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Prevalence of Metabolic Risk Factors Affecting Childhood Nephrolithiasis: A Report from a University Hospital in West of Iran

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Abstract

Background

The prevalence of urolithiasis in both infants and children is increasing. The metabolic features contributing to urolithiasis formation in children may vary from those in adult patients. The purpose of this study is to determine the prevalence of urinary metabolic abnormalities and related factors in infants and children with urolithiasis in Kermanshah, West of Iran.

Materials and Methods: In this cross-sectional study, 104 children and infants with urolithiasis who were admitted to the Pediatrics Nephrology Clinic of Imam Reza Hospital in Kermanshah, Iran in 2018 were investigated. Urinary metabolic abnormalities, including hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia and cystinuria, were examined using random urine samples.

Results: Of the 104 children (66 boys and 38 girls) examined, 64 (61.5%) had at least one urinary metabolic abnormality. Hypercalciuria was the most common (31 patients, 29.8%), followed by hyperuricosuria (27 patients, 26%), hyperoxaluria (20 patients, 19.2%), hypocitraturia (13 patients, 12.5%), and cystinuria (one patient, 0.96%). Hyperuricosuria (88.9%) and hypocitraturia (46.2%) were more common in infants younger than 12 months old compared to those older. No statistically significant association was observed between the frequency of urinary metabolic abnormalities with gender and family history of urolithiasis, but a significant relationship was found between age and prevalence of urinary metabolic abnormalities.

Conclusion

Hypercalciuria was the most common metabolic abnormality in the urine. Although detection of urinary metabolic abnormalities is important, the role of other variables, like nutritional and climatic factors in the development of childhood nephrolithiasis should be considered too, since no metabolic disorder have been found in more than a third of patients.

Key Words: Children, Infant, Hypercalciuria, Iran, Metabolic Abnormality, Urolithiasis.

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1- INTRODUCTION

Urolithiasis is a condition frequently seen in adults, and its occurrence in childhood is uncommon (1). Childhood urolithiasis is different from adults in presentation, etiology, and incidence. Recent studies show an increasing prevalence of pediatric urolithiasis (1, 2), which condition varies from 2 to 2.7% (3). It is more frequent in boys, with the male to female ratio from 1.2:1 to 4:1 according to various studies. Given the difficulties of diagnosis in the pediatric group, the actual prevalence of urolithiasis in children is probably higher than the reported figures. Delayed diagnosis and inappropriate treatment of pediatric urolithiasis may lead to kidney parenchymal damage, and it can be the etiological factor in 8% of pediatric chronic renal insufficiency (4).

Symptoms of urinary tract stones in children and infants are different from those of adults. This means that symptoms, which include restlessness and irritability, are often nonspecific and may even remain asymptomatic, especially in infancy, and other symptoms including abdominal pain, hematuria, and dysuria, especially in older children (5, 6). Risk factors for renal stone formation include genetic factors, metabolic conditions, infections, nutritional issues, environmental factors and congenital abnormalities (7, 8). Of the mentioned risk factors, urinary metabolic derangements have been reported to have an important role in childhood nephrolithiasis (9), and the risk of stone recurrence is higher in children with a metabolic condition (9, 10). Among the most studied, hypercalciuria, hypocitraturia, hyperoxaluria, cystinuria, and hyperuricosuria are well known metabolic abnormalities affecting in pediatric urolithiasis (10). Numerous studies have emphasized the need for metabolic studies in all children with urolithiasis to select the appropriate treatment approach and to prevent recurrence of stone formation (7, 10, 11). This is due to the importance and higher prevalence of urinary metabolic abnormalities in children with urolithiasis when compared to children without urinary tract stones (3). Idiopathic hypercalciuria has been cited as the most common metabolic abnormality with a prevalence of up to 80% (9, 12). However, a few studies have found hypocitraturia as the most prevalent metabolic abnormality (13). Some studies have attempted to find differences in metabolic abnormalities in boys and girls, considering the difference in the incidence rates of urinary tract stone in boys and girls and predominance in boys. However, it appears that, at least in case of metabolic factors, no difference exists between genders (2).

There is evidence for geographic variability in the prevalence of urolithiasis, having considered genetic factors and ethnicity along with dietary lifestyles, so the metabolic abnormalities predisposing to urolithiasis may vary in different areas (1). The aim of this study is to determine the frequency of urinary metabolic abnormalities and the related factors in children with urolithiasis from an area with less documented and published data in western Iran. The results of this study can contribute to our knowledge of metabolic risk factors in the formation of urinary tract stones and provide better management of this condition.

2- MATERIALS AND METHODS

2-1. Study Design

In this cross-sectional study, we evaluated 104 infants and children with urolithiasis who referred to the nephrology clinic of Imam Reza Hospital in Kermanshah, Iran from 2016 to 2018. The cases were rechecked for diagnosis of urolithiasis by an experienced sonographer, and in some selected cases by spiral computed tomography. Sample size, according to the type of study and

considering the prevalence of 33% for hypercalciuria from a previous study (4) among children with renal stone with 95% confidence level (CI), and the accuracy of 9%, was determined to be 104 children. The patients were selected consecutively.

2-2. Characteristics

Demographic data (age and gender), family history of kidney stones, and clinical symptoms/signs of kidney stones were collected by interviewing the patient's parents and physical examination. All patients' random urine samples, preferably taken in the early morning, were checked for calcium, citrate, oxalate, uric acid and creatinine. Nitroprusside tests for detecting cystinuria, urinalysis and urine culture were also performed for all patients. The results of urinary metabolic tests were further interpreted by the treating physician and recorded in the questionnaire.

2-3. Laboratory test

Normal values of the random urine parameters were used in accordance with the approved nephrology texts to diagnose the patient's urine metabolic abnormality (14), which is summarized in **Table.1**.

Table-1: Random solute to creatinine ratio by age, n=104, (14).

Urinary solute	Age	Solute to creatinine ratio	
		mmol/mol	Mg/mg
Calcium	0-1 years	2.29	0.81
	1-2 years	1.58	0.56
	2-3 years	1.41	0.50
	3-5 years	1.16	0.41
	5-7 years	0.85	0.30
	7-10 years	0,.71	0.25
	10-17 years	0.68	0.24
Oxalate	< 6 months	0.37	0.29
	6 months-2 years	0.26	0.20
	> 2-5 years	0.14	0.11
	6-12 years	0.08	0.063
	> 18 years	0.04	0.031
Cystine	< 1 months	85	180
	1-6 months	53	112
	> months	18	38
Uric acid	< 12 months	1.5	2.2
	1-3 years	1.3	1.9
	3-5 years	1.0	1.5
	5-10 years	0.6	0.9
	< 10 years	0.4	0.6
Citrate	0-5 years	0.25	0.42
	> 5 years	0.15	0.25
Magnesium	0-1 years	2.2	0.48
	1-2 years	1.7	0.37
	2-3 years	1.6	0.34
	3-5 years	1.3	0.29
	5-7 years	1.0	0.21
	7-10 years	0.9	0.18
	10-14 years	0.7	0.15
	14-17 years	0.6	0.13

2-4. Criteria

The criteria for entering the study included a urolithiasis greater than 3 millimeters in diameter with the posterior shadow documented with ultrasonography, and in few cease with computed tomography (CT). In patients with urinary tract infections, metabolic examination was performed after treatment. Exclusion criteria included the patients who last the follow-up.

2-5. Ethics

The study protocol was registered and confirmed by the Ethics Committee of Kermanshah University of Medical Science (95452). The aims of the study were explained to the parents of the children and consent was obtained for obtaining urine samples.

2-6. Data analysis

Data obtained by data collection forms were entered into the SPSS software (version 19.0). Descriptive indices, including frequency and percentage, were used to describe qualitative variables. Chi-square test was used to investigate the presence of metabolic disorders in urine, and gender, age group, and family history of urinary tract stones. Statistical significance was considered as 5%.

3- RESULTS

A total number of 104 children (66 boys and 38 girls) were studied. Regarding age distribution, 70 of the children were younger than 12 months of age (67.3%), 19 (18.3%) were from 12 to 24 months and 15 (14.4%) were older than 2 years of age. In 68 of the children (65.4%), a family history of urolithiasis was present. The most common clinical findings included irritability (83 patients), dysuria (58 patients), flank pain (45 patients), and abdominal pain (36 patients), respectively. Urinary tract infection (17 patients) was found the least common (**Table. 2**). In 41 of the children (38.5 %), no abnormalities were found in the urine samples. However, in the remaining patients (63 children, 61.5%), at least one abnormal urine composition was detected. In 40 cases, only one urinary metabolic abnormality was observed (hypercalciuria in 14 cases, hyperuricosuria and hypocitraturia each in nine cases, hyperoxaluria in eight cases and cystinuria in one). A combination of two metabolic abnormalities was detected in 18 cases. In five cases, a combination of three abnormalities (hypercalciuria, hyperoxaluria, and hyperuricosuria) was observed. In total, there were 24 (23.1%) cases with a mixed metabolic abnormality (**Table. 3**).

Table-2: The frequency of demographic characters in 104 infants and children with urolithiasis, Kermanshah, western Iran 2018 (n=104).

Variables	Sub-group	No.	Percentage
Gender	Boy	66	63.5
	Girl	38	36.5
Age groups, Month	< 12	70	67.3
	12-24	19	18.3
	> 24	15	14.4
Family history of urolithiasis	Yes	68	65.4
	No	36	34.6

Table-3: The frequency of urinary metabolic abnormalities in 104 infants and children with urolithiasis, Kermanshah, western Iran 2018.

Variables		No.	Percentage
Clinical findings	Irritability	83	79.81
	Dysuria	58	55.77
	flank pain	45	43.27
	abdominal pain	36	34.61
	Urinary tract infection	17	16.35
Urinary metabolic abnormalities	Hypercalciuria	31	29.8
	Hyperuricosuria	27	26
	Hyperoxaluria	20	19.2
	Hypocitraturia	13	12.5
	Cystinuria	1	0.96
Num urinary metabolic abnormalities	Normal	40	38.5
	One abnormalities	40	38.5
	Multi abnormalities	24	23

Hyperuricosuria was more common in infants younger than 12 months (88.9%) compared to those older than one year (p= 0.018). Hypocitraturia was also significantly more common in children younger than 12 months (46.2%) in comparison with older groups (p= 0.03) (**Table.4**). In this study, a significant relationship was found between age and prevalence of urinary metabolic abnormality, which means that the prevalence of metabolic urinary abnormality in infants aged 12 to 24 months was lower than the other two groups (under one year and over two years) (**Table. 5**).

Table-4: Determining the relationship between gender, age, and family history with each of the urinary metabolic abnormalities.

Urinary metabolic abnormalities	Gender Number (%)		P-value	Age group, month Number (%)			P-value	Family history of urolithiasis Number (%)		P-value
	Boy	Girl		< 12	12-24	> 24		Yes	No	
Hypercalciuria	22 (71.0%)	9 (29.0%)	0.21	22 (71.0%)	4 (12.9%)	5 (16.1%)	0.65	24 (77.4%)	7 (22.6%)	0.07
Hyperuricosuria	15 (55.6%)	12 (44.4%)	0.22	24 (88.9%)	1 (3.7%)	2 (7.4%)	0.018	17 (63.0%)	10 (37.0%)	0.47
Hyperoxaluria	10 (50.0%)	10 (50.0%)	0.13	14 (70%)	2 (10.0%)	4 (20.0%)	0.48	11 (55.0%)	9 (45.0%)	0.20
Hypocitraturia	10 (76.9%)	3 (23.1%)	0.22	6 (46.2%)	2 (15.4%)	5 (38.5%)	0.003	8 (61.5%)	5 (38.5%)	0.49

Table-5: Determining the factors associated with urinary metabolic abnormality.

Variables	Sub-group	With urinary etabolic abnormality Number (%)	Without urinary metabolic abnormalit Number (%)	P-value
Gender	Boy	42 (56.6%)	24 (60.0%)	0.35
	Girl	22(34.4 %)	16 (40.0%)	
Age groups, month	< 12	44 (68.8%)	26 (65.0%)	0.011
	12-24	7 (10.9%)	12 (30.0%)	
	> 24	13 (20.3%)	2 (5.0%)	
Family history of urolithiasis	Yes	41 (64.1%)	27 (67.5%)	0.45
	No	23(35.9%)	13(32.5%)	

4- DISCUSSION

Urolithiasis is now a considerable problem in Iranian children. It might lead to significant kidney damage if left untreated, although the real incidence of this condition has not been identified in Iran. In this study, we aim to evaluate metabolic abnormality in western Iran, and compare the results with other domestic and foreign studies.

The metabolic abnormality was found in nearly two-thirds of patients. The mean age of patients in this study was 14.2 months, and 70% of children were younger than one year old. Factors such as climate, diet, and socioeconomics are responsible for the wide geographic variation in the age distribution in various studies (6, 11). We found urolithiasis more common in boys, with male to the female ratio of 1.7. Although most studies represented a male predominance in childhood nephrolithiasis (4, 8, 11), reports of sex predominance in pediatric nephrolithiasis vary (6). In eastern Iran, Naseri et al. reported a higher incidence of kidney stones in girls (8), while in a 2009 study in Turkey, it was represented almost equally in boys and girls (4). In this study, by evaluating first-degree relatives of the patients with nephrolithiasis, we found a 65.4% positive family history. This rate is higher than the reports from the northern and central regions of Iran (6, 13), considering that positive family history in children with kidney stones is 11.8% to 75% in various studies (6, 11, 2). The reasons for the high positive family cases in our study are attributed to the role of family and tribal marriages in this region, and also the influence of dietary habits and environmental factors. This issue is of special importance for metabolic studies in children with nephrolithiasis in western Iran. The identifiable signs and symptoms of childhood nephrolithiasis are different from those in adults, and the condition may be asymptomatic or nonspecific in infancy (9, 10, 11), making diagnosis difficult (2).

We found irritability as the most common, and urinary tract infections as the least common presenting symptom, which is different from other studies in Iran (6, 8, 13, 14). This can be attributed to the lower age of most patients in this study. In various studies, metabolic abnormality was reported to be between 30% and 90%, depending on the geographical region (3, 6- 8, 13, 14). We documented metabolic abnormality in 61.5% of our patients, and 23.1% had a mixed abnormality. **Table.6** shows a comparison of the results of this study with various other studies.

Table -6: Comparison of the results of current study with various other studies in different countries.

Authore, Year, Reference	Country	Percentage metabolic abnormality
Elmaci et al., 2014 (2)	Turkey	83.2
Rizivi et al., 2007 (7)	Pakistan	87
Reddy gouru et al., 2015 (7)	India	90
Alpay et al., 2009 (4)	Turkey	87
Zubi et al., 2017 (11)	Canada	55
Yang et al .2017 (3)	China	97.5
Naseri et al., 2010 (8)	Iran	42.5
Mohamadjafari et al., 2014 (14)	Iran	35.1
Akhavan et al., 2017 (13)	Iran	92
Safaei et al., 2011 (6)	Iran	42.5
Tohidi et al (current study), 2018	Iran	61.5

According to the results of the present study, hypercalciuria is the most common urinary metabolic abnormality, followed by hyperuricosuria, hyperoxaluria, hypocitraturia and cystinuria. Moreover, more than one-third of patients did not have any urinary abnormalities. Apart from the association between age and urinary metabolic disorder, our findings showed a lower prevalence of urinary metabolic disorders in the 12 to 24 months age group. Nevertheless, gender and family history of urinary stones did not show a significant association with metabolic abnormality or any of its subtypes. There have been previous reports from other areas of Iran regarding metabolic risk factors in pediatric urolithiasis. For instance, in a study in northern Iran (14), 35% of children had the metabolic risk factor. This is much lower than the 61.5% which we observed in our study. However, the authors of the mentioned study (14) found other etiologies, including urinary tract infection in 10% and obstructive causes in about 4% of the studied cases. Similar to our findings, hypercalciuria, detected in 25% of the patients, was the most prevalent metabolic urinary abnormality (14).

However, (hypercalciuria was our most common finding) in another study from the central parts of Iran, hypocitraturia was the most prevalent urinary metabolic abnormality, detected in 56% of the patients (13). In our study, hypocitraturia was significantly more common in children younger than 12 months (46.2%) in comparison to older groups. Age distribution and geographical region are important factors to be considered. In the study in the central part of Iran (13), more than three-fourth of the patients were older than one year; however, in the current study, only about one-third of the patients were older than a year. Several studies have been conducted in the neighboring country of Turkey with varying results. In one study, including 162 children with urolithiasis (4), metabolic urinary abnormality was reported in 87% of the patients, which is much higher than what we found in the current study. Similar to our findings, hypercalciuria (found in 33.8% of the patients) was the most common metabolic condition. However, hypocitraturia was also a common finding which was similar in prevalence to hypercalciuria, detected in 33.1% of the patients. This is not in agreement with our findings that hypocitraturia and cystinuria were the least common, detected in only 12.5% and 0.19% of the patients.

This difference may, at least partly, be due to the difference in normal laboratory reference values. In a separate study conducted in Turkey on 143 children aged 2 to 6 years (2), about 83% of the patients had metabolic urinary abnormalities, and only 20% of the patients had hypercalciuria; while hypocitraturia and hyperuricosuria were detected in more than 20% of the patients (in 23.8% and 24.5% of the cases, respectively). As observed, age is an issue here too: the patients in Turkish study were older (2) (with the mean age of 3.7 years) compared to our patients who were mostly younger than one year old. There is evidence from other studies conducted in Turkey, that hypocitraturia was found the most common abnormality (9, 15) overall, but hypercalciuria was the most prevalent in those younger than 12 months of age (9).

In another study, this time in Canada, metabolic abnormality was detected in 55% of patients with hypercalciuria as the most common (11). Finally, in a 2017 study in China, the prevalence of metabolic abnormality in childhood nephrolithiasis was reported to be about 97.5%. Hypocitraturia has been shown as a major risk factor for stone formation; but, unlike our study and many other studies in other countries, the prevalence of cystinuria in Chinese children is much

higher than previous reports (48.7%), which can be attributed to a heterozygote genetic disorder in Chinese population (3). Another important factor in children with kidney stones is the patient's hydration status (1, 2, 16). In fact, most studies suggest the use of adequate liquids as the most important prevention and the primary treatment for kidney stones (17, 18). Increased fluid intake and proper hydration are essential for all children with nephrolithiasis. However, compliance with increased fluid intake, especially in younger infants, is not easy (2, 19).

Therefore, our first advice to all the parents of children with nephrolithiasis is increasing their fluid intake, which in turn increases the production of more dilute urine. Considering these findings, it appears that the metabolic urinary abnormality pattern may be different depending on geographic region and age groups. In our opinion, longitudinal cohort studies are required to follow the infant patients diagnosed with urolithiasis over time to find any changes in the trend of metabolic abnormalities.

4-1. Limitations of the study

The current study had some limitations including a relatively small number of patients and a short follow-up period. We were, therefore, unable to follow the patients to report the evolution of the stones and their composition in case of surgical treatment). Body weight and body mass index (BMI) had also been reported in some studies (16) to have a contributing role in metabolic disorders, which we likewise were unable to document. Other limitations included the impossibility of 24-hour urine collection for all patients, and most importantly, lack of the standard reference values for metabolic abnormality of urine in Iranian children.

5- CONCLUSION

Our results show a higher prevalence of metabolic urinary disorders in the west of Iran compared to the eastern regions, but lower than the prevalence of metabolic disorders in the central regions of the country and the eastern (India and Pakistan) and western (Turkey) neighboring countries. In this study, hypercalciuria was found to be the most common metabolic abnormality in the urine. We also considered age and geographical region as the two factors influencing the prevalence and type of urinary metabolic abnormality in different regions. In childhood nephrolithiasis, however, since no metabolic disorders have been found in more than a third of patients, the role of other variables like nutritional and climatic factors in the development of childhood nephrolithiasis should be considered.

6- CONFLICT OF INTEREST: None.

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