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ETIOLOGICAL EVALUATION IN PEDIATRIC URINARY STONE DISEASE

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Abstract

Aim: Urinary stone disease is an important health problem commonly seen in some regions of the world. Determining the etiology is important for effective treatment and prevention of recurrence. The aim of this study was to evaluate the demographic and clinical features, metabolic and other risk factors of children with urinary stone disease.

Methods: A total of 766 patients with urinary stone disease presented to our pediatric nephrology department over 15 years. The patients' demographic, clinical, and treatment data were retrospectively analyzed.

Results: The mean age at diagnosis was 61.6±52.7 months. The male/female ratio was 1.15:1. There was no significant difference in age at diagnosis between the sexes. The most frequent presenting complaint overall was abdominal pain. Chronic renal failure was present in 1.8% and family history in 57.5% of the patients. Metabolic abnormalities were detected in 51% of the patients, urinary tract infection in 44.8%, and urinary tract anomalies in 13.2%. No cause could be identified in the other 22.7% of the patients. Urinary tract infection was the most common etiology in patients younger than 1 year old, while metabolic risk factors were more frequent in patients aged 1-10 years. Metabolic abnormalities included hypercalciuria (51.7%), hypocitraturia (47.5%), hyperoxaluria (39.9%), hyperuricosuria (23.4%), and cystinuria (9.4%). Bilateral and multiple stones were associated with metabolic abnormalities ($p<0.001$ and $p=0.011$). Nearly all stones (96.5%) were located in upper urinary tract and 1.8% were in the bladder. Calcium oxalate was the most common type of stone (61.7%). In terms of treatment, 32.5% of patients received medical treatment, 7.9% underwent extracorporeal shock-wave lithotripsy, and 14.3% had surgery. During follow-up, 30.1% of patients exhibited complete resolution and the other 69.9% had persistent disease.

Conclusions: Urinary stone disease is an important health problem in childhood and requires a thorough evaluation of metabolic risk factors to clarify the etiology. Treating metabolic and structural abnormalities and controlling urinary tract infection are important to protect renal function and prevent recurrence.

Keywords: *Urinary stone, child, metabolic abnormalities*

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Introduction

Urinary stone disease (USD) is a widespread and important health problem, especially in endemic regions of the world. USD that is not diagnosed early and treated appropriately can lead to serious consequences such as chronic renal failure and a greater economic burden on the health system [1].

The prevalence of USD varies by geographic region depending on climate, dietary habits, and water and salt consumption [2, 3]. USD is responsible for 8% of cases of chronic renal failure in children in Turkey, which is one of the endemic countries [4].

USD is an important cause of morbidity, especially in children with recurrence [4]. Determining the etiology is key to selecting the appropriate treatment, avoiding complications, and preventing stone recurrence. Many factors such as metabolic abnormalities, anatomic defects in the urinary system, and urinary tract infection (UTI) contribute to stone formation. Approximately half of patients with urinary stones have a metabolic etiology, 25% have UTI, and approximately 20% have urinary obstruction and stasis [3]. USD associated with metabolic abnormalities is more common in children compared to adults, and results in more frequent recurrence [5].

As one of the countries in the "stone belt", this study aimed to evaluate the clinical features and underlying metabolic and other risk factors in children with USD presenting to our center.

Materials and Methods

This retrospective study included 766 pediatric patients followed for USD in the Pediatric Nephrology Department of the Turkish Ministry of Health Ankara Children's Hematology Oncology Training and Research Hospital between 1997 and 2012. This clinical study was approved by the ethics committee of our hospital.

Patients with urinary stones less than 3 mm in diameter and those who did not undergo metabolic evaluation were not included in the study. Medical records were screened to collect data regarding the patient's gender, age at diagnosis, family history, presence of consanguinity, history of UTI and other comorbid diseases, admitting symptom, medications used, and surgical procedures for stones. Recorded laboratory data included serum creatinine, urea, electrolytes, uric acid, pH, and bicarbonate, urine analysis, urine culture, urine amino acid levels, and solute/creatinine ratio in 24-hour urine or in spot urine samples for infants and young children. Metabolic evaluation included assessment of hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, and cystinuria. Normative pediatric values for components such as calcium, oxalate, and citrate were evaluated using the previously determined references [6].

The patients were divided into groups according to stone etiology: patients with at least one metabolic abnormality; patients with positive urine culture at first admission or a history of recurrent UTI; patients with concomitant urinary tract anomalies; and patients not included in any of these groups (idiopathic USD).

Urinary ultrasound (US) results were examined and stone location, size, and number as well as associated hydronephrosis and/or other urinary tract anomalies were recorded. In addition, the imaging records of patients who underwent computed tomography, intravenous pyelography, voiding cystourethrography, and renal scintigraphy were also reviewed. Control ultrasonographies after 6 months were recorded in patients who could be reached. Urinary stones were divided into those of the upper urinary tract (kidneys and ureters) and lower urinary tract (bladder and urethra). The presence of bilateral and multiple urinary stones was compared according to patient age and etiological factors.

Stones that passed spontaneously or could be retrieved surgically were analyzed using X-ray diffraction. The US findings of patients who had follow-up US examinations at least 6 months later were recorded.

Statistical Analysis

Statistical analysis of the data was performed using SPSS for Windows version 11.5 software package. Descriptive statistics were presented as mean ± standard deviation (minimum-maximum) for continuous variables and frequency and percentage for categorical variables. Pearson's chi-square test of independence, Fisher's exact chi-square test, and odds ratio test were used. The results were considered statistically significant at $p < 0.05$.

Results

Demographic and clinical characteristics

A total of 766 children (male to female ratio: 1.15/1) with a mean age of 61.6±52.7 months (0-211 months) were evaluated. Of these, 204 patients (26.6%) were 0-1 years old, 225 (29.4%) were 1-5 years old, 230 (30%) were 5-10 years old, 86 (11.2%) were 10-15 years old and 21 (2.7%) were over 15 years old. There was no statistically significant difference in age at diagnosis between the sexes.

Of the 499 patients whose family history could be reached in terms of kidney stones, 287 (57.5%) had a positive family history. The consanguinity rate was 29.8%.

Abdominal pain was the most common reason for hospital admission in all age groups (22.8%), while UTI-related symptoms were the most common reason in patients under 1 year of age and hematuria was the most common reason in patients aged 1-5 years. Other symptoms included hematuria (21.2%), UTI-related symptoms (20.7%), stone passage (8.0%), and urinary dysfunction (3.7%), and 16.7% of the patients were asymptomatic.

Comorbidity was present in 124 (16.1%) of the patients. Comorbid conditions included prematurity (2.7%), epilepsy (2.3%), hyperparathyroidism (0.78%), renal tubular acidosis (0.52%), antenatal hydronephrosis (0.52%), vitamin D toxicity (0.39%), hypercalcemia (0.13%) and Dent disease (0.13%).

Etiological factors

Metabolic abnormalities were detected in 391 patients (51%), UTI in 343 patients (44.8%), and urinary tract abnormalities in 101 patients (13.2%). Multiple etiological factors were identified in 220 patients (28.7%), while 174 patients (22.7%) had no known etiological risk factors and were classified as idiopathic (Table 1).

The etiological risk factors differed significantly by age, with metabolic abnormalities found to be significantly more frequent in the 1-5 and 5-10 years age groups compared to the 10-15 and >15 years age groups ($p<0.05$). UTI was significantly more common in patients under 1 year of age compared to the other age groups ($p<0.05$) and at 1-5 years of age compared to the 5-10 and 10-15 years age groups ($p<0.05$).

Table 1: Distribution of cases in terms of etiology based on the age groups

Age groups	n	Metabolic abnormalities	Urinary tract infections	Urinary tract anomalies	Idiopathic
<1 year-old	204	99 (48.5%)	126 (61.8%)	22 (10.8%)	37 (18.1%)
1-5 year-old	225	126 (56.0%)	108 (48.0%)	30 (13.3%)	41 (18.2%)
5-10 year-old	230	125 (54.3%)	72 (31.3%)	31 (13.5%)	60 (26.1%)
10-15 year-old	86	35 (40.7%)	29 (33.7%)	11 (12.8%)	30 (34.9%)
>15 year-old	21	6 (28.6%)	8 (38.1%)	7 (33.3%)	6 (28.6%)
p		0.020*	<0.001*	0.075	0.007*

* *statistically significant*

Table 2. The metabolic abnormalities in patients with urolithiasis

Metabolic abnormalities	Number of patients examined	Number of patients with metabolic disorder	%
Hypercalciuria	373	193	51.7
Hypocitraturia	204	97	47.5
Hyperoxaluria	278	111	39.9
Hyperuricosuria	197	46	23.4
Cystinuria	509	48	9.4

Idiopathic USD was less frequent in the under 1 year and 1-5 years age groups compared to the 5-10 and 10-15 years age groups ($p<0.05$).

Metabolic evaluation

Multiple metabolic abnormalities were identified in 87 patients (11.3%), while 304 patients (39.6 %) had only one metabolic risk factor. Hypercalcuria was the most frequently detected metabolic disorder in our patient group (51.7%) (Table 2). In our population of USD, 5.4 % of patients with hyperoxaluria are found to have seconder hyperoxaluria.

Urinary tract imaging

In urinary tract imaging with ultrasonography, 96.5% of stones were in the upper urinary tract, 1.8% were in the bladder, and the remaining were located in both the upper and lower urinary tract. In the evaluation of stone size with ultrasonography, 61.9 % are between 3-5 mm, 23.4 % are between 6-10 mm, 14.7 % are over 10 mm.

Urinary stones were bilateral in 204 of our patients (26.6%). The frequency of bilateral USD was significantly higher in patients with metabolic abnormalities ($p<0.001$) and within this group, bilateral USD was more frequent among patients with hyperoxaluria ($p<0.001$) and cystinuria ($p=0.003$).

Multiple urinary stones were detected in 359 patients (46.8%). Like bilateral stones, the frequency of multiple USD was significantly higher among patients with metabolic abnormalities ($p=0.011$) and especially those with hyperoxaluria ($p=0.012$).

There were significant differences in bilateral and multiple USD when compared according to age ($p<0.001$). The prevalence of bilateral and multiple USD was higher in patients under 1 year of age than in the other age groups ($p<0.05$ for both).

Of 101 patients with urinary tract anomalies, 20 had bifid pelvis, 19 had ureteropelvic junction stenosis, 12 had double collecting system, 12 had vesicoureteral reflux, 9 had atrophic kidney, 4 had rotation anomaly, 4 had horseshoe kidney, 4 had cortical cyst, 4 had parapelvic cyst, 3 had neurogenic bladder, 3 had ureterovesical junction stenosis, 2 had ureterocele, 2 had polycystic kidney, 1 had ectopic kidney, 1 had nephroptosis, and 1 had angiomyolipoma.

Stone analysis

Of the 175 patients who had urinary stone analysis, calcium oxalate stones (61.7%) were the most common type (Table 3).

Treatment and prognosis

Dietary modifications were recommended for all patients. In addition, 249 patients (32.5%) received medical treatment (citrate for alkalinization of urine, magnesium, hydrochlorthiazide, pyridoxine, thiopronin); 61 (7.9%) underwent extracorporeal shock wave lithotripsy; 110 patients (14.3%) underwent other surgical procedures and nephrectomy was performed in 3 patients.

Of the 316 patients with follow-up 6th months US, 95 (30.1%) had no stones (complete res-

olution), 221 (69.9%) had persistent USD, and 50.6% showed a reduction in stone size. Chronic kidney failure due to USD was seen in 14 patients (1.8%). Of these, 6 (42.8%) had metabolic abnormalities predisposing to USD (hyperoxaluria and hypercalciuria in 3, cystinuria in 1, hyperoxaluria and hypocitraturia in 1 and hypocitraturia in 1).

Tablo 3. Urinary system stones types

Stones type	n (%)
Calcium oxalate	108 (61,7)
Cystine	21 (12)
Struvite	20 (11,4)
Uric acid	9 (5,1)
Xanthine	2 (1,1)
Brushite	2 (1,1)
Calcium oxalate +struvite	5 (2,9)
Calcium oxalate +uric acid	3 (1,8)
Calcium oxalate +brushite	1 (0,6)
Xanthine +struvite	2 (1,1)
Xanthine +uric acid	2 (1,1)
Total	175 (100)

Discussion

Without early diagnosis and appropriate treatment, USD in children can lead to serious consequences, and is one of the causes of chronic renal failure in children [7]. In the present study, although the frequency varied according to age range, we determined that metabolic disorders, UTI, and concomitant urinary system anomalies were risk factors for stone formation, and patients with metabolic abnormalities were found to be at higher risk of bilateral and multiple USD. Therefore, timely assessment of the etiology and initiation of appropriate treatment can alter the course of USD in pediatric patients.

USD is a common condition that can be seen in children of any age, but there are studies showing that the incidence is higher before the age of 5 years [7-9]. In our study, 56% of the patients were younger than 5 years of age. The higher frequency of urinary tract anomalies, UTI, and metabolic abnormalities in the first year of life explains why USD is more common in children under 5.

In addition to genetic factors, environmental factors and dietary habits also have a role in stone formation [1]. People with a family history of stones are at higher risk of developing USD compared to the general population. Consanguinity is an additional risk factor [3]. In our study, 57.5% of patients had family history of USD, and consanguineous marriage was reported in 29.8% of cases. Acar et al.[10] reported that all patients with hypercalciuria had a positive family history. Elmacı et al.[8] determined the rates of family history and consanguinity as 76.5% and 41%, respectively, in their study. Moreover, there is a strong association between positive family history and stone recurrence [11]. The high rate of consanguineous marriage in our country may lead to an increase in inherited metabolic disorders, the emergence of USD in multiple members of the same family, and even recurrent USD.

The presenting complaints of patients with USD may vary according to age. In our study, although the most common admitting symptom among all age groups was abdominal pain, UTI was the most common in children under the age of 1 year and hematuria was the most common in children aged 1-5 years. Admission in preschool children is usually due to UTI, whereas admissions due to pain are more common in the older age groups [12, 13]. Similarly, Elmacı et al.[14] reported that hematuria was the most common symptom in their patient group, which had a mean age of 3.7±1.3 years. Children with UTI and hematuria, especially in the preschool period, should be assessed for urinary stones.

In our study, UTI (44.8%) was the next most common etiological factor after metabolic abnormalities. In addition, UTI may also present as a complication of USD [13]. In the literature, the incidence of UTI in USD has been reported to be between 8% and 70% [7, 15, 16], and an association between UTI and metabolic abnormalities has also been noted. Acar et al.[10] detected a positive correlation between recurrent UTI and hypercalciuria and a

negative correlation between recurrent UTI and urinary citrate excretion. In pediatric patients with recurrent UTI, it is important to be aware of the possibility of urinary stones, and these patients should be screened to enable early diagnosis and appropriate treatment screening in order to prevent kidney damage. Many children with USD have an underlying metabolic abnormality [12]. In previous reports, metabolic abnormalities were seen in 45-84.4% of pediatric patients [8, 11, 12]. In our study, the most common etiological factor in urinary stones was metabolic abnormalities (51%), particularly hypercalciuria. Consistent with our findings, hypercalciuria was also reported as the most common metabolic disorder in previous studies [12, 17, 18]. In some studies, hypocitraturia was the most common metabolic abnormality [9, 16, 19]. Spivacow et al.[12] detected hypercalciuria in 40% and hypocitraturia in 37.8% of their patients. Similar to some other studies, hypocitraturia was the second most common metabolic disorder in our study group [8, 10, 18]. In our study, hyperoxaluria and hyperuricosuria were detected 39.9% and 23.4%, respectively. The rate of uric acid stone is higher in the eastern and central region of our country. Dietary habits affect the etiology of kidney stones. Diets rich in animal protein lead to higher urinary excreatin of uric acid, calcium and oxalate [11]. Cystinuria is the etiological factor of up to %10 of all urinary stones in children, with similar rates in our series [20].

Another etiology of USD is underlying structural anomalies, which lead to stasis and induce crystal formation in the urinary tract. Once crystals start to form in the urinary tract, they can grow and become urinary stones. In USD, the prevalence of anatomical abnormalities in the urinary tract has been reported as 10-20% [11, 21]. Urinary tract anomalies were detected in 13.2% of the children in the present study. Anatomical abnormalities also predispose to infections, which in turn aggravate precipitation [7, 21]. Therefore, even more caution is warranted regarding UTI in stone patients with underlying urinary tract anomalies.

Some etiological factors may be more prominent in certain age groups. USD is likely to occur earlier in patients with metabolic abnormalities [21]. In the present study, metabolic abnormalities were statistically more frequent in the 1-5 and 5-10 age groups compared to the older age groups. Stones associated with UTI were more common in patients under 1 year of age compared to other age groups. In many studies it has been reported that UTI is more common in preschool children with urinary system stones and especially in children under the age of 1 year [13, 22]. Elmacı et al.[14] detected metabolic disorders in 83.2% of the patients in their study of preschool children. Bak et al.[17] showed that the mean age at diagnosis was lower in stone patients with metabolic and infectious etiology compared to others.

The stone location, number, size can be determined an inexpensive, common, easily accessible and radiation-free imaging tool such as US, without further examination. In the diagnosis and follow-up of USD, stone location, number, and size are determined using US in our study. We observed in this study that nearly all stones (96.5%) were located in the upper urinary tract. Bladder stones are common in endemic regions due to dietary habits; however, recent data show that the majority of pediatric urinary stones are located in the upper urinary tract, regardless of endemicity [12, 13, 21]. Considering that our country is one of the endemic regions, bladder imaging is important, especially in patients with signs of bladder irritation such as hematuria, dysuria, and frequent urination, in order to detect bladder stones that may lead to obstruction and postrenal kidney failure. Urinary tract US is also used to evaluate the number of stones and whether they are unilateral or bilateral. Bilateral, multiple, and recurrent USD can lead to progressive kidney injury and subsequent chronic renal failure [3]. Metabolic impairment should be suspected in patients with bilateral and multiple urinary stones. In our study, bilateral and multiple stones were detected in 26.6% and 46.8% of patients, respectively, and were more common in patients with metabolic disorders and

those under 1 year of age. A study by Çeliksoy et al.[18] showed that multiple stones and UTI were more common in the 0-2 years age group, and multiple stones were more common in the presence of cystinuria. Shahta et al.[23] reported that 39.2% of patients had multiple urinary stones, 61.8% had bilateral stones, and 72.5% of patients with multiple stones had metabolic disorders. In a study by Bak et al.[17], 24% of patients had multiple and bilateral stones and all had an underlying metabolic cause. In our study, it was shown that bilateral stones were associated with hyperoxaluria and cystinuria and multiple stones were associated with cystinuria. Ertan et al.[21] found that cystinuria was more common in bilateral and multiple stone patients and that bilateral and multiple stones were more common in patients under 12 months of age, similar to our study. Patients who are younger than 1 year of age and have a metabolic risk factor such as hyperoxaluria and cystinuria should be followed with urinary tract US at regular intervals for new stones, especially in the kidney with no stones previously.

One limitation of this study was its single-center and retrospective design. In addition, not all patients included in the study were screened for all metabolic risk factors, and not all patients had follow-up US data.

Conclusion

Urinary stone disease is a common condition associated with progressive kidney injury. Identifying the etiology facilitates the management of the disease and helps improve prognosis. Metabolic abnormalities, especially hypercalciuria, are among the most common etiological factors and together with UTI play an important role in the early onset of USD. The incidence of bilateral and multiple urinary stones is higher in children under 1 year of age and in the presence of underlying metabolic disorders. A detailed examination to identify the underlying risk factors is critical to provide appropriate treatment and prevent recurrent USD and kidney damage.

Conflict of interest
The author declare that they have no conflict of interest.

Ethical approval
Ethical approval was obtained Department of the Turkish Ministry of Health Ankara Children's Hematology Oncology Training and Research Hospital Ethics Committee 16.03.2011

Author contributions
Mihriban İnözü, taking responsibility in necessary literature review for the study, planning methodology to reach the conclusions, data collection and/or processing, taking responsibility in the writing of the whole or important parts of the study.
Banu Acar, constructing the hypothesis or idea of research and/or article, planning methodology to reach the conclusions, organizing, supervising the course of progress and taking the responsibility of the research/study.
Fatma Özcan Sıkı, data collection and/or processing
Fatma Şemsa Çaycı, data collection and/or processing
Tuğrul Tiryaki, reviewing the article before submission scientifically besides spelling and grammar.
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