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Clinical Characteristics and Metabolic Abnormalities in Pediatric Urolithiasis in South East Iran

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Introduction: To investigate clinical presentation, metabolic risk factors and urinary tract abnormalities in paediatric urolithiasis.
Materials and Methods: Between 2011 and 2012, 100 children (53 boys and 47 girls) were treated for urolithiasis. Clinical presentation, calculus localisation, urinary tract infection status, presence of anatomic abnormalities and urinary metabolic risk factors were retrospectively evaluated.
Results: The most common clinical features on admission were restlessness/irritability (62%), flank pain (33%) and gross hematuria (4%). Twenty-one percent of patients were detected incidentally during evaluation for other conditions. Urine random tests revealed metabolic abnormalities, including hypercalciuria (56%) and hypocitraturia (64%) in most cases. Anatomic malformation (32%) and urinary tract infections (UTI)(9%) were other presentations.
Conclusions: We concluded that most patients were symptomatic and hypocitraturia was the most common risk factor.

Keywords: Urolithiasis; Urinary Tract; Pediatrics, Demographic Factor; Hypercalciuria.

Running Title: Metabolic Abnormalities in Pediatric Urolithiasis.

Introduction

Urolithiasis is known to be an uncommon pediatric disorder, with an incidence of approximately 2%–3%. The incidence of urolithiasis in children is approximately 10% of that in adults. However, the true incidence of childhood urolithiasis might be underestimated due to lack of routine practice of using ultrasonography in children with specific and non-specific UTI symptoms [1,2]. Urolithiasis in children occurs in all age groups and usually shows a male preponderance.

A wide geographic variation in urolithiasis prevalence has been documented, which might be due to differences in diet, fluid intake, ethnicity and climate [3]. In certain regions, such as South Asia and the Middle East, urinary stones are endemic. The calculi observed in developing countries are often located in the bladder and predominantly comprise ammonium acid, urate and uric acid. However, most of the calculi found in kidneys or ureters comprise either calcium oxalate or calcium phosphate [1]. Certain metabolic and genitourinary anomalies are known to predispose to urolithiasis in paediatric patients, with approximately 30% of cases displaying

genitourinary anomalies. Anatomical or functional obstruction predisposes children to stone formation by promoting stasis of urine and subsequent infection [3]. Urolithiasis is associated with an identified metabolic abnormality in approximately 40%–50% of children. The most commonly observed are hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia and cystinuria, with hypercalciuria and hypocitraturia being the most common [1-3]. The prevalence of paediatric urolithiasis in Zahedan population of South East Iran has been recently increased and it is therefore important to recognize and effectively treat the condition at an early stage. In this retrospective study, we evaluated demographic characteristics, metabolic factors, clinical presentations and anatomical abnormalities of 100 children with urolithiasis who referred to a paediatric nephrology clinic in Zahedan.

Materials and Methods

We retrospectively reviewed the records of 100 children with urolithiasis referred to our paediatric nephrology clinic between 2011 and 2012. Children enrolled had calculi of greater than 3 millimetres in diameter with posterior shadow, documented by renal ultrasonography or spontaneous passage. If UTI was detected or recent stone passing occurred, metabolic studies were postponed. Renal scintigraphy, voiding cystography or intravenous pyelography was performed as indicated. Children taking drugs that could potentially affect mineral metabolism were excluded from the study. Results of clinical and laboratory data, including gender, age at diagnosis, presenting symptoms, UTI status, stone localization, presence of urinary tract abnormalities, urinary metabolic evaluation (including urinary citrate, oxalate, calcium, uric acid, cystine and magnesium**)**, serum biochemistry analysis (including urea, creatinine, uric acid, calcium, phosphorus, magnesium and alkaline phosphatase), blood pH and bicarbonate levels were reviewed. Urine culture was performed for all patients. In infants and non-toilet trained patients, a random urine sample was checked and interpretation of urine chemicals was based on solute to creatinine. In older children, urine was collected for measurement over a 24-h period. Normal values reported in the literature for 24 h and spot urine analysis are summarized in table 1. Urine calcium was measured using o-cresolphthalein complexone method in an analyzer using a commercial kit. Urinary oxalate and citrate levels were measured enzymatically using a Pars Azmoon kit. Urinary uric acid was measured by enzymatic colorimetric analysis using a Pars Azmoon kit. Urinary magnesium was measured by spectrophotometry using the atomic absorption method. Cystine was detected using Nitroprusside. Urinary creatinine was measured by buffered kinetic Jaffe reaction method. The study protocol was approved by the ethics committee of Zahedan University of Medical Sciences. Statistical analysis was performed using SPSS 17. Data was expressed as mean and percentage and tested for statistical significance using Mann–Whitney U test. $P<0.05$ was considered significant.

Table1. Normal values of urinary solute excretion

Salute	24-hour urine	Spot urine
Calcium	<4 mg/kg/day	<0.8-0.2 mg/mg
Oxalate	<50 mg/1.73m/day	<0.15-0.03 mg/mg
Uric acid	<10.7 mg/kg/day or 815mg/1.73m	<0.53 mg/dl GFR
Citrate	>300-400 mg/1.73m/day	>0.2-0.4 mg/mg
Cysteine	<75 mg/1.73m/day	<0.075 mg/mg
Magnesium	<88 mg/1.73m/day	>0.12 mg/mg

Result

Of 100 patients, 53 were male and 47 female. Age ranged from 2 months to 15 years. Thirty three percent of children were less than one year old, 55% aged between 1 and 5 years and 11% were older than 5 years. Of children younger than 1 year at diagnosis, 76% were male. The most common clinical feature on admission was restlessness/irritability (62%). This was accompanied by flank pain (33%) and gross hematuria (4%). Twenty one percent of cases were detected incidentally during evaluation for other medical conditions. Other symptoms at presentation included dysuria, passing stones, urinary retention, enuresis, vomiting, abdominal pain and stone drop. UTI was present in 9% of patients, and in all cases, the organism responsible was Escherichia coli. In ultrasound evaluation the most frequently involved site was the kidneys (84%). Ureter and kidney, ureter, bladder and

urethra were involved in 5%, 11%, 3% and 2% of cases, respectively (table 2). Stones were located bilaterally in 18 patients and this was significantly associated with infants (P< 0.001). Seventy six percent of children had one calculus in their urinary tract system. The mean stone diameter was 6.45 ± 3.2 mm (range 3.5–27 mm). There were no significant differences in stone diameters between males and females (P= 0.32). However, there were significant differences between age groups (P=0.02). Anatomic malformation was found in 32 children (32%). This included vesicoureteral reflux (4%), ureteropelvic junction stenosis (10%), ureterovesical junction obstruction (2%), bilateral duplicated system (1%), ureterocele and bilateral duplicated systems (3%) and megaureter (2%). Other cases displayed pyelocalyceal hydronephrosis in ultrasonography without obstruction (polymegacaliosis).

Table 2. Radiological data of cases

Location		%
Localization of stone	Bilateral	18%
	Multiple	24%
Upper urinary tract	Calix	69%
	Pelvis	15%
Lower urinary tract	Ureter	11%
	Bladder	3%
	Urethra	2%
Upper and lower urinary tract		5%
Anatomic abnormality of urinary tract	Vesicouretral reflux	4%
	Uretropelvic junction obstruction	10%
	Uretrovesical junction obstruction	2%
	Double collecting system	1%
	Double collecting system with uretrocle	3%
	Megaureter	2%
	Pyelocalycial hydrnephrosis without obstruction	10%

Urine analysis revealed metabolic abnormalities in most cases. These included hypercalciuria (56%), hypocitraturia (64%), hyperoxaluria (36%), hyperuricosuria (13%), hypocitraturia plus hypercalciuria (40%), hyperoxaluria plus hypercalciuria (23%) and hyperuricosuria plus hypercalciuria (12%). Two children had cystinuria. No metabolic abnormalities were observed in 14 patients. Serum chemistry, blood pH and bicarbonate levels were within the normal limits in all but two patients presented distal renal tubular acidosis. Stone analysis was performed in four cases. Results showed that the most common stone compositions were calcium oxalate, calcium oxalate plus uric acid and calcium magnesium phosphate.

Discussion

The prevalence of paediatric urolithiasis in Iran has not been previously defined. However, it is an important disease due to many complications and diverse etiologic conditions and reports regarding its predisposing factors vary between countries. A previous report indicated that 75% of children and adolescents with urolithiasis have an identifiable predisposing factor [3]. This prospective study defined various potential predisposing factors in children with urinary calculi in Zahedan, South East Iran. We reported a male/female disease incidence ratio of 1.1:1, similar to that in previous Iranian studies reporting an incidence of 1.1:1–1.4:1 [4-10]. Other studies, including those of Ertan et al. [1-3] and Wumaner et al. [1-3] reported a male predominance as well [3,4]. Many previous studies of paediatric urolithiasis, including those from Iran, reported a mean patient age of 3.9–8.1 years [8,9]. In our study, 55% of children aged between 1 and 5 years.

The major clinical manifestations of paediatric urolithiasis may be due to UTIs, movement of calculi or urinary tract obstruction. In our study, restlessness and flank pain were the most common clinical manifestations of urolithiasis, occurring in 62% and 33% of patients, respectively. This is consistent with previous studies, where 21% to 41% of children reported abdominal and flank pain [6,7,8,11,12]. Furthermore, restlessness and presence of UTI have been reported as the most common clinical findings in infant urolithiasis [7,10,13] and it has been speculated that restlessness could be a clinical reflection of colicky pain. Gross hematuria was uncommon in our study (4%) compared with other reports that documented levels of 7%–35.6% [6,10,12,13-17]. In a previous study, Guven reported an infant admitted with anuria due to ureteral obstruction by stones [2]. Similarly, our study reported anuria in two children due to this

condition. Recurrent UTIs have been previously shown to be a risk factor for paediatric urolithiasis. Furthermore, the presence of stones can lead to UTIs due to urinary stasis and associated metabolic abnormalities [6,7,11,12,17-19], and it is recommended that all urolithiasis patients undergo a urine culture test. UTIs were found in 9% of children in our study. This is less than previous studies where findings of 16%–46% were reported. Sometimes stones are asymptomatic. Reports from Turkey [2,14] have shown that 18.8% and 23.5% of stones were detected incidentally. This is consistent with our finding that 21% of urolithiasis cases were detected incidentally during evaluation for other medical conditions. A wide range of structural abnormalities have been associated with urolithiasis. Partial obstruction can lead to UTIs or defects in renal acidification, hypocitraturia. It has been reported that approximately 10%–19% of pediatric patients with urolithiasis have urinary tract malformations [1] and a study by Safaei found urologic abnormalities in 14.3%. In our study, 17% of patients displayed urologic abnormalities. This comprised 4 cases of vesicoureteral reflux and 13 of obstructive uropathies. This incidence is within the range of previously reported levels of urologic abnormalities (8%–17.8%) [7,8,11]. In addition, our study found abnormal ultrasonography in 32% of cases. Vesicoureteral reflux in our study was found in 4% of patients, similar to that of a previous investigation (Naseri et al.). This may be due to the low incidence of UTIs in our cohort resulting in fewer performed cystogram studies.

Pediatric urolithiasis is associated with metabolic abnormalities in 30%–86% of patients, depending on the location of the studies [1,19-24]. In our study, urine analysis revealed metabolic abnormalities in most cases. Specifically, we found that most patients displayed hypocitraturia (64%), consistent with a recent study [5]. However, these results are in contrast with the findings of Naseri et al. who reported hypocitraturia in 2.1% of patients. Many factors influence citrate excretion including age, weight, urinary pH, diet, metabolic acidosis and UTI status. The method of citrate measurement may also influence the results [21]. These factors may explain the variability of citrate excretion results found in different studies from the same country. Geographic variability may also affect mineral secretion levels. In a Turkish study, Alpay found metabolic abnormalities in 87% of the cases, including hypercalciuria (33.8%), hypocitraturia (33.1%), hyperoxaluria (26.5%), hyperuricosuria (25.4%), hypocitraturia plus hypercalciuria (21.1%), hyperphosphaturia (20.8%) and cystinuria (5.7%). In another Turkish study, Gürgöze detected metabolic abnormalities in 92% of cases, including hypocitraturia and hypocalciuria in 40% and 42% of patients, respectively. In another study, hypocitraturia was found in both healthy and stone-forming children as 48.8% and 69.8%, respectively [23]. These studies confirm that hypocitraturia is a common metabolic abnormality in patients with urolithiasis, particularly in those with calcium oxalate stone disease.

Because the rate of urinary mineral excretion decreases with ageing, it is unsurprising that in a study the most common metabolic risk factors found for paediatric urolithiasis were hypercalciuria (79.6%) and hypocitraturia (40.9%) [8]. Similarly, in the study of Bilge, based on children with a mean age of 16.8 ± 14.9 months, metabolic abnormalities were found in 17.8% of cases, with hypercalciuria as the most common (88.9%) [13]. In general, hypercalciuria appears to be the most common metabolic factor with estimated rates of 37%–74% [1]. The large range may be due to ethnic and geographic differences.

Hyperoxaluria accounts for 2%–20% of metabolic abnormalities, with more recent studies suggesting a much higher possible frequency of 25%–50% [1,18,11,12]. Sepahi et al. detected hyperoxaluria in 14.2% of their patients and in another study hyperoxaluria was detected in 18.4% of cases [10]. Here, we found a hyperoxaluria rate of 36%, similar to that found by Alpay (26.5%). This report noted that oxalate excretion should be evaluated as a routine practice in paediatric urolithiasis, because it is a risk factor to stone formation, particularly in hypercalciuric cases. Hyperuricosuria is found in 2%–10% of children and adolescent with metabolic stone formation [1]. Hyperuricosuria was detected in 13% of our patients, consistent with previous reports [5,9]. Furthermore, Emlaci reported hyperuricosuria in 24.5% of infants with urolithiasis, while Göknar reported a rate of 40% [(17]. Regarding cystinuria, it is generally observed in 2%–8% of paediatric urolithiasis patients [1,5,7,9,10]. We reported an incidence on the lower limit of this range (2%). Occasionally a combination of metabolic abnormalities is observed. In our study, hyperuricosuria plus hypercalciuria was seen in 12% of children. Other studies reported rates of 7.7% (Safaei et al), 3.3%

(Naseri et al) and 16.8% (Elmac A). The qualitative analysis of stones obtained after their passage is one of the most important diagnostic measurements. Only one-third of all stones are composed of a single substance. Stone analysis was performed in four of our cases and the most commonly found compositions were calcium oxalate, calcium oxalate plus uric acid and calcium magnesium phosphate, respectively. Kirejczyk studied the association between paediatric kidney stone composition and urinary metabolic disturbances [15]. They reported that calcium oxalate was the major component of stones (73%), followed by struvite (13%) and calcium phosphate (9%).

Uric acid was present in almost a half of stones but in minor amounts. In other studies, Elmac reported the results of 28 stone analyses, revealing calcium oxalate or phosphate, cystine and uric acid in 15, 9 and 4 patients, respectively [12]. Wumaner et al. reported that the predominant stone composition in pure forms is ammonium urate (58.9%), whereas the predominant mixed stone composition is a calcium oxalate mixture (91.1%). Uric acid-containing stones comprised 54% of the total [4]. In another study, calcium oxalate monohydrate was the principal component of idiopathic stones (58.2%), which is more frequent in children (68%) than infants (51.7%) [18]. These findings are similar to those of a previously published French study [25].

Conclusions

Identification of specific predisposing metabolic factors in paediatric patients with urolithiasis is important in developing effective therapeutic practices.

Acknowledgement

The study protocol was approved by the ethics committee of Zahedan University of Medical Sciences.

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Conflict of Interest

None declared

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