Predisposing Factors for Infantile Urinary Calculus in South-West of Iran

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Introduction. Urinary calculi in infants are relatively infrequent, but their incidence has increased in the recent decades. The aim of this study was to investigate the clinical presentation, metabolic risk factors, and urinary tract abnormalities in infants suffering from kidney calculus.

Materials and Methods. A total of 152 infants were admitted between 2009 and 2012 with ultrasonography-proven urolithiasis. A Foley catheter was fixed and 24-hour urine samples were analyzed for calcium, citrate, oxalate, uric acid, and magnesium. For detecting cystinuria, qualitative measurement of urinary cystine was done by nitroprusside test. Urinary tract structural abnormalities were also evaluated.

Results. The mean age at the diagnosis of kidney calculus was 5.46 months (range, 15 days to 12 months). The most common clinical findings were restlessness and urinary tract infection. A family history of calculi was found in 67.1% of the patients and 68.4% were born to consanguineous marriages. Metabolic abnormalities and urinary tract abnormalities were found in 96.1% and 15.1% of children, respectively. Urinary tract abnormalities were more common in girls. The most common metabolic risk factors were hypercalciuria (79.6%) and hypocitraturia (40.9%). Hyperoxaluria and hypomagnesuria were found in about 28% of patients, both of which were associated with bilateral urolithiasis.

Conclusions. These findings show that urinary metabolic abnormalities are very common in infants with urolithiasis. Appropriate evaluation of urinary metabolic parameters can lead us to proper diagnosis and treatment.

INTRODUCTION

Urinary calculi in infants are relatively infrequent, but its incidence has increased in the recent decades.[1] This may be due to increased awareness to this entity or routine use of ultrasonography examination in children presented with specific or nonspecific symptoms for urinary calculus. The knowledge of the pathophysiology of urinary calculus in children has increased in the recent years. Predisposing factors for urinary calculus in childhood are multifactorial, including genetic inheritance, nutrition, metabolic abnormalities, environmental factors, infectious causes, and urinary tract abnormalities.[2] Most children with urinary calculi have an underlying metabolic abnormality, including hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria,

and cystinuria.[3,4]

There are ample data about urinary calculus in children,[5-8] but there have been few studies specifically on metabolic risk factors in infants.[9-11] All previous studies in infants have been based on biochemical tests on a random urine sample that is an alternative method instead of standard 24-hour urine collection. The aim of the present study was to evaluate the clinical presentation, metabolic risk factors, and urinary tract abnormalities of infants suffering from urinary calculi in the south-west of Iran.

MATERIALS AND METHODS

This study was carried out on 152 infants with urinary calculus admitted to Abuzar Children Hospital, the main referral center for sick children in Ahvaz, south-west of Iran. Recruitment was between July 2009 and March 2012. The study protocol was approved by the ethics committee of the Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences. Infants (younger than 12 month old) were enrolled when the calculus was diagnosed by a renal ultrasonography or spontaneous passage. The definition of urinary calculus was based on the presence of highly echogenic focus ($\geq$1mm) with posterior acoustic shadowing of the calculus. Infants with kidney failure and genitourinary anomalies and those who were taking drugs that could affect mineral metabolism (corticosteroids, diuretics, and anticonvulsants) were excluded.

Data of the patients was recorded for sex, age, consanguinity marriage of parents, family history of urinary calculus, and presenting symptoms. In all of the patients, urine culture was done. In patients with urinary tract infection (UTI), all studies were postponed to recover after infection. The urinary tract was initially evaluated for structural abnormalities by renal ultrasonography. Renal scintigraphy using dimercaptosuccinic acid, voiding cystourethrography, and intravenous pyelography were performed, as indicated. The calculus diameter and its location were determined by ultrasonography.

A Foley catheter was fixed and 24-hour urine samples were measured for urine volume and analyzed for calcium, citrate, oxalate, phosphate, uric acid, and magnesium. Blood samples were analyzed for venous blood gas and serum creatinine, urea, calcium, phosphorus, sodium, potassium, alkaline phosphatase, and parathyroid hormone. Abnormal values for urine constituents were defined as follows: hypercalciuria, >4 mg/kg/d; hyperoxaluria, >50 mg/1.73 m^2 body surface area per day; hypocitraturia, < 320 mg/1.73 m^2 per day; hypomagnesuria, < 1.24 mg/kg/d; hyperuricosuria, >815 mg/1.73 m^2 per day (Table 1).[12-15] For detecting cystinuria, qualitative measurement of urinary cystine was done by nitroprusside test.

Continuous variables were expressed as mean ± standard deviation and the discrete variables were expressed as percentage. The chi-square test and the Fisher exact test were used to examine the significance of difference between the proportions (nominal data) and the Student t test to find out the significance of difference between the means (numerical data). A P value less than .05 was considered significant.

RESULTS

The participants consisted of 152 infants with kidney calculi, of whom 89 (58.6%) were boys (girl-boy ratio,1:1.4). The average age of the infants was 5.46 ± 3.06 months (range, 15 days to 12 months). Family history of kidney calculi was found in 67.1% of patients, 68.4% of whom were born from consanguineous marriages and 31.6% were of second-rate family.

Restlessness (56.3%) and UTI (30.9%) were the most frequent presenting symptoms. Other presenting symptoms included hematuria, fever, nausea and vomiting, failure to thrive, bad smelling of urine, poor feeding, diarrhea, and calculus drop. Moreover, 1 patient was diagnosed prenatally.

The calculi were detected incidentally in 40.3% of patients. They were located in the right and

**Table 1.** Characteristics of Infants With Kidney Calculus*

Characteristic	Boys	Girls	All Patients
Mean age at diagnosis, mo	5.24	5.77	5.46
Family history of calculus	70.9	61.7	67.1
Consanguinity marriage	31.7	31.4	31.6
Presenting symptoms			
Metabolic abnormalities	93.3	100	96.1
Restlessness	67.4	52.1	56.3
Urinary tract infection	18.5	48.3	30.9
Renal tubular acidosis	15.3	17.7	16.2
Structural abnormalities	6.7	27	15.1
Without risk factor	6.7	0	3.9
None (incidental finding)	43.5	35.8	40.3

*Values are percentages, except for mean age.

left kidney in 23% and 35.2% of the infants, respectively, and bilateral calculi were found in 41.8%. The mean calculus diameter was 3.8 mm (range, 1mm to 13mm).

Urinary tract abnormalities were diagnosed in 15.1% of patients, which were significantly more common in girls (P = .001). These structural abnormalities included hydronephrosis, ureteropelvic junction stenosis, and vesicoureteral reflux. All of these patients had metabolic abnormalities, too.Metabolic abnormalities were found in 96.1% of the children; however, no predisposing factor was observed in 3.9% (Table 1).

The most common risk factors were hypercalciuria and hypocitraturia (Table 2). Hypercalciuria was found in 79.6% of patients, of whom 44% were boys. The mean 24-hour calcium excretion was 7.06 ± 4.46 mg/kg/d. Renal tubular acidosis was found in 16.2% of the infants with hypercalciuria. In all cases, serum calcium and alkaline phosphatase was normal. The mean 24-hour calcium excretion showed a positive correlation with the mean of urine volume (P<.001), hyperuricosuria (P = .002), and it was significantly lower in cases with hypocitraturia (P = .002). Uric acid hyperexcretion was detected in 23% of the infants, who had hypercalciuria (P < .001; Figure). Renal tubular acidosis was found in 29.4% of these patients (P = .02). Hypocitraturia was found in 40.9% of the cases, of which 55.9% were boys. Hypocitraturia was significantly more common in hypercalciuric infants and those with normal uric acid excretion (69.4%, P =.002 and 77.4%, P = .02, respectively). Hyperoxaluria and hypomagnesuria were found in 28% of the patients and both of them were significantly associated with bilateral urolithiasis (P = .006 and P =.005, respectively). Cystinuria was detected in 3.3% of the patients, of which 60% were bilateral.
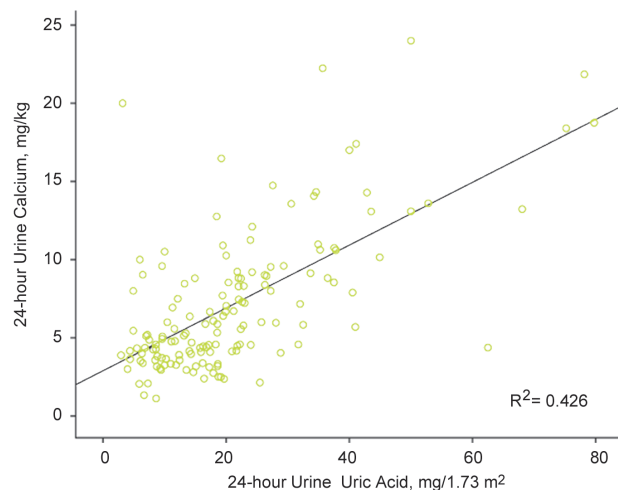
Correlation between hypercalciuria and hyperuricosuria.

DISCUSSION

Infantile nephrolithiasis is not a rare situation in Iran, and the diagnosis of small calculi by well-improved pediatric ultrasonography has been increasing in the recent years. This study presented metabolic risk factors, anatomic abnormalities, clinical presentation, and familial history of infants with urinary calculi in south-west of Iran. There are several studies on urinary calculi which include children younger than 1 year. Some of them have been produced in Turkey, Armenia, the United Kingdom, Iceland, Iran, Iraq, and Italy.[9,10,16-21]. However, metabolic risk factors were evaluated in this study by using 24-hour urine collection that is more reliable than random urine examination.

The frequency of metabolic abnormalities varies from 15% to 90% of cases in the literature [14,22-24]. In the present study, 96.1% of the infants had metabolic abnormalities. Hypercalciuria (79.6%) was the most frequent metabolic abnormality. This result is similar to most previous studies focusing on pediatric patients and infants.[7,8,10,12,25,26] The second most

Table 2. Metabolic Risk Factors in Infants With Kidney Calculus and Their Subgroups

Risk Factor	Overall Percentage	Boys		Parents With Consanguineous Marriages		Family History of Calculus		Bilateral Calculi	
		Percentage	P	Percentage	P	Percentage	P	Percentage	P
Hypercalciuria	79.6	55.4	.11	66.3	.60	68.9	.33	41.3	.80
Hypocitraturia	40.9	58.9	.69	76.5	.45	70.6	.82	34.8	.27
Hyperoxaluria	28.6	60.0	.66	60.0	.55	67.6	.68	61.8	.006
Hyperuricosuria	23.0	54.3	.55	68.4	.75	74.3	.30	46.9	.49
Hypomagnesuria	28.0	60.6	.68	60.0	.39	64.5	.64	65.4	.005
Cystinuria	3.3	80.0	.31	75.0	.87	60.0	.54	60.0	.32

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frequent metabolic abnormality was hypocitraturia, which was found in 40.9% of the infants. Similar to this study, Acar and colleagues and Alpay and coworkers showed that hypocitraturia was the second important risk factor.[24,27] However, low urinary citrate excretion had been reported as the most frequent metabolic abnormalities in children with urinary calculi in some studies.[1,28] In this study, concurrent hypercalciuria and hypocitraturia were found in 20.4% of the infants. Bastug and colleagues proposed that the most common underlying metabolic abnormality in infants with urinary calculi was hyperuricosuria (56%).[9] In other studies, uric acid hyperexcretionwas detected in 10.6% to 54% of the children.[8,24-26] In the present report, however, hyperuricosuria was detected in 23% of the infants.

Urinary tract abnormalities have been considered as a predisposing factor for the formation of kidney calculi that promoted crystal retention and calculus formation with urinary stasis.[22] In the present study, urinary tract abnormalities were detected in 15.4% of the infants. In other studies, it has been reported that about 10% to 19% of the children with calculi had an abnormality of the urinary tract.[9,18,19,26,29]

The previous studies on kidney calculi in infants have revealed boy preponderance, with the ratio varying from 1:1 to 4:1,[9,10,25,30-32] and in some reports of pediatrics, boys and girls were affected equally.[18,33] In this study, the boy-to-girl ratio was 1.41:1.In addition, all metabolic abnormalities were more common in the boys; however, this difference was not significant.

Urinary calculi can occur in all ages. In this study, the average age of diagnosis was 5.46 months with a range of 15 days to 12 months, 69.7% of whom were younger than 6 months. The family history of urinary calculus and consanguineous marriages may increase the expectation of genetic forms of metabolic abnormalities. In this study, parents of 68.4% of the infants had consanguineous marriage (including 31.6% second-rate family). In 2 studies from Turkey, 27% and 14% of patients were born from consanguineous marriages.[10,30] Positive family history was detected in 67.1% of our patients. In 2 reports of pediatric surgeons, positive family history in children with kidney calculi was 11.8% and 22%,[19,34] and different rates were reported in Argentina (78.7%), Italy (69% to 78%), Turkey (63.5%), and the United Kingdom (33%).[7,9,17,35]

In the present study, restlessness and UTI were most common clinical presentations. In similar studies on infantile urolithiasis, UTI and restlessness were the major clinical symptoms.[9,10] Restlessness could be the clinical reflection of colicky pain in infants. In other studies focusing on children, not specifically infant, UTI (especially in girls) and restlessness were also the most frequent presenting symptoms.[7,8,24,32]

CONCLUSIONS

The most common urine metabolic risk factors in infants with urinary calculi are hypercalciuria and hypocitraturia. Furthermore, when an infant is presented with nonspecific symptoms for kidney calculus, such as restlessness or UTI, a renal ultrasonography could be performed for detecting nephrolithiasis. However, if the kidney calculus is diagnosed, measurement of urinary metabolic risk factors by evaluation of 24-hour urine collection can lead us to proper diagnosis and treatment.

CONFLICT OF INTEREST

None declared.

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