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ORIGINAL PAPER

Metabolic and demographic characteristics of children with urolithiasis in Western Turkey

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Abstract Pediatric urolithiasis is an endemic disease in Turkey. We evaluated the clinical, radiological and metabolic features of children with urolithiasis in Western Turkey. We retrospectively reviewed the records of 85 children with urolithiasis who were followed-up between 2004 and 2010 in Pediatric Nephrology Department of Celal Bayar University, Manisa. The male/female ratio was 1.23/1. The mean age at diagnosis was 66.1 months (range 3–210 months). Family history of urolithiasis was found in 58 (68.2%) patients. 23 (27%) patients were born from consanguineous marriages. Stones were located in the upper urinary tract in 79 (92.9%) patients. In 66 (77.6%) patients, stones were single-sided and 41 (48.2%) patients had multiple stones. Calcium oxalate stones were the most common one among patients in whom stone analysis was performed (78.5%). Hypocitraturia was the most commonly detected urinary metabolic risk factor. In patients who were under 12 months of age at diagnosis, hypercalciuria was the most commonly seen urinary metabolic risk factor. At the end of follow-up period, 24 patients became free of stone disease and 4 patients had recurrence. In conclusion, metabolic abnormalities are common in pediatric stone patients and are strongly associated with recurrence. Considering that urolithiasis in children is an important risk factor for renal failure, early diagnosis, detailed metabolic evaluation and implementing appropriate treatment and follow-up protocols may prevent recurrence and renal damage.

Keywords Urolithiasis · Child · Metabolic risk factors · Clinical features · Recurrence

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Introduction

Urolithiasis is a major health problem with its high morbidity, high management costs and potential for end-stage renal disease [1]. The wide geographic variations in the incidence of lithiasis in childhood appears to be related to climatic, dietary, genetic and socioeconomic factors [2, 3]. In Turkey, urolithiasis is considered to be endemic. The incidence was reported as percentage and 17 of patients under 14 years of age [4, 5]. Another study reports the incidence of urolithiasis in Turkish school children as 0.8% [2]. Urolithiasis has multiple etiologies and in Turkish studies, metabolic factors was shown to have a role in approximately 20–30% of stone disease in children [6, 7]. The risk of recurrences in children with stones is high, especially when the cause is metabolic [6]. It was reported that the most common metabolic risk factor for stone formation is idiopathic hypercalciuria, which has been described in 75–80% of children with urolithiasis and stone disease in these children usually shows recurrence [2, 5].

In this retrospective study, we evaluated the metabolic risk factors, clinical features and demographic characteristics of 85 children with urolithiasis in Western Turkey.

Patients and methods

We retrospectively reviewed the records of 85 children with urolithiasis who were followed-up between 2004 and 2010 in Department of Pediatric Nephrology in Celal Bayar University, Manisa. The records were reviewed for clinical and laboratory data, including gender, age at diagnosis, follow-up duration, consanguinity, family history, presenting symptoms, the history of urinary tract infection, stone localization, presence of anatomical abnormalities of urinary tract, presence of microscopic hematuria and persistent pyuria, urinary metabolic examinations, blood tests, analysis of stone composition, treatment modality and prognosis. Tests for metabolic risk factors, including hypercalciuria, hypocitraturia, cystinuria, hyperoxaluria, hyperuricosuria and hypomagnesuria were carried out. The diagnosis of urinary abnormalities was based on two consecutive examinations. Serum urea, creatinine, uric acid, calcium, phosphorus, magnesium, alkaline phosphatase, parathyroid hormone, blood pH, bicarbonate and urinary sediment, urine density and pH were measured in all patients. Urine volume was measured for 24-h urine collections. Urine culture was performed in all patients. The diagnosis of urolithiasis was made using both plain urinary system X-ray and urinary system ultrasonography (USG). X-ray diffraction method was used for stone analysis.

Urinary calcium was measured by *o*-cresolphthalein complexone method in an analyzer using a kit (Roche Diagnostics GmbH, Mannheim). Urinary oxalate estimation was performed by spectrophotometric enzymatic method using a commercial kit (Trinitiy Biotech plc, Wicklow, Ireland). Urinary uric acid was measured by enzymatic colorimetric method with uricase in an analyzer using a kit (Roche Diagnostics GmbH, Mannheim). Urinary citrate was measured by spectrophotometric enzymatic method using a commercial kit (R-Biopharm AG Landwehrstr 54, Darmstadt). Urinary magnesium was measured by spectrometry of atomic absorbtion method. Cystine was measured by high-performance liquid chromatography method with an UV detector. Urinary creatinine was measured by buffered kinetic Jaffé reaction method in an analyzer using a kit (Roche Diagnostics GmbH, Mannheim). Normal values reported in the literature for 24 h and spot urine analysis were taken into consideration (Table 1).

Statistical analysis were performed with SPSS 11.0 for Windows. Data were expressed as mean ± SD and percentages. Mann–Whitney *U* test was used to compare mean values of age at diagnosis between males and girls. χ^2 test and Fisher's exact test were used to analyze categoric variables. A $P < 0.05$ was considered to be statistically significant.

Table 1 Normal values of urine [6–9]

24-h urine	
Calcium	<4 mg/kg/day
Oxalate	<40 mg/1.73 m^2/day
Uric acid	<10.7 mg/kg/day or <815 mg/1.73 m^2/day
Citrate	>400 mg/g creatinine or >320 mg/1.73 m^2/day
Cystine	<75 mg/1.73 m^2/day
Magnesium [7]	<88 mg/1.73 m^2/day
Total volume	>20 ml/kg/day
Spot urine	
Calcium/creatinine [7]	
0–6 months	<0.8 mg/mg
7–12 months	<0.6 mg/mg
1–18 years	<0.2 mg/mg
Oxalate/creatinine	
<6 months	<0.3 mg/mg
6 months–4 years	<0.15 mg/mg
>4 years	<0.1 mg/mg
Uric acid	<0.53 mg/dl GFR
Citrate/creatinine	>0.51 g/g
Cystine/creatinine [9]	<0.075 mg/mg
Magnesium/creatinine [8]	>0.12 mg/mg

This study was approved by the Ethics Committee of Celal Bayar University, Medical School.

Results

The study population consisted of 85 children, among which 47 (55.3%) were males and 38 (44.7%) were females. The male/female ratio was 1.23/1. Mean age at diagnosis was 66.1 months (range 3–210 months) in all patients, 57.6 months (range 3–184 months) in males and 76.7 months (range 3–210 months) in females. 28 (32.9%) children were younger than 12 months of age at diagnosis of whom 19 (67.9%) were male ($P = 0.1$). Follow-up duration was 17.9 months (range 1–69 months). Family history of urolithiasis was found in 58 (68.2%) patients. 23 (27%) patients were born from consanguineous marriages. The presenting symptoms were abdominal pain (36.5%), flank pain (11.8%), macroscopic hematuria (22.4%), dysuria (14.1%) nausea and vomiting (20%), restlessness (15.3%) and stone drop (3.5%). Stones were detected incidentally in 18.8% of patients. Urine analysis, at presentation, revealed microscopic hematuria in 39 (45.9%) patients and urinary tract infection in 22 (25.9%) patients. There were history of recurrent urinary tract infection in 23 (27%) patients. Of all patients, 31.9% of boys and 21.1% of girls had recurrent urinary tract infection ($P = 0.2$). 10

(35.7%) of them were younger than 12 months of age at diagnosis 8 of whom were boys ($P = 0.4$). Persistent pyuria was found in 8 (9.4%) patients. The most common organism responsible for urinary tract infection was *Escherichia coli*. Other organisms detected were *Klebsiella*, *Pseudomonas* and *Proteus*. Clinical and demographic data of patients are shown in Table 2. Radiological data of patients are shown in Table 3. Not presented in Table 3, 39.3% of the patients, who were under 12 months of age at diagnosis had bilateral stones ($P = 0.009$), 64.3% of them had multiple stones ($P = 0.038$) and 39.3% of them had bilateral and multiple stones ($P = 0.009$). 14 patients had stone analysis. Calcium oxalate were the most common compound (78.5%). Stone analysis results are shown in Table 4. A single urinary metabolic risk factor was present in 42 (49.4%) patients and multiple factors were present in 34 (40%) patients. The remaining 9 (10.6%) patients had no metabolic risk factor. Hypocitraturia was the most common urinary metabolic risk factor (32.9%). Hypercalciuria was more common in boys ($P = 0.043$) and cystinuria was more common in patients who had bilateral or multiple stones ($P = 0.02$). There were no other significant difference between urinary risk factors and gender or multiple stones. In addition, there was no significant difference between urinary risk factors and positive family history, consanguinity or bilateral stones. In patients who were under 12 months of age at diagnosis, hypercalciuria was the most common urinary metabolic risk factor. 13 of 57 (22.8%) patients had low urinary volume. Serum chemistries, including urea, creatinine, uric acid, calcium, phosphorus, magnesium, alkaline phosphatase, parathyroid hormone, blood pH and bicarbonate were within normal limits in all patients. Metabolic findings are shown in Table 5. Treatment modalities applied included dietary recommendations that were made to all patients. Other treatment approaches used were medical treatment, extracorporeal shock wave lithotripsy (ESWL) and surgical intervention. Medical treatment was composed of antibiotic prophylaxis for urinary infections (23 patients), and specific treatments according to metabolic risk factors. Treatment modalities are shown in Table 6. At the end of follow-up period, 24 (28.2%) patients became free of stone

Table 2 Clinical and demographic data of patients

	n (%)
Patients	85
Male	47 (55.3)
Female	38 (44.7)
Male/female	1.23
The mean age at diagnosis (months)	66.1
The mean follow-up time (months)	17.9
Positive family history	58 (68.2)
Consanguinity	23 (27)
Presenting symptoms	
Abdominal pain	31 (36.5)
Flank pain	10 (11.8)
Macroscopic hematuria	19 (22.4)
Dysuria	12 (14.1)
Nausea and/or vomiting	17 (20)
Restlessness	13 (15.3)
Stone drop	3 (3.5)
Incidental	16 (18.8)
UTI at admission	22 (25.9)
History of recurrent urinary tract infection	23 (27)
Urine analysis	
Microscopic hematuria	39 (45.9)
Persistent pyuria	8 (9.4)

Table 3 Radiological data of patients

	n (%)
Plain X-ray	
Radiopaque	61 (71.8)
Radiolucent	24 (28.2)
Localization of stone	
Bilateral	19 (22.4)
Multiple	41 (48.2)
Upper urinary tract	79 (92.9)
Parenchyma	35 (41.2)
Pelvis	15 (17.6)
Calix	36 (42.4)
Lower urinary tract	15 (17.6)
Ureter	13 (15.3)
Bladder	3 (3.5)
Urethra	2 (2.4)
Upper + lower urinary tract	9 (10.6)
Anatomical abnormality of urinary tract	5 (5.9)
Vesicoureteral reflux	2 (2.3)
Ureterovesical junction obstruction	1 (1.2)
Ureteropelvic junction obstruction	1 (1.2)
Double collecting system	1 (1.2)

Table 4 Stone analysis of patients

	n (%)
Calcium oxalate dihydrate	3 (21.4)
Calcium oxalate monohydrate	3 (21.4)
Calcium oxalate dihydrate + calcium oxalate monohydrate	3 (21.4)
Calcium oxalate monohydrate + calcium phosphate	2 (14.3)
Calcium phosphate	2 (14.3)
Calcium magnesium phosphate	1 (7.1)

Table 5 Metabolic findings of patients

	n (%)	Male (% of male)	Female (% of male)	*P*
Single urine metabolic risk factor	42 (49.4)			
Multiple urine metabolic risk factor	44 (40)			
No urine metabolic risk factor	9 (10.6)			
Hypercalciuria	20 (23.5)	15 (31.9)	5 (13.2)	0.043*
Hyperoxaluria	23 (27.1)	10 (21.3)	13 (34.2)	0.1
Hypocitraturia	28 (32.9)	16 (34)	12 (31.6)	0.8
Hyperuricosuria	17 (20)	9 (19.1)	8 (21.1)	0.8
Cystinuria	18 (21.2)	10 (21.3)	8 (21.1)	0.9
Hypomagnesuria	10 (11.8)	5 (10.6)	5 (13.2)	0.7

* $P < 0.05$

Table 6 Treatment modalities of patients

	n (%)
Medical treatment	18 (21.2)
ESWL	12 (14.1)
Ureteroscopy	3 (3.5)
ESWL + ureteroscopy	1 (1.2)
Surgery	6 (7)
ESWL + surgery	3 (3.5)
Ureteroscopy + surgery	1 (1.2)

disease and 4 (4.7%) patients had recurrence. In 4 (4.7%) patients, the stones passed spontaneously, in 12 (14.1%) patients stones were eliminated by ureteroscopic basket extraction, ESWL or surgically and 8 (9.4%) patients showed spontaneous remission.

Discussion

The incidence and etiology of urolithiasis varies according to geographic areas [4]. In South East Asia, Turkey, Far East, East Europe and South America which are all known as the stone zone of the world, bladder calculi are endemic and are related to dietary factors, such as cereal based and low protein diet [3, 4, 6]. Pediatric urolithiasis is endemic in South East Turkey, which may be due, in part, to the extremely hot and dry climate, leading to dehydration [4, 7].

Reports of sex preponderance in childhood urolithiasis are varying but most epidemiological studies report male predominance [2, 3]. The male/female ratio was reported to be between 1.1 and 4 in most of the reports [6, 10]. In Turkey, male/female ratio of 1.68:1 was reported by Tabel et al. [6] and 2.3:1 by Bak et al. [7]. In the other studies, Dursun et al. [2] reported male/female ratio of 1:1.1 and female preponderance reported by Ece et al. [4] was thought to be associated with higher incidence of urinary tract infections (UTIs) in girls. In a study from the United States, Novak et al. [11] reported the male predominance in the first decade and female in the second. In our patients, male/female ratio was 1.23/1.

From various countries studies reported a mean age of 4.2–9.4 years for urolithiasis [2, 6]. In our study, the mean age at diagnosis was 66.1 months (range 3–210 months). It was similar to the other reports from Turkey [6, 7]. Girls were diagnosed in younger ages than boys, but this was not statistically significant ($P = 0.1$). In a study from Kuwait, Al-Eisa et al. [12] reported that the early presentation of stones compared with the other studies in the world may support the fact that genetic component plays a role in the etiology of stone formation. In the literature, the ratio of family history varies from 12 to 50% in different studies [2]. A family history of stone disease was found in 58 (68.2%) patients in our study. This ratio was in concordance with studies from Argentina and Italy, but higher than other studies from Turkey [5, 7, 8, 10]. This may suggest a significant contribution of genetic factors to the pathogenesis of urinary stones, possibly as a result of interaction of genetic and environmental factors [13]. In our study, positive family history of urolithiasis was detected in 22 (78.6%) of 28 patients younger than 12 months of age at the diagnosis ($P = 0.1$). Previous research reports demonstrated that rates of family history of urolithiasis for infants vary between 11.8 and 78.7% [8]. Consanguineous marriages were found in 23 (27%) of our patients. In addition, 7 (25%) of 28 patients younger than 12 months of age at the diagnosis were from consanguineous marriages ($P = 0.7$). Positive family history of urolithiasis and frequent consanguinity may increase the genetic susceptibility and lead to earlier presentation [7].

Major clinical manifestations of pediatric urolithiasis may be secondary to UTI, movement of calculi or urinary tract obstruction. Abdominal and flank pain is the most common clinical manifestation of urolithiasis and occurs in 40–75% of children [4]. These symptoms may be seen with or without hematuria and UTI [14]. Nonspecific symptoms, such as vomiting and restlessness are frequently seen in infancy [2]. The most common presenting symptoms of our patients were abdominal pain (36.5%) and macroscopic

hematuria (22.4%). These symptoms were similar to the symptoms reported in other studies [3, 6]. Urine analysis revealed microscopic hematuria in 39 (45.9%) patients and urinary tract infection in 22 (25.9%) patients at the diagnosis. Microscopic hematuria was detected in up to 90% of children with urolithiasis [15]. Many studies reported that urinary oxalate, uric acid and calcium may cause hematuria by damaging the uroepithelium [6].

It has been reported that about 10–20% of children with urolithiasis have underlying anatomical abnormality of urinary tract [2, 7]. In our study group, 5 (5.9%) patients had anatomical abnormalities. This was less than reported by Dursun, Tabel and Alpay et al. [2, 7, 10]. Anatomical abnormalities are conducive to stone formation by allowing urine stasis as well as predisposing to infection [16]. Infection of the urinary tract with urease producing organisms can produce de novo urolithiasis and also infection itself exacerbates underlying metabolic factors. The incidence of UTI in children with urolithiasis has been reported to be 8–70% in the literature [2]. Infection-related stones account for 2–24% of children with nephrolithiasis. Boys are more commonly affected and persistent pyuria is a characteristic finding [17]. In our study, the history of recurrent UTI was found in 23 (27%) patients. Boys had recurrent UTI more than girls ($P = 0.2$). 10 of them were younger than 12 months of age and 8 of these infants were boys, but this was not statistically significant ($P = 0.4$). Lifetime UTIs are more common in girls [9], but during the first year of life, the male:female ratio is 2.8–5.4:1 [18]. Our results were consistent with literature.

Investigation of metabolic disorders and chemical analysis of the calculi are important for the appropriate management of stone disease. Metabolic disorders were reported to be present in 12.3–96% of children with urolithiasis [4, 5]. Idiopathic hypercalciuria was the most frequent urinary metabolic risk factor found, being detected in 40–69% of the cases in several reports [5]. In Turkey, the incidence of idiopathic hypercalciuria as the most common factor, reported as 38% by Tabel et al. [7] and 40% by Acar et al. [19]. Alpay et al. [10] reported also hypocitraturia as an important risk factor for stone formation in southern and western regions of Turkey. Tefekli and Tekin found that hypocitraturia was the most prevalent metabolic risk factor in children. The relatively high frequency of hypocitraturia in the Turkish series may be related to local dietary habits or other regional causes [5]. In our study, hypocitraturia was the most commonly detected metabolic risk factor. We also found that hypercalciuria was more common in boys ($P = 0.043$), but this was not in concert with findings of Edwardson and Dursun et al. [2, 13.]. In our study, there were no significant differences between other urinary risk factors and genders. Dursun et al. [2] also showed that hyperuricosuria was more common in females and hyperoxaluria was more common in males, but these were not statistically significant. Up to 70% of children with idiopathic hypercalciuria have a family history of urolithiasis [14]. In our group, 75% of hypercalciuric patients had family history of urolithiasis. There were no significant differences between urinary risk factors and positive family history or consanguinity. Dursun and Naseri et al. [2, 20] reported no significant differences regarding association of urinary risk factors and family history. Palito et al. [5] found a high rate of positive family history in pediatric patients with hypercalcuria, hyperuricosuria or a combination of both. Acar et al. [19] reported that hypercalciuria was detected in all children with positive family history. In our study, 13 of 57 (22.8%) patients had low urinary volume. Low urinary volume was reported to be the most common associated abnormality, and the single most important factor that should be corrected to avoid recurrence [21]. With the improvement of living standards in Turkey, the diagnosis of urolithiasis is now possible at earlier ages [2]. We found at least one urinary metabolic risk factor in 85.7% of the patients younger than 12 months of age at diagnosis ($P = 0.4$). The most common metabolic cause for these infants was hypercalciuria (32.1%). This was identical to other studies reported in the literature [8].

We demonstrated that the majority of the stones (92.9%) were located in the upper urinary tract. As similar to our results, recent studies from Turkey have reported a higher rate of upper urinary system stones [6, 7, 10]. We found no statistically significant association between localization of the stones and urinary metabolic risk factors. The presence of bilateral and multiple urolithiasis should arouse strong suspicion of metabolic disorders [3]. 75% of cystinuric patients develop stones in both kidneys and more than 80% of them develop their first stone within the first two decades. An early appearance of the stones seems to be more likely in male patients [22]. We found that cystinuria was more common in patients with bilateral or multiple stones ($P = 0.02$). In addition, in our study, cystinuria was seen in males more than females ($P = 0.9$). Bilateral or multiple stones were more commonly detected in patients who are under 12 months of age at diagnosis in our study and it was statistically significant. The majority of stones in children are composed of calcium oxalate (45–65%) or calcium phosphate (14–30%) [16]. In our patients, group calcium oxalate stones were found in 11 (78.5%) of 14 patients. The high calcium oxalate rate was similar to the other studies [2, 4, 6, 7]. The appearance of a stone on imaging studies depends on its composition [23]. Majority of the calculi, especially struvite, calcium, oxalate and cystine stones are radiopaque [24]. In our study, 61 (71.8%) patients had radiopaque stones.

As a therapeutic approach, dietary precautions were administered to all patients. 23 patients who had recurrent

UTI were given antibiotic prophylaxis. Medical treatment except antibiotic prophylaxis was performed in 18 (21.2%) patients. Other treatments used were ESWL, surgical intervention or combination of these therapy modalities.

Prevention of new stone formation is important. In several reports, recurrence rates range from 6 to 54%, with a mean interval of 3–24 years [4, 6]. In our study, the mean duration of follow-up was 17.9 months (range 1–69 months) and the recurrence rate was 4.7%. The recurrence rates were reported as 5.5% by Bak et al. [6] and 24% by Kit et al. [15]. At the end of follow-up period, 24 (28.2%) patients became free of stone disease. Spontaneous passage of urinary stones in childhood has been reported to occur in 8–50% of cases. Özokutan et al. [14, 15] reported the rate of spontaneous passages as 3.5%. In our study, 4 (4.7%) patients passed their stones spontaneously. Alpay et al. reported that in 29% of the microlithiasis patients, spontaneous remission occured during the follow-up period [10]. 8 (9.4%) of our patients occured spontaneous remission. In 12 (14.1%) of the patients, stone-free disease was provided by ureteroscopic basket extraction, ESWL or surgically. In majority of patients, the calculi persisted during our follow-up period.

In conclusion, urolithiasis in children is known as an important risk factor for renal failure due to delays in diagnosis and treatment. Metabolic abnormalities are common in pediatric stone patients and are strongly associated with recurrence. With early diagnosis, detailed metabolic evaluation and appropriate treatment and follow-up protocols recurrence and renal damage can be prevented.

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