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Metabolic risk factors in children with urolithiasis: Single centre experience in southwest Turkey

Ürolitiazisli çocuklarda metabolik risk faktörleri: Güneybatı Türkiye'den tek merkez deneyimi

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Abstract

Purpose: To investigate the demographic characteristics, clinical features, and metabolic risk factors of children with urolithiasis.

Materials and methods: This retrospective study included 98 patients (48 boys, 50 girls) with urolithiasis diagnosed by ultrasonography. The mean age at presentation was 59.8 (1-192) months, and the mean follow-up period was 5.5 (1-27) months. Clinical and laboratory data including gender, age at diagnosis, presence of family history of renal stone, follow-up duration, presenting symptoms, the history of urinary tract infection (UTI), stone localization, presence of anatomical abnormalities of the urinary tract, presence of microscopic or macroscopic hematuria, pyuria, urinary metabolic examinations, blood tests, analysis of stone composition, treatment modality, and prognosis were assessed.

Results: The most common symptom was restlessness in infants (<1year) and abdominal or flank pain in older children. Microcalculi (stone diameter <3mm) and calculi (>3mm) were found in 29.6% and in 70.4% of the patients, respectively. Hypercalciuria was the most common abnormality, followed by hypomagnesiuria. Nearly half of the hypercalciuria cases were <1 year old. Recurrent urinary tract infection was detected in half of the patients. Four patients underwent extracorporeal shock-wave lithotripsy, four underwent open surgery, and the other 90 were treated with conservative treatment. Spontaneous passage occurred in 17 patients. Stone analysis revealed calcium-oxalate in 82.4% of the 17patients. At the time of their last visit, 70% of the patients that were treated with conservative treatment, either had stones that disappeared or diminished in size with appropriate therapy.

Conclusion: In terms of stones disappearance or decrease in the size of the stones, it seems that children younger than 1 year have more disadvantages than older children. Microcalculi in children should be taken into consideration because we found that 3/5 of these cases had urinary metabolic abnormalities.

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Key words: Cystinuria, Hypercalciuria, Hyperuricosuria, Hypomagnesiuria, Microcalculi.

Özet

Amaç: Ürolitiazisli çocukların demografik, klinik özelliklerini ve metabolik risk faktörlerini araştırmak.

Gereç ve yöntem: Bu retrospektif çalışmada ultrasonografi ile tanı alan ürolitiazisli 98 hasta (48 erkek, 50 kız) çalışmaya alındı. Başvuru yaş ortalaması 59.8 (1-192) ay ve takip süresi (1-27) ortalama 5,5 aydı. Klinik ve laboratuvar bulgular olarak cinsiyet, tanı anındaki yaş, ailede üriner taş hikayesi, izleme periyodu, başlangıç semptomları, idrar yolu enfeksiyon öyküsü, mikroskobik veya makroskobik hematüri varlığı, piyüri, üriner metabolik hastalık, kan tetkikleri, taş analizi, tedavi modalitesi ve prognoz belirlendi.

Bulgular: En sık görülen belirti bebeklerde huzursuzluk (< 1 yaş) ve daha büyük çocuklarda karın veya yan ağrısıydı. Mikrokalkul (taş çapı < 3mm) ve kalkül (taş çapı > 3mm), hastaların sırasıyla % 29.6 ve % 70.4 'ünde saptandı. Hiperkalsiüri hastalarda en sık saptanan anormallik olurken, hipomagnezüri 2. sıklıkta onu takip etti. Hiperkalsiüri olgularının yaklaşık yarısı 1 yaş altındaydı. Tekrarlayan idrar yolu enfeksiyonu hastaların yarısında tespit edildi. Dört hastaya extrakorporal şok dalga litotripsi uygulandı, 4 hastaya açık ameliyat yapıldı ve diğer 90 hasta konservatif tedavi ile tedavi edildi. Spontan pasaj 17 hastada görüldü. Taş analizi ile 17 hastanın % 82.4 'ünde kalsiyum oksalat taşı olduğu saptandı. Son kontrolde, konservatif tedavi alan hastaların % 70'inde taşların kaybolduğu veya uygun tedavi ile küçüldüğü saptandı.

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Sonuç: Taşların kaybolması veya boyutunun küçülmesi açısından, 1 yaş altındaki çocuklar büyük çocuklara gore daha çok dezavantaja sahip gibi görünmektedir. Çalışmamızda bu vakaların 3/5'inde üriner metabolik anormallik saptanması nedeni ile çocuklarda mikrokalkülün metabolik açıdan değerlendirilmesi önemlidir.

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Anahtar sözcükler: Sistinüri, Hiperkalsiüri, Hiperürikozüri, Hipomagnezüri, Mikrokalkül.

Introduction

Urolithiasis in children is an important cause of morbidity worldwide [1]. Symptoms of urinary tract stones are often non-specific, particularly in infants and young children and the stones may remain asymptomatic for a long time. Different incidence rates and etiological factors are reported in children with urolithiasis, reflecting differences in geographic, genetic and socioeconomic backgrounds [2]. The prevalence in children has been reported to be between 2-2.7% [3, 4]. However, significant increase in the incidence of urolithiasis in childhood has also been reported during the last decade [5]. Renal stone formation is a complex process that depends on several factors, including the urinary concentration of stone-forming ions, urinary pH and flow rate, various metabolic factors of crystallization and anatomic factors that facilitate urinary stasis [6]. It is important to identify risk factors because this may allow specific interventions to reduce recurrence or prevent stone formation in those at risk [1, 7]. Meanwhile, genetic inheritance, nutrition, metabolic abnormalities, environmental factors are also predisposing factors. Turkey is accepted as one of the endemic areas of urolithiasis in the world [8].

In this study, we aimed to investigate the demographic characteristics, clinical features, family history, and metabolic risk factors of children with urolithiasis, factors that affect the prognosis of the stone and to compare with other studies from Turkey and the world.

Material and Methods

We reviewed medical records of 103 children with urolithiasis who were followed-up between 2009 and 2013, in the Department of Pediatric Nephrology in Pamukkale University, Denizli. Two patients with bladder stones, two patients who had vesicoureteric reflux in the voiding cystourethrography and one patient who had obstruction in the MAG3 sintigraphy were excluded from the study. Therefore, the study group consisted of 98 patients. The study was approved by the Pamukkale University Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Clinical and laboratory data including gender, age at diagnosis, presence of family history of renal stone, follow-up duration, presenting symptoms, history of urinary tract infection (UTI), stone localization, presence of anatomical abnormalities of the urinary tract, presence of microscopic or macroscopic hematuria, pyuria, urinary metabolic examinations, blood tests, analysis of stone composition, treatment modality, and prognosis were assessed. Urolithiasis was diagnosed by ultrasonographic (US) evaluation in all the patients. Urinary calculi $\leq$ 3 mm were defined as microlithiasis and urinary calculi >3 mm as urolithiasis [9]. Serum urea, creatinine, uric acid, calcium, phosphorus, magnesium, alkaline phosphatase, sodium, potassium, chloride, blood pH, bicarbonate, urinary sediment, urine density and pH were measured in all the patients. Parathormone (PTH) was not studied because the patients were normocalcemic. Tests for metabolic risk factors including hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, hypomagnesiuria and cystinuria were carried out at least twice from random (un-timed) urine samples in patients younger than 5 years old, and from 24 hours urine collection in older children. The values of urine metabolic results of the patients were compared with normal values [2, 8-11]. Urine cultures were performed in all the patients. Urine samples for culture were obtained by bladder catheterization in children $\leq$ 3 years, and by clean-catch midstream urine in older children. In patients with UTI, metabolic evaluation was performed after the treatment of UTI. Voiding cystourethrography (VCUG) was performed in children with recurrent UTI in order to determine vesicoureteric reflux, and MAG-3 sintigraphy was performed in children with pelvicaliectasy or ureteric dilatation in order to determine obstruction.

The stones were obtained by spontaneous passage, extracorporeal shock-wave lithotripsy (ESWL) or open surgery in seventeen children. Analyses of the stones were performed by infrared spectroscopy and X-ray powder diffraction methods. All the patients were

advised to take fluids over 2.5 L/m^2/day, except the very young children. The patients who had metabolic risk factors were treated according to the underlying metabolic abnormalities. Dietary treatment included reduction of dietary sodium, protein or oxalate, increased consumption of lemon juice (because of its high citrate concentration), foods rich in magnesium, and pharmacological treatment including oral potassium citrate and/or hydrochlorothiazide. Patients with recurrent UTI were treated with prophylactic antibiotics. All the patients were followed up monthly for evaluation of the stone status. US, urine pH, density, microscopic examinations, and urine culture were performed monthly until the stones disappeared. In patients who were stone free in their follow up visits, US was performed three times consecutively in order to prevent overlooking any microcalculi.

Descriptive statistics and chi-square tests were performed as statistical analysis using the computer, Statistical Package for Social Sciences (SPSS) version 18.

Results

The study population consisted of 98 children with urolithiasis among which 48 were boys and 50 were girls. The mean age at diagnosis was 59.8 months (range: 1-192 months), 61.2 months in girls and 58.4 months in boys ($p>0.05$). The mean follow-up duration was 5.5 months (range 1-27 months). At the time of diagnosis 41 (41.8%) patients were <1 year of age. Family history of urolithiasis was present in most of the patients (59.2%). One child had temporary renal insufficiency. Blood pressure, serum electrolytes, blood pH and bicarbonate were all normal in the remaining patients. The most common presentation symptom was restlessness (53.6%) in patients <1 year of age, abdominal or flank pain (52.6%) in older patients. Hematuria was detected in 35 (35.7%), pyuria in 19 (19.4%), and both hematuria and pyuria in 8 (8.2%) patients at presentation.

Stones were located in the kidney (84 in the renal calyces, 9 in the renal pelvis) in 93 patients (95%), in the ureter in 3 (3%), and in both the kidney and ureter in 2 (2%). 29.6% of the patients had microcalculi (stone diameter ≤3mm) and 70.4% had calculi (stone diameter >3 mm). Most patients had multiple stones. Demographic characteristics, symptoms and the stone status at presentation of the patients are shown in table 1.

Table 1. Clinical and demographic characteristics of patients

Characteristic	n (%)
The age distribution	
<1 years	
1-5 years	41 (41.8%)
5-10 years	22 (22.4%)
>10 years	15 (15.3%)
Presenting symptoms and findings	20 (20.4%)
Abdominal/flank pain	
Restlessness	30 (30.6%)
Urinary tract infection	22 (22.4%)
Macroscopic hematuria	20 (20.4%)
Nausea and vomitting	12 (12.2%)
Dysuria	8 (8.2%)
Incidental	2 (2%)
	4 (4.1%)
Stone size	
≤3 mm (microcalculi)	29 (29.6%)
>3 mm (calculi)	69 (70.4%)
Stone number	
Single	36 (36.7%)
Multiple	62 (63.3%)
Total	98

History of recurrent urinary tract infection was present in 50 (51%) patients.

Among 98 patients, 17 (17.3%) had spontaneous passage of the stone, 4 underwent ESWL, and 4 underwent open surgery. Stone analysis was performed In 17 patients. Among these, the most dominant composition of the urinary stones was calcium oxalate (82.4%), with calcium oxalate dihydrate (weddellite) in 2, calcium oxalate monohydrate (whewellite) in 5, weddellite+whewellite in 7, xanthine in 2, and struvite stone in 1 patient.

Hypercalciuria was the most common metabolic abnormality found in 38 patients (38.8%). Nine patients had multiple urine metabolic risk factors. On the other hand, in 33 patients (33.6%) urine analysis revealed no metabolic risk factors (Table 2). At the end of the study the findings of the patients who had persisted calculi were compared with the patients in whom it had disappeared, there were no statistically significant differences between gender, family history and metabolic risk factors. 48.3% of the patients with hypercalciuria were <1 year old and all were normocalcemic (Table 3).

Table 2. Metabolic analysis of urine in all patients (N=98)

	Patients		**< 1 year old**	**≥ 1 year old**
	N	**%**	**N**	**N**
Hypercalciuria	31	31.6	14	17
Hypomagnesiuria	14	14.2	3	11
Cystinuria	4	4.2	3	1
Hyperuricosuria	2	2.1		2
Hypocitraturia	3	3.1		3
Hyperoxaluria	2	2.0		2
Hypercalciuria + Hypocitraturia	4	4.1		4
Hypercalciuria + Hyperoxaluria	3	3.1		3
Hypocitraturia + Hypomagnesiuria	1	1.0		1
Hyperuricosuria + Hypomagnesiuria	1	1.0	1	
Normal	33	33.6	20	13
Total	98		41	57

Table 3. Demographic characteristic and metabolic analysis of urine in children below 1 year of age (N=41

	Boy		**Girl**	
	N	**%**	**N**	**%**
Risk factors				
Hypercalciuria	10	71.5	4	28.5
Non-hypercalciuria	3	42.8	4	57.2
Hypomagnesiuria	*1*		*2*	
Cystinuria	*2*		*1*	
Hyperuricosuria + hypomagnesiuria	*0*		*1*	
Normal	12	60.0	8	40.0
Total	25	61.0	16	39.0

At the time of their last visit, 69 (70.4%) patients were stone free or the stone had diminished in size and microcalculi was in 30.4 % of them. In 11(11.2%) there was no alteration in the stone size and localization, in 6 (6.1%) stone size increased, and in 12 (12.2%) stones recurred. 25 of 38 patients with hypercalciuria (65.8%), and 11 of 15 patients with hypomagnesiuria (73.3%) were either stone free or had stones that diminished in size. 3 of 4 patients with cystinuria (75%) had recurrence of the stone. All hypocitraturia, uricosuria, and hyperoxaluria patients were stone free or the stone had diminished in size with adequate

treatment. In 61% of patients younger than 1 year old, and in 78.9% of patients older than 1 year old, the stone had either disappeared or diminished in size (p=0.03). 39 of 50 patients (78%) who had recurrent UTI history were either stone free or the stone had diminished in size with antibiotic prophylaxis.

80.7% of the patients older than 1 year old, and 56.1% of patients younger than 1 year old had stone diameter >3 mm (p=0.008). In 17 of 29 patients with microcalculi (58.6%), urine metabolic analysis revealed normal results. In 25 of 30 patients (83%) who were treated with potassium citrate and/or hydrochlorothiazide according to their underlying urine metabolic risk factor, Stone had diminished in size or completely disappeared. In one of 4 patients who underwent ESWL, stone recurred during the follow-up period, urine metabolic analysis revealed hypercalciuria and stone analysis showed whewellite. Two patients with xanthine stone had recurrence of stone during the follow up period. There was a positive family history of urinary stone disease in these patients, whereas no history of consanguineous marriage was present.

Discussion

Depending on geographic, genetic and socioeconomic factors, different incidence rates and etiological factors are reported in children with renal stone disease [12, 13]. If the diagnosis is delayed, renal stones may cause considerable morbidity and renal damage [1]. It has been reported that 4 to 11% of all cases of chronic renal failure in Turkey have been secondary to urinary stone disease [14, 15] .Urinary stone disease is a considerable childhood health problem in many places of the world and in our country.

Urolithiasis can occur at any age, but is rare in children compared with adults. In our study group, although the mean age at diagnosis was about 5 years (range:1month-16 years) nearly half of the patients were <1 year of age, while in other reports from Turkey this age group consisted 22.9-32.9% of the patients [11, 16, 17] . This finding is one of the remarkable aspects of the study. In the current literature, renal stone disease in childhood is reported to be more common in males [18, 19]. Although in Turkey, previous studies reported male predominance as well [11, 20], in our study there was no significant difference in gender (male/female ratio 0.96:1).

Symptoms of urinary tract stones are often non-specific, particularly in infants and young children [2]. Abdominal, flank, or pelvic pain occurs in approximately 50% of children who have urolithiasis, most often in older children and adolescents. Gross or macroscopic hematuria had been reported in 33% to 90% of children who have urolithiasis and occurs equally across age groups [10]. The most common presenting symptom in our study group was restlessness in patients <1 year old, and abdominal and/or flank pain in older children.

The ratio of family history varies from 27.4 to 80% in different studies from the world [5, 7, 21]. A positive family history of urolithiasis was present in more than half of our patients (59.3%). In other studies from Turkey, Ertan et al. [11] found 68.2%, Gurgoze and Sari [16] found 55.4%, Dursun et al. [17] found 54.7% positive family history of stone disease in children with urolithiasis, which were similar to our results, while Acar et al. [22] found it to be 24%. This may be related to the genetic tendency towards urolithiasis in Turkish children, because of high rates of consanguineous marriage.

Stones were located in the upper urinary tract in most of the patients (95%). Similar to our results, Safaei and Mleknejad [7] reported that 90.4% of the stones were in the upper urinary tract in children with urolithiasis in their study group. Bladder stones were present in only two patients and they were excluded from the study. Primary bladder stones which were reported to be related to lower UTI used to be very frequent, but they have almost disappeared in the industrialized countries. This also could be due to the control of UTI with prophylactic antibiotics. Nevertheless, bladder calculi still accounts for up to 5% of urinary calculi worldwide, and they are frequent in endemic areas [23].

History of recurrent UTI was present in half of our patients, while in other reports from Turkey it has been reported to be between 10.6%-68% [11, 16, 17, 22]. The patients with culture proven recurrent UTI were followed up with antibiotic prophylaxis and interestingly, none of them had a break through urinary tract infection during the follow up period. It has been reported that antibiotic prophylaxis following UTI does not certainly prevent recurrence of infection [24]. In our study group, a lack of any UTI recurrence on antibiotic prophylaxis may be due to the short follow up period of our patients, besides antibiotics. Moreover, recurrent urinary tract infections point to calcium phosphate

stones rather than calcium oxalate. Although according to our results a control of UTI seems to have a negative effect for stone formation and size, however, there is insufficient data for this inference.

Investigation of metabolic abnormalities in the urine and chemical analysis of the calculi is important in order to manage renal stone disease appropriately [11]. In the literature, hypercalciuria is reported to be the most common metabolic cause of pediatric urinary calculi [10]. Hypercalciuria was also the most common metabolic abnormality in our study, and all patients with hypercalciuria were normocalcemic. Interestingly, the second common metabolic risk factor was hypomagnesiuria, unlike other reports about pediatric urolithiasis from Turkey. Citrate and magnesium are known substances that are found in urine and prevent stone formation, so that hypocitraturia and hypomagnesiuria have been established as risk factors for formation of calculi [25]. Our study was performed in the southwest region of Turkey. Ertan et al. [11] found hypocitraturia in the western region of Turkey, Gurgoze and Sari [16] also found hypocitraturia as the most common risk factor for renal stone disease in their study group in the eastern region of Turkey, while Dursun et al. [17] found hyperuricosuria, and Acar et al. [22] found hypercalciuria as the most common metabolic risk factors in the central region of Turkey. These differences indicate the geographic, cultural, and dietary factors that affect the cause of urolithiasis, even within the same country.

Among 98 patients, stone analysis was available in 17 and most of these (82.4 %) were calcium oxalate, similar to previous reports [5, 11, 16, 17]. One of the patients with struvite stone underwent left nephrectomy operation due to dysfunction of the kidney with xanthogranulomatous pyelonephritis. Interestingly, 2 patients who had spontaneous passage of the stones, the stones analysis revealed xanthine stones. Both of them had hypouricemia and low uric acid excretion, and they suffered from frequent stone recurrences during the follow up period.

We are aware of the limitations in our study which should be addressed in future research. Firstly, the mean in the follow up period of the patients is relatively short. Secondly, genetic evaluation could not be performed in two patients with xanthine stones. Another limitation is the limited value for detecting renal stones of sonography [26, 27]. However, all the US examinations were performed by the same expert pediatric radiologist in appropriate conditions. For the cases in which the findings were not clear, US were repeated.

In conclusion, hypercalciuria and hypomagnesiuria were the most common metabolic risk factors. In terms of stone disappearance or decrease in the size of the stones, it seems that children younger than 1 year have more disadvantages than older children. We suggest that microcalculi in children should be taken into consideration because we found that approximately 3/5 of these cases had urinary metabolic abnormalities. Recurrent UTI prevention with prophylactic antibiotics may contribute to the improvement of urolithiasis. Patients presenting with restlessness, especially infants with positive family history must be evaluated in terms of renal stone disease by ultrasonographic evaluation. Identifying the underlying metabolic risk factor in patients with urolithiasis is important in order to choose the appropriate treatment modality, to prevent new stone formation or stone recurrence, and to prevent renal damage.

Conflict of interest: The authors declared no conflict of interest.

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