has been proposed as an essential etiology of monosymptomatic nocturnal enuresis (MNE).

Objectives: We may suspect that patients with MNE may be at risk of stone formation hence the objective of this paper was to assess the risk in MNE children using Bonn Risk Index (BRI).

Patients and Methods: The urinary work-up of 204 children (83 with MNE and 121 controls) included urinary calcium (Ca), magnesium (Mg) and sodium (Na) excretion, Ca/creatinine ratio, BRI, ionized calcium (Ca^{2+}), Mg/creatinine and Ca/citrate ratios, urinary citrates and oxalates (Ox).

Results: Ca/creatinine and Mg/creat ratios were higher in the MNE group. There were no differences in Mg and Ca amount in urine and Mg/Ca ratio between MNE and the reference group. Both groups differed in Mg and Ca excretion per kg of body mass. MNE children differed from controls regarding BRI, Ox and urinary Ca^{2+} . No differences in urinary citrate excretion nor Ca/citrate ratio between MNE and the controls were found. Correlations between factors important in the crystallization process in MNE children were recorded.

Conclusion: MNE patients may be at risk of oxalate nephrolithiasis. Further studies to assess the role of the BRI and Ca/citrate ratio in predicting stone formation in MNE children are needed.

Implication for health policy/practice/research/medical education:

Although monosymptomatic enuresis (MNE) is a widespread problem in pediatric population, the pathophysiology is still unclear. It is likely multifactorial with increasing evidence that disturbances in urinary electrolytes excretion especially hypercalciuria (HC) play an important role. An interesting question arises whether patients with MNE may be at risk of stone formation. To the authors' best knowledge, no publications are available in the literature that address this problem. In the first study of its kind, we describe the risk factors for urinary stones in children with MNE based on the most valuable parameters: Bonn Risk Index (BRI) and Ca/citrate ratio in urine.

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Introduction

Hypercalciuria (HC) is one of the most common electrolyte disturbances in children and adolescents. Several publications have appeared in recent years documenting disturbed calcium-phosphate balance in monosymptomatic enuresis (MNE) (1-4). Increased ionized calcium (Ca^{2+}) levels were described in pediatric urolithiasis and MNE (5,6). Al-Waili et al (7) described HC in primary nocturnal frequency of micturition in adult patients. Previous studies indicate that clinical

manifestation of HC may be accompanied with dysuria, nocturnal, diurnal and urge incontinence. The successful treatment of HC improves the symptoms whereas interruption or reducing medications lead to relapse (8,9).

HC was observed in all age groups starting from infancy to adolescence regardless of gender (8,10). Penido et al (8) stated that HC was predominantly diagnosed in school-age children and most frequently was associated with urolithiasis. Idiopathic HC, similarly to nephrolithiasis, is hereditary (11) and is described as a risk factor for

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urinary stone formation (12). Diagnosis of HC is based on the urinary calcium excretion and Ca/creatinine ratio calculation (13). However, HC is not the only parameter that influences stone formation as it is well-known that stone formation was observed in a patient with laboratory parameters within the normal range. Stone formation is initiated by an imbalance between promoting and inhibiting urinary factors (14). Bonn Risk Index (BRI) is a method for estimating the threat of calcium oxalate crystal formation, and is calculated based on Ca^{2+} concentration and ammonium oxalate (Ox^{2-}) in a sample of native 24 h urine collection (15). Taking all the above into account, we may suspect that patients with MNE can be a stone formation risk group.

Objectives

The main purpose of our study was to determine the risk of stone formation in MNE children based on BRI and selected inhibitors (magnesium and citrates) and promoters (calcium and oxalate) of crystallization estimation in urine.

Patients and Methods

Study design

This prospective analysis was conducted on 204 children divided into two groups. The study group comprised 83 children with MNE, whose median age was 9.66 years (66 boys and 17 girls). All of them were under the care of the department of pediatrics and nephrology between 2007-2012.

In order to be eligible to enter the study group, patients must meet the following criteria including the age between 4-17 years with the clinical diagnosis of MNE (16) refractory to non-pharmacological management. The children with normal renal function [glomerular filtration rate (eGFR) greater than 90 mL/min/1.73 m²] with serum creatinine and calcium concentrations in the normal range were included. The completed 24 hours urine collection was obligatory. To prevent urine loss, the enuretic children were woken two times during the night. The completeness of 24 hours urine collection was assessed by the comparison of the total creatinine in the sample with the reference values (17).

Patients with the current urinary tract infection (UTI) or recorded UTI in the past medical history were excluded. The exclusion criteria were also the presence of any endocrinopathy or metabolic disorder. The children's medical records were analyzed to determine gender, age, anthropometric parameters (weight, height and BMI; body mass index), supplementation of calcium and vitamin D as well as pharmacotherapy in the six months prior to the study.

We compared the results with the reference group

of 121 participants, with the median age of 9.99 years (91 boys and 30 girls) with the past medical history of inguinal hernia from whom we collected urine samples for the measurements once during the project. The control participants were invited to the study while attending the hospital for the control surgical visits.

Biochemistry assessments

Serum concentration of creatinine was measured by standard methods on biochemical analyzer Cobas Integra 800, Roche. eGFR was calculated according to the Counahan-Barratt equation using serum concentration of creatinine according to the presented formula: $0.43 \times L (\text{cm}) / \text{Scr} (\text{mg/dL})$, L – length, Scr – serum concentration of creatinine.

The urinary workup included; urinary calcium and magnesium excretion in 24-hour collection and expressed per kg of body mass, urinary sodium (Na) excretion, Ca/creatinine ratio (with the cut-off below 0.21), BRI ratio calculated based on Ca^{2+} and Ox^{2-} , oxalate excretion (Ox) (mmol/1.73 m²/24 h), Mg/creatinine ratio, urinary citrate in 24 h urine collection adjusted to the urinary creatinine and expressed as a citrate/creatinine ratio (mg/g creatine/24 h) and total citrate excretion (mg/24 h, mmol/24 h), additionally calculated on body surface (mmol/1.73 m²/24 h).

Materials and Methods

The 24-hour urine samples were collected with no preservatives and stored at a temperature of +4°C. The measurements were carried out within 4 hours after collection all in duplicate. Urinary levels of the calcium and magnesium were assessed with the Cobas-Integra 800 (Roche) and expressed as Ca/creatinine, Mg/creatinine, Mg/Ca ratios. To estimate BRI, urinary Ca^{2+} concentration was measured using calcium ion selective electrodes (Rapidlab 855; Bayer, Leverkusen, Germany) and titrated with ammonium oxalate (Ox^{2-}) solution (40 mmol/L) at a rate of 0.75 mL/min. The onset of spontaneous crystallization was detected using an Eppendorf photometer (filter 585 nm) with a decrease in light transmission to 98% of the initial value. The mean value was derived from the amount of added ammonium oxalate and calculated for 200 ml of urine (15). Each analysis was repeated twice. The results of BRI were presented as $[\text{Ca}^{2+}] \text{ mmol/L} / (\text{Ox}^{2-}) \text{ mmol} = 1/\text{L}$. Calibration and the quality assurance procedure, based on the calibration curves, were carried out every day. Urinary pH was determined using a microcomputer pH-meter (model CP-315M; Elmetron, Zabrze, Poland). Urinary citrates were assessed by enzymatic methods using a commercial set (R-Biopharm AG, Darmstadt, Germany). 24-hour citrate excretion was expressed in absolute values, adjusted for urinary creatinine. A stone risk index was

determined by the urinary calcium/citrate (Ca/citrate) ratio.

Ethical issues

The research followed the tenets of the Declaration of Helsinki (18). The Ethics Committee of Medical University of Bialystok approved this study (R-I-002/553/2013). Accordingly, written informed consent taken from all participants or their parents before any intervention.

Data analysis

Data analysis was performed using Statistica 10.0 (StatSoft Inc., Tulsa, OK, USA). Normal distribution of data was tested with the Shapiro-Wilk W test. All studied

parameters were analyzed using nonparametric tests: Mann-Whitney and Spearman. Values of $P < 0.05$ were considered significant.

Results

The characteristics of the studied children are presented in Table 1. Groups were age, height, weight, BMI and also sex-matched. Serum creatinine concentration and urinary creatinine excretion (g/24 h) did not differ significantly between the MNE patients and the reference group. Ca/creatinine and Mg/creatinine ratios were higher in the MNE group. Several risk factors were greater in MNE than in reference group (UNA, Ox, UCa²⁺, BRI) while others had lower values in MNE (Ox²⁻, Ucitrate in mmol/1.73m²/24 h). Notably, some risk factors were the same in both

Table 1. The median values, ranges and comparisons of basic demographical data and examined parameters in MNE children and reference groups

Parameters	MNE	Reference group	P value
	Median (minimum maximum)	Median (minimum maximum)	
Age (y)	9.7 (4.2-16.9)	9.9 (4.2-16.9)	0.9
Height (cm)	137.5 (107-188)	143 (108-191)	0.27
Weight (kg)	32 (12.1-111)	36 (16-113.4)	0.25
BMI (kg/m ²)	16.16 (9.48-31.41)	17.52 (12.21-31.58)	0.27
Screat (mg/dL)	0.51 (0.28-0.91)	0.49 (0.31-0.93)	0.69
Ucreat (g/24 h)	0.58 (0.29-2.08)	0.73 (0.32-1.88)	0.1
UCa/creatinine (mg/mg/24 h)	0.12 (0.01-0.78)	0.09 (0.02-0.196)	0.04*
UCa (mg/kg/24 h)	2.06 (0.16-10.58)	1.7 (0.37-3.48)	0.04*
UCa (mmol/24 h)	1.58 (0.24-9.87)	1.51 (0.27-4.48)	0.15
UMg/creatinine (mg/mg/24 h)	0.1(0.02-0.41)	0.08 (0.01-0.16)	<0.001**
UMg (mg/kg/24 h)	1.79 (0.53-5.62)	1.6 (0.27-2.88)	0.002**
UMg (mmol/24 h)	2.52 (0.44-6.34)	2.35 (0.55-4.94)	0.08
UMg/Ca (mg/mg/24 h)	0.45 (0.04-0.94)	0.42 (0.12-2.13)	0.84
UNa (mmol/24 h)	107.95 (46.1-186.3)	81.1 (20.4-164.19)	0.01*
eGFR (mL/min/1.73m ²)	133.88 (91-316.64)	143.3 (92.19-222.33)	0.01*
24 h urine collection (mL)	750 (350-2700)	700 (250-2300)	0.25
24 h urine collection (mL/kg)	25.53 (6.58-72.06)	20.53 (5.91-62.16)	0.03*
Ox (mmol/1.73 m ² /24 h)	0.46 (0.05-0.93)	0.29 (0.06-0.46)	<0.0001**
UCa ²⁺ (mmol/L)	0.44 (0.01-1.97)	0.28 (0.12-0.82)	0.001*
Ox ²⁻ (mmol/200 mL)	0.71 (0.13-9.23)	1.35 (0.34-4.19)	<0.001**
BRI (1/L)	0.55 (0.002-11.81)	0.19 (0.03-1.89)	<0.001**
Ucitrate (mg/gcreat/24h)	515.9 (29.1-2192.7)	532.4 (401.4-1229.2)	0.12
Ucitrate (mg/24 h)	313.43 (14.82-1447.15)	445.8 (155.8-1615.8)	0.01
Ucitrate (mmol/24 h)	1.63 (0.08-7.53)	2.32 (0.81-8.41)	0.01
Ucitrate (mmol/1.73m ² /24 h)	2.58 (0.16-10.61)	3.08 (1.76-6.02)	0.002*
pH of urine	6.25 (5.44-7.68)	6.35 (5.43-6.32)	0.26
UOsm (mOsm/kgH ₂ O)	637 (226-1212)	565 (240-1135)	0.02*
Ca/citrate ratio(mg/mg/24 h)	0.168 (0.018-3.72)	0.153 (0.039-0.42)	0.116

MNE, monosymptomatic enuresis; Screat, serum creatinine; Ucreat, urinary creatinine; UCa²⁺, urinary ionized calcium; UOx, urinary oxalate; Ucitrate, urinary citrate; BMI, body mass index; eGFR, Estimated glomerular filtration rate; BRI, Bonn's Risk Index; UOsm, urine osmolality.

* $P < 0.05$, ** $P < 0.001$

groups (UCa in mmol/24 h, UMg in mmol/24 h, UMg/Ca, Ucitrate in mg/g creatine/24 h, Ca/citrate). The values of 24 h urine production in ml per kg of body mass were higher in MNE children compared with the controls.

Additionally, we analyzed 24 h urine collection osmolality. Median osmolality in MNE children was statistically significant higher than in the reference group.

Correlations between factors that play an essential role in the crystallization process in MNE children's urine are included in Table 2. The BRI demonstrated a negative correlation with height ($R = -0.076$), weight ($R = -0.099$), and age ($R = -0.059$) in the reference group, but was not statistically significant. We also found a negative correlation between BRI and height ($R = -0.191$), weight ($R = -0.293$), and age ($R = -0.191$), but only weight ($P < 0.05$) was statistically significant. We found statistically significant negative correlations between BRI and urinary Na excretion ($R = -0.474$, $P < 0.05$) in the reference group, and positive association in the MNE group ($R = -0.329$), but this was not statistically significant ($P > 0.05$). The Ca/creatinine ratio and urinary Ca excretion in mg/kg of body mass in 24 h urine collection demonstrated positive correlations with BRI, and are shown in Figure 1. There were no statistically significant correlations between BRI and Mg excretion in the reference group. Statistically significant positive correlations between BRI and Mg excretion in MNE children are shown in Figure 2. We found positive correlations between BRI and Mg/Ca ratio both in the reference and the MNE groups ($R = 0.781$, $P < 0.05$; $R = 0.682$, $P < 0.05$, respectively). There were no correlations between BRI and urinary citrate excretion (mg/24 h, mg/g creatine/24 h, mmol/24 h, mmol/1.73 m²/24 h). We found a positive correlation between BRI and Ca/citrate ratio both in MNE children ($r = 0.702$, $P < 0.05$) and the reference group ($r = 0.0727$, $P < 0.05$).

Discussion

Since it is known that HC can be diagnosed in children with MNE, an interesting question is whether these patients are at risk of stone formation. Increased calcium excretion is not the only cause of stone formation. Our results describe for the first time the risk factor of stone formation in MNE children based on the most valuable parameters: BRI and Ca/citrate ratio in urine (15,19,20). Co-occurrence of HC with hypocitraturia increases the potential risk of kidney stone formation or recurrence (20). Many authors have postulated that disturbed proportions between urinary calcium and urinary citrate concentrations determines the stone formation risk (5,222).

The results of our investigations show that MNE children present HC. BRI and calcium/citrate excretion are elevated in this group as well. There are no studies focusing on the risk of nephrolithiasis in MNE children. Abdominal pain and hematuria are the most frequent clinical findings in patients with HC; however, nocturnal enuresis, diurnal incontinence, urgency, supra pubic pain, and urethralgia were reported in 8% patients with HC (8). The expression of symptoms is different in individual cases and it is possible that nocturnal enuresis only manifests in HC children. Previous research has demonstrated that HC is observed regardless of gender and race (10,23). Penido et al (8) confirmed that the higher prevalence of HC is present among the school-age children. In the literature, several theories have been proposed to explain an age-dependent decrease in the prevalence of enuresis. One of them states that the maturation of the central nervous system might be the possible cause (24). On the other hand, an increased rate of spontaneous remission could be also caused by normalization of calciuria depending on the age. Unfortunately, our study was not

Table 2. Correlations between main factors play an important role in crystallization process in MNE children urine

	Ca (mmol/24h)	Ca (mg/kg/24h)	Mg (mmol/24h)	Mg (mg/kg/24 h)	Ca ²⁺ (mmol/L)	UOx	Na	Citrate
	R	R	R	R	R	R	R	R
Ca (mmol/24 h)	X	0.842*	0.476*	0.369*	0.763*	-0.084	0.217	-0.091
Ca (mg/kg/24 h)	0.842*	X	0.258*	0.638*	0.896*	0.025	0.266	0.016
Mg (mmol/24 h)	0.476*	0.258*	X	0.504*	0.339*	-0.028	0.502*	0.128
Mg (mg/kg/24 h)	0.369*	0.638*	0.504*	X	0.658*	0.159	0.478*	0.196
Ca ²⁺ (mmol/L)	0.763*	0.896*	0.339*	0.658*	X	-0.007	0.381*	0.015
UOx	-0.084	0.025	-0.028	0.159	-0.007	X	-0.021	0.093
Na	0.217	0.266	0.502*	0.478*	0.381*	-0.021	X	0.249
Citrate	-0.091	0.016	0.128	0.196	0.015	0.093	0.249	X

Ca, calcium; Mg, magnesium; UOx, urine oxalates in mmol/1.73 m²/24 h; Na, sodium (mmol/24 h); Citrate (mg/g creatine/24 h); MNE, monosymptomatic enuresis children.

Significant value: * $P < 0.05$.

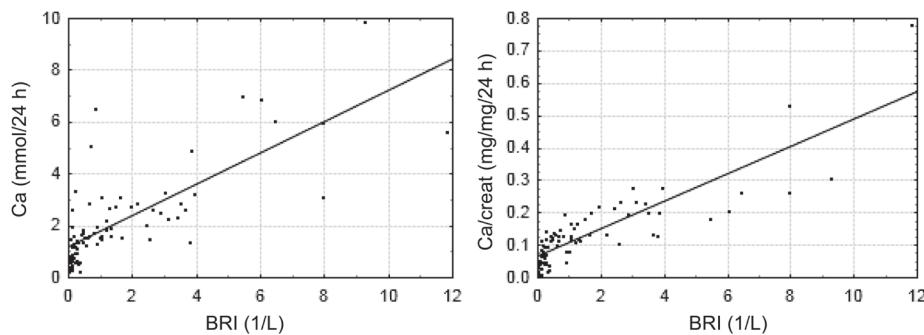


Figure 1. Correlations between BRI and Ca/creatinine ratio and urinary Ca excretion in mg/kg of body mass in 24 h urine collection in children with monosymptomatic enuresis.

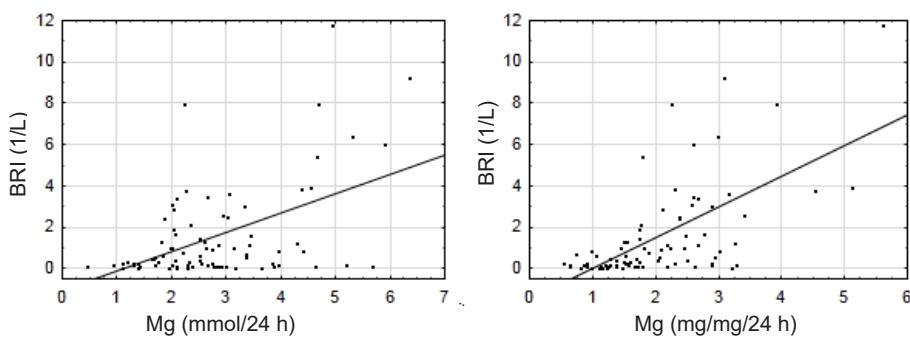


Figure 2. Correlations between BRI and Mg excretion (mmol/24 h and mg/kg/24h) in children with monosymptomatic enuresis.

designed to assess dietary restriction effects on MNE children; however, we are planning to estimate daily diet in children with both nephrolithiasis and nocturnal enuresis. MNE and nephrolithiasis are strongly related to family presentation and also hereditary (25). Are there any clinical implications of this similarity?

This study raises one more question. Do we always take very detailed patient history and do we correctly classify enuretic patients as monosymptomatic? Accordingly, we should pay more attention to lower urinary tract (LUT) symptoms both at the time of estimation and in the past, and try to find any symptoms suggesting LUT dysfunction and related to HC in MNE children.

Our paper presents an innovative finding that there was a positive correlation between magnesium excretion and BRI. This may suggest some unknown and unexplored mechanism inhibiting stone formation. Magnesium is one of the main stone formation inhibitors and may possibly be used to protect MNE children from nephrolithiasis. Additionally, we did not find any differences in another important crystallization inhibitor – citrates – between MNE and healthy individuals. It is possible that stone formation risk in MNE children is due to a calcium-magnesium imbalance.

The authors' attention was focused also on the

correspondence between other factors that play a crucial role in the crystallization process and promote stone formation such as sodium excretion. Increased dietary sodium intake leads to high excretion in urine and increases calcium excretion. On the other hand, increased sodium excretion in MNE children may cause enuresis via increased urine production. This finding raises the question if a low-sodium diet could help solve MNE children's problems and decrease calcium excretion and therefore risk of stone formation. A low-sodium diet recommendation may be more useful than fluid restrictions in this group of children. Clearly, further research will be needed to validate the correlations between increased sodium excretion, enuresis incidents and the threat of stone formation.

The proposed study design allows us to conclude that increased BRI, Ca/creatinine ratio, Na excretion, decreased Ca/Mg ratio, and low-urinary Mg excretion may predispose MNE children to stone formation.

Numerous authors have described HC in enuretic children (26-29). As it is known that HC is diagnosed and BRI is elevated in MNE children, it is worth assessing all factors influencing the calcium-phosphorus balance, such as; vitamin D, parathormone, alkaline phosphatase and its interrelations to assess the risk of nephrolithiasis and

osteoporosis in MNE children as well. The differences in calcium excretion between MNE children from different continents may be due to a disturbed calcium balance caused by a vitamin D deficit, e.g. in children from central European countries this deficit was well described and confirmed, and vitamin D supplementation is recommended. The differences in calcium excretion are also related to the various dietary habits of people in many countries. We strongly believe that the results of this research may have implications for better understanding why enuretic children have problems with bone mineral density.

Our study has some limitations. Firstly, urodynamic studies were not performed. The correlation between our results with BRI and the urodynamic parameters would be desirable. According to the actual recommendations, these investigations are not obligatory in MNE. However, it is advisable to perform uroflowmetry in MNE children with elevated BRI as children suffering from urolithiasis can present abnormal LUT function. Thus, further research is necessary to extend our knowledge of bladder function and BRI in children with MNE before and after initial treatment. Another limitation was the inability to estimate the effects of different treatments, which can lead to a BRI decrease. The key limitations of this research are that we did not assess family history regarding HC and nephrolithiasis as well as other promoters and inhibitors of crystallization such as osteopontin.

In summary, BRI could be used to assess the risk of urinary stone formation and nephrolithiasis development in MNE patients. Those with increased BRI should be identified and initial diagnostics for HC should be applied before any intervention. An uroflowmetry should be recommended for all patients with MNE and nephrolithiasis.

Conclusion

Patients with MNE may be at the risk of nephrolithiasis. More research into this subject is still necessary before obtaining a definitive explanation to the role of BRI and calcium/citrate ratio in predicting stone formation in MNE children.

Limitations of the study

Our study has some limitations. First of all at the moment of the study all participants did not develop stones in the urinary tract. Taking into consideration the fact that stone-forming processes is quite long we aimed at assessing the risk factors predisposing to the stone formation in MNE children in the future. What is more, we did not assess family history regarding HC and nephrolithiasis. Another limitation was the inability to estimate the effects of different treatments, which can lead to a BRI decrease.

Finally, we did not assess other promoters and inhibitors of crystallization such as osteopontin.

Authors' contribution

AL, JOB and AKK were the principal investigators of the study. AL, JOB, JKK, TP and AKK were included in preparing the concept and design. JKK, TP and AKK revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

Authors declare no conflict of interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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