Urolithiasis in the First 2 Months of Life

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Introduction. There is limited data about urolithiasis in young infants. We reviewed clinical, imaging, and biochemical data of urolithiasis in the first 2 months of life.

Materials and Methods. In an 11-year period, 77 of the 1172 children diagnosed with urolithiasis (6.8%) were 60 days old and younger (64.9% boys and 35.1% girls). Routine diagnostic assessments included urinalysis and urine culture; measurement of calcium, uric acid, oxalate, and creatinine in nonfasting random urine; measurement of blood urea nitrogen and serum creatinine, sodium, potassium, calcium, and phosphorus levels; and venous blood gasometry. Urinary calculi were diagnosed using tridimensional ultrasonography with 5-MHz, 7.5-Mhz, and 10-MHz probes.

Results. The most common symptom was irritability (37.6%). A family history of urinary calculi was documented in 49.4% of the patients. The calculi were 0.5 mm to 6 mm in length. Eight infants (10.4%) had urinary tract infection. Hypercalciuria was found in 21 of 62 patients (33.8%). There were no cases of hyperuricosuria, hyperoxaluria, or struvite calculus. Vesicoureteral reflux was reported in 9 of 20 patients who underwent voiding cystourethrography. Two-thirds of asymptomatic and 85% of symptomatic infants were diagnosed during summer and autumn, and the peaks of calculus visits were in September, October, and November. Of 43 infants (55.8%) who were followed up (Mean, 16.2 ± 15.2 months), none needed calculus removal interventions.

Conclusions. Hypercalciuria is the most common urinary metabolic abnormality in young infants with urinary calculus. Infection was not an important factor for our cohort in the pathogenesis of the disease.

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INTRODUCTION

Data on urolithiasis in infancy are limited.[1] Infantile urolithiasis represents 20% of the total pediatric urolithiasis research in the literature.[2] The incidence of pediatric urolithiasis in the age group of children younger than 2 years is more than 20%,[3] which is rising all around the world.[4] Urolithiasis in infants can cause considerable morbidity.[5] It accounts for 1 in 1000 to 7600 of hospital admissions.[6,7] Based on the literature, no extended study has not been reported defining the prevalence of urolithiasis in infants younger than 2 months. This study presents a retrospective review of clinical, imaging, and biochemical details of 77 young infants (≤ 2 months) with urinary tract calculi who were evaluated and followed up during an 11-year period.

MATERIALS AND METHODS

Study Population

From October 2002 to 2013, a total of 1172 children with urolithiasis were evaluated by the nephrology clinic of a tertiary academic health center. Stone disease was diagnosed by tridimensional kidney-

bladder ultrasonography using 5-MHz, 7.5-MHz, and 10-MHz probes. In the majority of cases, the diagnosis of urinary calculi was confirmed by performing at least two ultrasonography one of which done by an expert radiologist in the field of pediatric sonography. Metabolic evaluations were done, including urinalysis; urine culture; measurement of calcium, uric acid, oxalate, and creatinine concentrations in nonfasting random urine; measurement of blood urea nitrogen and serum levels of creatinine, uric acid, sodium, potassium, calcium, and phosphorous; and venous blood gasometry in all cases. However, serum uric acid, venous blood gasometry, and urine oxalate and calcium results were available in 58 (75.3%), 65 (84.4%), 51 (66.2%), and 62 (80.5%) infants, respectively. Urinalysis was performed in all, but urine culture was obtained and recorded in 62 (80.5%) patients since urinalysis was normal at presentation. Serum magnesium and cyanide-nitroprusside test (CNT) were assessed for 27 (35.1%) and 47 (61%) patients, respectively.

Standard definitions were used to detect urinary metabolic abnormalities (Table 1).[8] Normal and abnormal serum levels of calcium, magnesium, and uric acid were defined based on the types of laboratory kits which were applied. All children aged 2 months and less (77 infants; 6.8%) were enrolled in this retrospective study without considering any exclusion criteria. Data on underlying diseases such as chronic diarrhea and administration of medications that predispose stone formation (such as furosemide) were collected.

Screening for Urological Anomalies

Urinary tract anomalies including vesicoureteral reflux and obstructive uropathies such as ureteropelvic junction obstruction account for stone formation.[9] Imaging studies for detecting urological anomalies were undertaken for patients with high-risk conditions such as hydronephrosis, dilated ureter, or hydroureteronephrosis not proportionate to calculus sizes or in the kidney-ureter unit with no calculus. In addition, voiding cystourethrography was done in case of urinary tract infection (UTI) or postnatal follow-up of abnormal prenatal ultrasonography. Diethylene triamine pentaacetic acid renal scintigrpahy was done in infants suspected to have anatomical obstructive uropathies (ureteropelvic junction obstruction or ureterovesical junction obstruction).

Treatment and Follow-up

Treatment included encouraging mothers to increase the number of feedings of their babies, using liquids such as water in the intervals between feeding, and keeping infants in cool temperature, especially in summer. Polycitra-potassium solution was recommended in symptomatic cases, asymptomatic patients with a calculus size of 3 mm and larger (nephrolithiasis), and those with multiple microlithiasis (calculi < 3 mm). Oral alkali was recommended at a dose of 1 mL/kg in divided doses, which was gradually adjusted to reach a urinary pH of 6.5. In hypercalciuric cases, hydrochlorothiazide, 1 mg/kg to 1.5 mg/kg was added to alkali treatment, however it was reported that low dose of the drug was also effective in controlling hypercalciuria.[10]

In patients with a positive CNT, higher doses of alkali were recommended to reach a urinary pH of 7 to 7.5. As the measurement of random urine cysteine was not available and the diagnosis of cystinuria was not confirmed in those with a positive CNT,

Table 1. Definitions Used in the Study

Condition	Definition
Hypercalciuria[9]	Urine calcium-creatinien ratio ≥ 0.8 mg/mg
Hyperoxaluria[9]	Uirne oxalate-creatinine ratio > 0.26 mmol/ mmol
Hyperuricosuria[9]	Urinary uric acid excretion > 3.3 mg/dL glomerular filtration rate
Borderline serum calcium	Serum calcium level of 10.21 mg/dL to10.99 mg/dL
Hypercalcemia	Serum calcium level ≥ 11 mg/dL
Hypomagnesaemia	Serum magnesium level < 1.2 mg/dL in neonates and < 1.5 mg/dL in infants
Hypermagnesemia	Serum magnesium level > 2.6 mg/dL in neonates and > 2.3 mg/dL in infants
Hypouricemia	Serum uric acid levels < 3.6 mg/dL in boys and < 2.3 mg/dL in girls
Hyperuricemia	Serum uric acid levels > 8.2 mg/dL in boys and > 6.1 mg/dL in girls
Microlithiasis	Calculus size < 3 mm
Nephrolithiasis	Calculus size ≥ 3 mm

cystine chelators were not recommended. According to the severity of clinical symptoms and sizes of the calculi, the patients were followed every 1 to 3 months by ultrasonography and urinalysis, and in hypercalciuric patients, measurement of urinary claclium-creatinine ratio in random nonfasting urine to evaluate the response to treatment, adequacy of alkali therapy, and resolution of hypercalciuria, respectively. Treatment with oral alkali was recommended until patients reached the stone-free condition or had single microlithiasis (calculus < 3 mm) with no special symptom.

Statistical Analyses

The chi-square and independent *t* tests were used for comparisons of variables in normocalciuric versus hypercalciuric patients. The 1-way analysis of variance test was used to compare variables in different seasons. *P* values less than .05 were considered significant.

RESULTS

The enrolled infants included 75 term (97.4%) and 2 preterm infants (2.6%), aged 4 to 60 days (mean, 43.18 ± 16.7 days). Fifteen children (19.5%) were 28 days old or younger. They were 50 boys (64.9%) and 27 girls (35.1%; male-female ratio, 1.85). The types of feeding were breast milk for 36 (46.8 %), formula for 5 (6.5%), and both for 11 (14.3%). The type of feeding was not recorded in 25 charts (32.5%). A family history of urinary calculus was positive in 38 (49.4%) patients, and in 16 (20.7%), the parents were not sure about the family history. No documented history of furosemide administration was presented. One patient had severe gastroesophageal reflux and chronic dehydration with mixed alkalosis. It was not clear whether chronic dehydration and alkaline blood pH were triggering factors for stone formation or no.

Table 2 illustrates main symptoms at presentation. Urinalysis was normal in the majority of patients (54 cases; 70.1%). Random nonfasting urinary pH and specific gravity at presentation were 6.34 ± 1.16 and 1011.0 ± 7.9, respectively. Eight infants (10.4%) had UTI at presentation, but no case of infection with urease-positive bacteria was reported. All of those who presented with UTI received ceftriaxone (age > 1 month) or cefotoxime (age ≤ 1 month) for treatment of infection. A diagnosis of calculus had been made before antibiotic initiation in all of the infants.

Table 2. Clinical Manifestations in 77 Infants With Urinary Calculus

Main Clinical Manifestations at Presentation	Number of Patients (%)
Irritability	28 (36.4)
Asymptomatic*	15 (19.5)
Vomiting	12 (15.6)
Dysuria	11 (14.3)
Urinary tract infection	6 (7.8)
Urine discoloration	6 (7.8)
Straining	5 (6.5)
Failure to thrive	2 (2.6)
Acute kidney failure	2 (2.6)
Spontaneous stone passage	2 (2.6)
Interrupted voiding	2 (2.6)
Cyanosis when voiding	2 (2.6)
Gross hematuria	1 (1.3)
Distended abdomen (due to bladder distension)	1 (1.3)
Decreased urine volume	1 (1.3)

*Ultrasonography was requested mainly for postnatal follow-up of prenatal hydronephrosis.

Microlithiasis and nephrolithiasis were found in 58 (75.3%) and 19 (24.7%), respectively. The urinary calculi were unilateral in 36 patients (46.8%) and mainly were located in the left kidney (n = 26; 33.8%). The locations of the calculi were the kidney (renal calyces with or without renal pelvises). Vesicoureteral reflux was reported in 10 kidney-ureter units of 9 of 20 infants (45%) who had the criteria for undergoing voiding cystourethrography. The grades of vesicoureteral reflux were 2 in 6 units, 3 in 3 units, and 5 in 1 unit. Diuretic renography was done in 3 infants which were reported normal.

Table 3 illustrates a summary of details of the enrolled patients by the presence of hypercalciuria, which was found in 21 of 62 infants (33.8%). Hypercalcemic hypercalciuria (urine calcium-creatinine ratio ≥ 1.15) was noted in 1 patient (1.3%). In this patient, serum phosphorus and alkaline phosphates levels were in reference ranges and serum parathyroid hormone level had not been checked because of the short follow-up. The other 20 patients had normocalcemic hypercalciuria. In the normocalciuric group (41 infants), normal and borderline serum calcium levels (borderline range, 10.4 mg/dL to 10.9 mg/dL) were found in 36 (87.8%) and 5 (12.2%), respectively. Urine specific gravity at presentation was significantly higher in the normocalciuric group as compared

Table 3. Characteristic of 77 Infants With Urinary Calculus Hypercalciuria*

Characteristics	All	Hypercalciuria		*P*
		Yes	No	
Age, d	43.2 ± 16.7	44.0 ± 16.7	43.0 ± 18.2	.83
Sex				
Male	50	12	25	
Female	27	9	16	.77
Urine calcium-creatinine, mg/mg	0.65 ± 0.49	1.23 ± 0.36	0.35 ± 0.18	.09
Urinary uric acid excretion, mg/dL GFR	0.49 ± 0.29	0.53 ± 0.32	0.45 ± 0.27	.15
Urine oxalate-creatinine, mmol /mmol	0.04 ± 0.03	0.04 ± 0.02	0.04 ± 0.03	.63
Number of calculi	4.1 ± 2.0	3.9 ± 2.0	4.5 ± 2.0	.26
Maximum calculus size, mm	2.3 ± 1.4	2.4 ± 1.5	2.5 ± 1.4	.97
Nonfasting urine pH at presentation	6.3 ± 1.2	6.5 ± 1.1	6.2 ± 1.1	.40
Nonfasting urine specific gravity at presentation	1011 ± 8	1007 ± 4	1012 ± 9	.049

*Values are presented as number (%) or mean ± standard deviation. GFR indicates glomerular filtration rate.

to the hypercalciuric group (P = .049; Table 3).

Microlithiasis and nephrolithiasis were found in 16 (76.2%) and 5 (23.8%) patients with hypercalciuria, and there was no case of nephrocalcinosis. Biochemical evaluations in hypercalciuric patients were not remarkable in 16 patients (76.2%), while they showed metabolic acidosis with alkaline urine pH in 1 (4.8%), hypourecemia in 2 (9.5%), hypomagnesaemia in 1 (4.8%), hypokalemia in 1 (4.8%), and hypercalcemia in 1 (4.8%). Biochemical evaluations were unremarkable in 76.2% of the hypercalcuric infants, which indicated idiopathic hypercalcuria.

Hyperuricosuria and hyperoxaluria were not found in any of the patients. A positive CNT was reported in 4 of 47 infants (8.5%). Abnormal acid-base status was found in 4 patients, including metabolic acidosis and mixed alkalosis each in 2 cases. Serum magnesium levels were low in 1 of 27 patients (35%) and high in another one. Hypouricemia was found in 12 of 58 patients (20.7%). One patient had transient hyperuricemia (serum uric acid level, 10.7 mg/dL), which returned to normal levels without any treatment. The etiology of transient hyperuricemia was unknown.

The highest frequency of calculus diagnosis was observed in late summer and early autumn. In the 15 asymptomatic patients, the disease was diagnosed in the spring, summer, autumn, and winter in 3 (20%), 4 (26.7 %), 6 (40%) and 2 (3.3%), respectively. Two-thirds of asymptomatic patients and 85% of symptomatic ones were detected in the summer and autumn seasons. The number and maximum sizes of the calculi, random nonfasting urine pH and specific gravity and urine calcium-creatinine ratio in different seasons were compared between the seasons of diagnosis (Table 4). Urine pH was significantly lower in the winter (P = .042).

Forty-three patients (55.8%) were followed up at least for 1 to 56 months (mean, 16.2 ± 15.2 months). At the end of the follow-up, 25 patients (58.1%) reached a stone-free condition and 13 (30.2%) had active calculus disease characterized by stone formation in 9 (20.9%) and increased calculus sizes in 4 (9.3%). The calculus sizes were decreased during the follow-up in 14 infants (32.5%), whereas no changes were reported in 2 (4.6%). None of the patients needed nonmedical interventions for calculus removal.

DISCUSSION

Whereas it is rare in North American newborn

Table 4. Characteristics of Calculi and Urine Parameters by Season*

Variable	Spring	Summer	Autumn	Winter	*P*
Number of calculi	4.09 ± 2.30	4.30 ± 1.90	4.03 ± 2.10	4.42 ± 1.90	.93
Maximum calculus size, mm	2.77 ± 1.87	2.15 ± 1.22	2.21 ± 1.19	2.38 ± 1.58	.64
Nonfasting urine pH at presentation	6.85 ± 1.46	6.66 ± 0.99	6.32 ± 1.16	5.44 ± 0.72	.04
Nonfasting urine specific gravity at presentation	1016 ± 10	1009 ± 6	1009 ± 8	1015 ± 8	.10
Urine calcium-creatinine, mg/mg	0.75 ± 0.71	0.52 ± 0.32	0.67 ± 0.47	0.73 ± 0.57	.57

*Values are presented as mean ± standard deviation.

infants and children,[11,12] in countries where childhood urolithisis is endemic, urinary calculus in infants is not a very rare situation.[13] Association of hypercalciuria with hypervitaminosis D in infants has been reported.[14] Restlessness and vomiting have been reported as the most common symptoms of urolithiasis in infants.[15] Majority of our patients presented with irritability, and in contrast to some studies on children and infants with urolithiasis,[16,17] UTI was not a common presentation in our series.

In pediatric populations, mostly girls are affected by urinary calculus,[4,15] while publications on urolithiasis in infants have reported a male preponderance[1,13,18]; we noted a finding similar to that in the current study. In childhood urinary calculus disease, hypercalciuric stone formers are more frequently girls,[19] while the current study revealed that hypercalciuria is more prevalent in boys up to the age of 2 months. In addition, similar to our report, Alpay ad coworkers[8] reported a positive family history of urinary calculus in about half of infantile urolithiasis cases.

Among pediatric stone formers, younger patients are more likely to have an identifiable metabolic risk factor.[4] Güven and colleagues[1] identified at least 1 metabolic abnormality in 46% of their patients. Although CNT was positive in 8.5% of cases, we did not have any confirmed case of cystinuria. This test is a reliable and useful method for screening of cystinuria, but false positive and negative results exist that decrease the sensitivity.[20,21] Metabolic abnormalities, urological anomalies, and infectious calculi have been determined in 43%, 8 %, and 2% of cases, respectively.[15] Comparing with our current study, it seems that association of urolithiasis with hypercalciuria and urological anomalies are more common in the first 2 months of life than older childhood ages. Hypercalciuria has been considered as the most common metabolic abnormality in pediatric stone formers,[22-24] whereas a review study in Asian pediatric stone formers revealed hypocitraturia as the main metabolic abnormality (68.2% of cases).[23] We had not measured urinary citrate excretion in our patients.

Although in our patients, urinary calculi were not available for analysis, available evidence including absence of infection with urease-positive microorganisms, course of disease, and response to alkali treatment can help us to rule out presence of some types of urinary calculi, mainly struvite calculi. Higher urinary pH in children compared to adults may be a reason as to why younger patients form more calcium-based and fewer uric acid calculi.[4] Concentrated urine, low urine pH and high calcium, sodium, oxalate, and urate levels are known promoting factors which accelerate calcium oxalate stone formation.[11] Urine specific gravity in neonates and infants is usually within a narrow range of 1.002 to 1.004 and 1.002 to 1.006, respectively.[25] In our patients, it was 1011.0 ± 7.9 (range, 1003.1 to 1018.9), which presents a concentrated urine for infants. In our normocalciuric group, since urine specific gravity at presentation was significantly higher than hypercalciuric cases, it seemed to be the main predisposing factor for stone formation. An indirect relationship between pH and age in pediatric patients has been suggested. Defoor and colleagues reported a mean urine pH of 6.44 for children versus 6.05 for adults (P = .001).[26] The pH of urine is normally varying between 4.4 and 8. Uric acid and cysteine calculi are formed in acidic urine, while calcium oxalate calculi can be formed with acidic, neutral, and alkaline pH.[25] The mean urine pH in our enrolled infants was 6.34 ± 1.16, and it was significantly lower in those who were diagnosed in the winter. Despite lower pH at winter, the highest frequency of calculus diagnosis was observed in late summer and early autumn.

The risk of kidney calculi greatly increases in summer months.[27] In adults, renal colic visits is significantly higher in June, July, and August as compared with December, January, and February.[24,25] Increased incidence of calculi in warmer seasons are due to perspiration, low urinary volume, circannual variation, and increased urinary calcium excretion.[24,27,28] We found the peak of calculus visits in September, October, and November. A 2- to 3-month interval between peak temperatures and peak rates of the disease have been reported.[29] In adults it can be supposed that decrease intake of citrate sources such as fruits and vegetables are responsible for a higher urine pH in winter, but the reasons for such difference in infants is not clear.

Follow-up of infants (≤ 1 year old) have shown a stone-free condition in 17 (34%), increased number of calculi in 10 (20%), decreased in number in 16 (32%), and recurrence detected in 7 (14%).[2] In our cohort, 25 patients (58.1%) reached a stone-free

condition. New stone formation and increased calculi sizes were reported in 9 (20.9%) and 4 (9.3%) patients, respectively. Stone sizes were decreased in 14 (32.5%), whereas no changes in calculi sizes were found in 2 patients (4.6%).

Limitations of this study were as follows: that we did not measure the cysteine-creatinine ratio in those with a positive CNT to confirm the diagnosis of cysteinuria. Another limitation was about lack of measurement of urinary citrate excretion, but the reasons that we did not measure citrate in random urine included limited data about normal ranges of urinary citrate excretion in children and absence of any definition for hypocitraturia based on random urine.[30] The other limitations are about the method of diagnosis of calculi. Although spiral abdominal computed tomography is the most sensitive method for detecting urolithiasis, kidney-bladder ultrasonography is more practical since it is more available, less expensive, and most importantly, free from radiation exposure. It should be noted that ultrasonography cannot detect calculi located in the distal ureters (mainly nonobstructing distal ureter urolithiasis). Lack of enough follow-up in about 45% of our cases was a negative point of our study. However, in 55% of cases who were followed up, no cases needed any procedure for calculus removal. It is possible that patients with poor follow-up had required surgical or nonsurgical interventions for calculus removal. Whether urolithiasis in small infants commonly has a favorable course is a question that needs more investigation with long-term follow-up.

CONCLUSIONS

We found that like childhood urolithiasis, idiopathic hypercalciuria is the main abnormal urinary metabolic factor for stone formation in small infants. In addition, it seems that infection is not an important factor in the pathogenesis of urinary calculus disease in this age group.

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CONFLICT OF INTEREST

None declared.

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