Iraqi JMS

Published by Al-Nahrain College of Medicine
ISSN 1681-6579
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-nahrain.edu.iq

Metabolic Risk Factors for Urolithiasis in a Group of Iraqi Children

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Abstract

Background Pediatric urolithiasis (UL) should not be underestimated, because it is associated with significant morbidity, particularly because stones tend to recur.

Objective To study the demographic characteristics, clinical manifestations, metabolic disorders and some risk factors for stone formation in a group of Iraqi children.

Methods A total of 96 children with UL comprised 66 males and 33 females with an age range 0.1-14 years were studied for the period from 1st of January 2009 to the end of December 2011.

Results Positive family history was present in 29 patients (30.2%); all of them had metabolic disorder. Recurrence rate of stone was recorded in 41 (42.7%); of them 28 (68.3%) had metabolic disorder. The commonest clinical presentation was urinary tract infection in 40 (41.7%). Urine culture was positive in 57 (59.3%) children predominated by E.Coli in 23 (40.3%). Twenty four hour urine collection were positive for metabolic disorders in 84 patients (87.5%) and mainly hypercalciurea in 53 (63 %), hyperoxalurea in 31 (36.9%), hyperuricosurea in 23 (27.3%), and cystinurea in 15 (17.8%). Staghom calculi were detected in 6 patients (6.2%), all are associated with infection. Chemical analysis show calcium salt as major component in 22 out of 33 stones (66.6%). Predisposing risk factors for stone formation was established in 91 patients (94.8%) while no etiology could be found in 5 (5.2%). Metabolic disorders were the major risk for stone formation in 54 (56.3%), infection in 21(21.8%) and renal anomalies in 16 (16.7%).

Conclusion Metabolic disorders were found to be the major predisposing factors to stone formation among this group of Iraqi children. Early presentation, family history of stone disease, high recurrence rate of UL, bilateral and multiple stones are all indicators for metabolic disorders which mandate complete metabolic evaluation in pediatric stone formers.

Keywords Urolithiasis, stones, metabolic, children

Introduction

Pediatric Urolithiasis (UL) should not be underestimated, because it is associated with significant morbidity, particularly because stones tend to recur. As compared with the adult population, a far higher proportion of pediatric patients have a well-defined underlying condition that favors stone formation (e.g., metabolic disorders, infections, urinary tract anomalies). For these reasons, it is imperative to evaluate carefully all pediatric stone patients as soon as stone disease is recognized and to pay great attention to the prevention of further stone formation [1,2].

The two mechanisms by which metabolic factors enhance stone formation include: 1. Solute excess: high urinary concentrations of calcium, oxalate, uric acid, and cystine due to increased renal excretion and/or low urine volume cause solute excess. 2. Decrease levels of inhibitors of

stone formation: Natural inhibitors of urinary stone formation include citrate, magnesium, and pyrophosphate [3-7].

In 20 to 25 percent of children with UL, urinary tract infection (UTI) is detected or there is a history of a UTI. Infection may be the primary cause of a stone or occur concomitantly with a underlying urinary metabolic abnormality or structural abnormality [8].

Congenital and structural abnormalities that are accompanied by urinary stasis are associated with UL. Urinary stasis predisposes to crystal and stone formation [2,9]. Patients who have surgically augmented bladders are at risk for nephrolithiasis, most commonly bladder stones composed of struvite [10].

The incidence of UL in children varies worldwide with the highest incidence occurring in endemic areas, such as in Turkey and Thailand. Stones were more commonly found in Caucasian children and rarely in African-American children. Incidence of UL is lower in children than in adults [4]. The Objectives of this study were to evaluate pediatric UL in a group of Iraqi children regarding some demographic characteristics, clinical presentation, laboratory findings, metabolic disorders and characteristics of stones and chemical composition.

Methods

This cross sectional study was based on 96 children with UL for the period from 1st of January 2009 to the end of December 2011. Those patients with UL were evaluated, treated, and followed up in the pediatric nephrology clinic in Al-Imamian Al-Kadhymian Medical City in Baghdad.

Presence of stone disease was confirmed in all case; radiologically by renal sonography with or without plain abdominal radiograph or patient passed at least one urinary calculus.

All children with renal stones whether newly diagnosed or recurrence were included. Children with renal tubular acidosis or nephrocalcinosis were excluded from the study.

Full recording of the patient characteristics and stone data was done. All children were examined physically and underwent the following investigations: Urinalysis, urine culture. Blood biochemistry test: urea, creatinine, sodium, potassium, calcium, phosphorus, uric acid, and alkaline phosphatase level. Twenty-four hour urine determination of urinary calcium, oxalate and uric acid was performed for all children.

Hypercalciuria (HCa) was defined as urine calcium excretion >4 mg/kg/24 h, Hyperoxaluria (HOx) was defined as urine oxalate excretion >55 mg/1.73 m^2/24 h, Hyperuricosuria (HUr) was defined as uric acid excretion > 815 mg/1.73 m^2/24 h [3,4,11-17].

Serum and urine amino acid excretion were tested for all children using paper chromatography and the nitroprusside test for diagnosis of cystinuria [3,13,17].

Stones from 33 patients that were removed surgically or obtained by spontaneous passage were analyzed chemically.

Voiding cystourethrography (VCUG) and intravenous pyelography (IVP) were done to some patients as indicated. VCUG was done in patients with recurrent urinary tract infection (UTI), and suspected vesicoureteral reflux (VUR). IVP was performed in some cases of suspected renal anomalies.

All of the urinary stones were classified into four groups according to the predisposing risk factor for their occurrence [4,13,15-18].

(1) Metabolic stones: stones predisposed by metabolic disorder.

(2) Anatomic stones: stones that formed with anomalies of urinary system.

(3) Infection stones: children with recurrent UTI with one or more of the following: **A**. staghorn calculi **B**. urine culture of Proteus **C**. Stone chemical analysis of calcium phosphate carbonate, or magnesium ammonium phosphate **D**. associated VUR

(4) Idiopathic stones: The stones that are formed without metabolic, anatomic or infectious etiology.

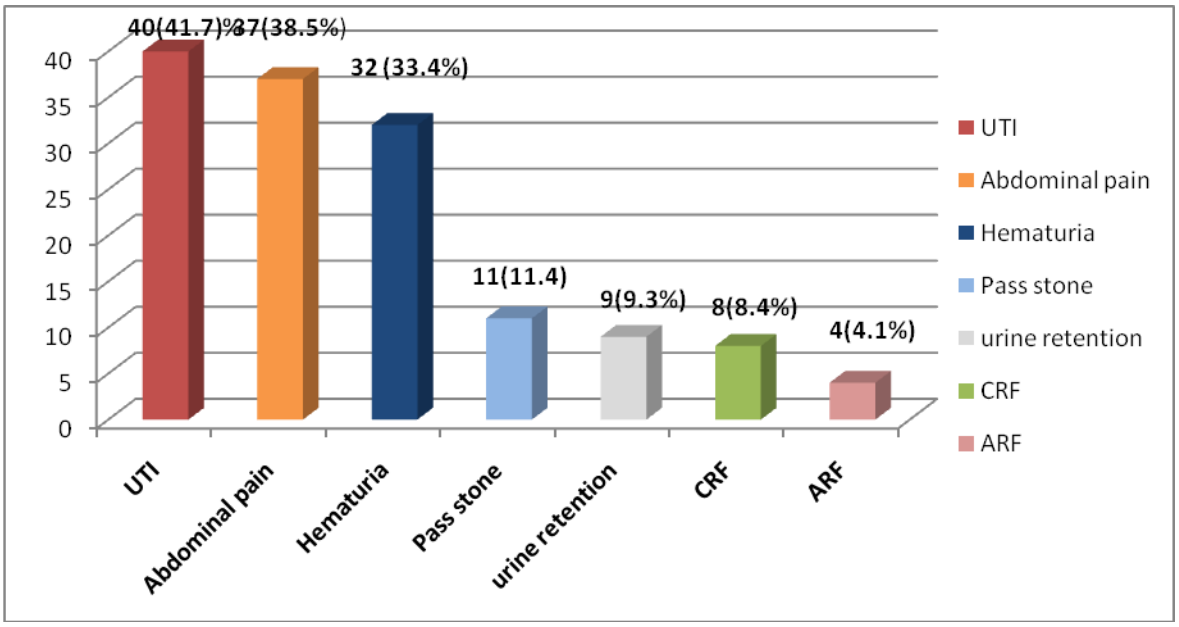
Patients received follow-up testing every 1-2 months; serial US was used to track UL status and was scheduled at every 4-6 months.

Results

Patient population consisted of 96 children with UL, 63 (65.6%) were males and 33 (34.3%) were females with male to female ratio 1.9:1. Their age ranged between 0.1 to 14 years (mean age 3.54 ± 3.389 SD years). The majority of patients 46 (47.9%) were in the 1-5 years age group.

Family history of UL was reported in 29 patients (30.2%); all of them had metabolic disorders. Forty-one patients (42.7%) experienced recurrences, and 28 patients of them (68.3%) had metabolic disorders. Recurrence occurred after an initial diagnosis of stone disease during their lifetime.

Clinical presentation was dominated by UTI in 40 (41.7%) as seen in Fig. 1. Urine culture was positive in more than half of children 57 (59.3%) which is predominated by *E. coli* in 23 (40.3%) of positive cases (Fig. 2).



*Patient may have more than one presentation, CRF: Chronic Renal Failure, ARF: Acute Renal Failure

Fig. 1. Clinical presentation of patients with Urolithiasis

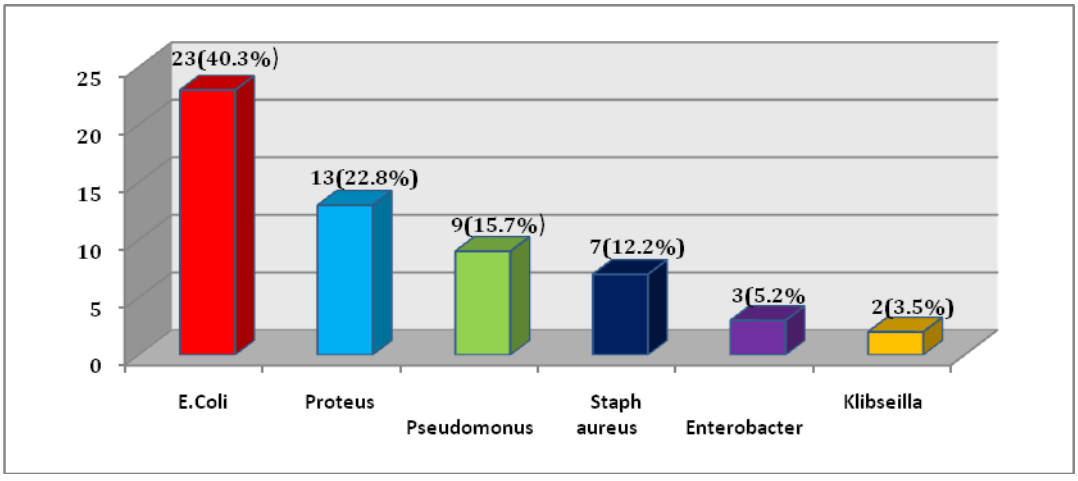


Fig. 2. Urine Culture results of patients with Urolithiasis

Twenty-four hours urine results were positive for metabolic disorders in most cases 84 (87.5%). Hypercalciurea was the commonest detected in 53 patients (63%), 46 out of 84 patients with metabolic disorder had single metabolic urine disorder while the other 38 had multiple urine metabolic disorders (Table 1).

Table 1. Single and multiple urine metabolic disorder in patients with urolithiasis

Single urine metabolic disorder in 46 patients with UL		
Disorder	**No.**	**%**
Hypercalciurea	17	36.9
Hperuricosurea	18	39.1
Cystinurea	9	19.6
Hyperoxalurea	2	4.4
Multiple urine metabolic disorder in 38 patients with UL		
Disorder	**No.**	**%**
Hypercalciurea-hperoxalurea	29	76.3
Hypercalciurea-cystinurea	4	10.5
Hypercalciurea-hyperuricosurea	3	7.9
Hyperuricosurea-cystinurea	2	5.3

Stone data reflect that 36 patients (37.5%) had multiple stones, 26 (72.2%) of the multiple calculi were related to metabolic disorders. Most patients 40 (41.6%) had small size stones (<1 cm) as calculated by US, Staghrn calculi were detected in 6 patients (6.2%), all were associated with infection (Table 2).

Forty-five patients (46.8%) had stones in more than one site. Right kidney was the commonest site for stone location, involved in 58 patients (60.4%), while urinary bladder was involved in 6 patients (6.2%). Bilateral stones found in 41 (42.7%) of whom 23 (56%) had metabolic disorders, and 5 out of 6 bladder stones were proved as infection stone. Chemical stone analysis was done for 33 patients as shown in Table 2. Calcium oxalates is the most common mixture identified in 13(39.4%) patients as pure or mixed.

Risk factors for stone formation were established in 91 (94.8%) while no predisposing factor could be found in 5 (5.2%). Metabolic disorders were the major risk for stone formation in 54(56.3%), infection in 21 (21.8%) and renal anomalies in 16 (16.7%) as shown in Fig. 3.

Table 2. Stone Data in patients with urolithisis

Feature		No	%
No. of stones	1 stone	33	34.3
	2 stones	27	28.1
	>2 stones	36	37.5
Size of stones	<1cm	40	41.6
	1-2cm	32	33.3
	>2cm	18	18.7
	Staghorn	6	6.2
Composition of stones	Ca+Oxalate	8	24.2
	Ca+Phosphate (ph)	3	9
	Ca+UA	4	12.1
	Ca+UA+Ph+Mg	1	3
	Ca+UA+Ph+oxalate	1	3
	Ca+Oxalate+UA	2	6
	Uric Acid	2	9
	UA+Ammonium +Ph	1	3
	Ca+oxalate+carbonate	2	6
	Cystine	7	21.2
	Ca+Cystine+Ph	1	3
	UA+Ph+Carbonate	1	3

As described from above results, metabolic disorders were detected in 84 patients; as a pure metabolic disorder in 54 patients (56.3%), and in other 30 as mixed metabolic disorder with other factor.

Although UTI was documented in 57patients at presentation, only 21 out of 57 of those patients (21.8%) fulfill the criteria of infection stones; from those 21 patients; 16 patients were associated with metabolic disorders, one patient with anomalies and 4 patients had metabolic infectious and anomalies.

Sixteen (16.7%) patients with UL were due to anatomical renal anomalies; 10 out of these 16 were associated with metabolic disorders and the other 6 patients had pure renal anomalies; the associated renal anomalies were described in (Table 3).

Discussion

Many studies have reported a male predominance in childhood UL [4,14,15,18-20]. In agreement with many studies [14,15,18,19,21-23], nearly half of our patients were below 5 years of age. Early evaluation by ultrasonography in addition to high rate of metabolic disorders among our cases, which led to early presentation, was a leading cause of early identification of stone disease

A family history of UL was reported in wide range of 7.3-78.7% in previous studies [3,4,14,15,18,19, 22-24] .In this study, all patients with family history of UL had metabolic disorder for UL. This finding was highlighted by 3 previous studies [4,15,18]. This finding reflects the genetic basis of metabolic disorders for stone formation.

Recurrence risk in this study was 42.7% and 68% of them had metabolic disorders. Recent Turkish study found nearly similar rate of recurrence (44%) and that children with at least one identifiable metabolic abnormality tended to have higher recurrence rates than the others [25]. Recurrence of UL is a consequence of most metabolic disorders [8].

Most common reported clinical presentation of UL in children are abdominal pain and hematuria [3-5,14,15,18,19,23,24,26]. Not so like our results, which showed predominance of UTI (41.7%)? Several studies have noted a strong association between UL and UTI [3,5,14,18,19,21-24,27]. We believe that UTI was a complication of stones rather than predisposing factor, as infection stones were detected in only 21 patients out from 57 patients with documented UTI among our cases.

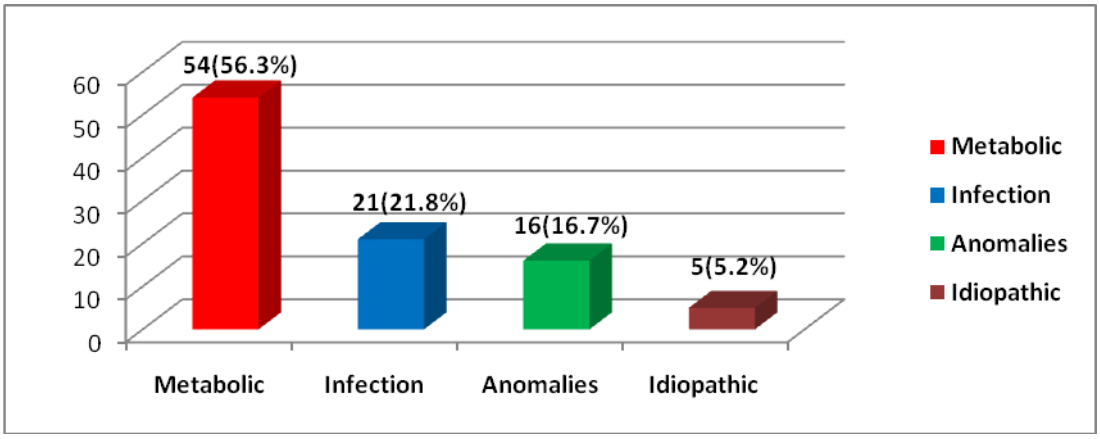


Fig. 3. Predisposing risk factors of patients with urolithiasis

Similar to Al Rasheed et al study [28], *Escherichia coli* was the most frequent bacteria isolated while Proteus dominated in others [18,23].

Metabolic disorders were detected with variable rates in children with UL ranging from 10.6% to 92% from different regions [3-5,14,15,18,28].

In a previous Iraqi series, metabolic disorders were detected in 72% of children with UL [15], compared with 87.5% in this study. This increase in metabolic disorders among Iraqi children with UL reflects changing environment and dietary habits both as important risk factors for UL, which need to be further studied.

In agreement with most studies from different regions [3-5,15,18,19,23,27], we detected hyper-calciuria as commonest metabolic disorder.

Interestingly, cystinuria was detected in 15 of our patients (17.8%). Lower results came from other studies [4,14,18,19,23,24,27]. Our cultural habits with high rate of first-degree cousin marriages might explain our results as cystinuria is known autosomal recessive inherited disorder.

Multiple and bilateral stones were recorded in variable rates in many studies [4,14,18,19,24,28]. In this study, 72.2% of the multiple stones and 67.6% of the bilateral stones were related to metabolic disorders. This relation between

metabolic disorder with bilateral and multiple stones was confirmed by 2 authors [4,31]. These findings led us to think that metabolic disorders dominate cases with multiple and bilateral stone. A correlation between staghorn calculi and infective stones was noted in this study, also found by many authors [17,29,30]. In consistent with results of many studies [3,4,14,15,18,19,24,25,28], majority of stones were located in the upper urinary tract among our patients.

Table 3. Associated renal anomalies in 16 patients with urolithiasis

Associated anomalies/causes	No.	%
Neurogenic bladder	6	6.2
Single kidney	3	3.1
Polycystic kidney	3	3.1
PUJ obstruction	2	2.08
Duplex system	2	2.08

In agreement with several studies, calcium oxalate was the most frequent chemical compound in UL [4,14,18,19,22,24,25,26,28]. Calcium oxalate stones are linked to dietary habits, although this effect is more prominent among adults more than children However, Calcium oxalate stone caused by genetic diseases is proportionately more frequent in children [18].

Similar to us, most literature reviews from various regions of the world revealed an underlying predisposing factor for stone formation in a large proportion of their studied series. (3, 4, 14, 15, 19, 23, 24, 26, 27).

Like our results, metabolic disorders ranked first etiology for UL in most studies [3,4,14,15,19,23,24,26,27]. Over the past decades, the etiology of UL in children has shifted from predominantly infectious to metabolic causes [14,32]. Early presentation, family history of stone disease, high recurrence rate of UL, bilateral and multiple stones are all indicators for metabolic disorders, which were observed in this study, and this observation was also confirmed by a recent study from Turkey [4]. Most of the studies that addressed etiologic classification reported a ratio of 10.7–26% for Infectious stones [4,18,24,26,28] which is near to our results.

Previous studies reported similar renal anomalies with various rates [4,18,19,26,28]. Urinary tract anomalies with stasis, but no infection, leading to CaOx stones, while the growth of calcium phosphate stones is facilitated by infection and a high urinary pH [18,26]. The profile of predisposing risk factors for UL of the present study was in accordance with previous Iraqi study held on 2005 [15].

In conclusion, UL among a group of Iraqi children had male predominance, early onset of presentation, high rate of positive family history and recurrence of stone disease. UTI was the commonest clinical presentation with *E. coli* as predominant pathogen isolated by urine culture. Hypercalciuria was the commonest metabolic abnormality as single or multiple and Calcium oxalate was the commonest type of stones. Predisposing factor of UL was established in majority of cases.

Early presentation, family history of stone disease, high recurrence rate of UL, bilateral and multiple stones are all indicators for metabolic disorders, which mandate complete metabolic evaluation in pediatric stone formers to determine the possible metabolic disorder with early treatment.

Future studies are needed including patients of UL from other Iraqi governorates. Pediatrician should have higher concern of possible UL with mentioned clinical presentation, with early referral to pediatric nephrology / Urology clinic.

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Received 28th Jul. 2013: Accepted 21st Oct. 2013.