

The Relationship between Urinary Reflux and Nephrolithiasis in Children: A Cross-Sectional Study

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Abstract

Background

Urinary reflux is a probable reason of nephrolithiasis among children. This study aimed to assess the relationship between urinary reflux and other reason of stone formation in children.

Materials and Methods

This cross-sectional study was carried out with 199 children diagnosed with nephrolithiasis using ultrasonography in Hazrate Masumeh Pediatrics Hospital, Qom- Iran. The patients who met the exclusion criteria including: the size of stone less than 2mm, congenital diseases of kidney and cyst or tumor, other disorders with similar ultrasound evidence of kidney stone, the use of ceftriaxone during the last 3 months, and incomplete medical record, were excluded. Variables including baseline characteristics of the samples, the presence of hematuria, pyuria, UTI, size of stone, and the findings of ultrasonography and the Voiding Cystourthrography (VCUG), were collected retrospectively. Data analyzed by SPSS version 19.0 software.

Results

A total of 199 children with the mean age was 27.7 ± 27.9 months were included in the study. Overall, 83.9% of the children had normal conditions regarding urinary reflux, with the total urinary reflux rate of 16.1%. The most prevalent observed clinical manifestation was irritability (45.2%) followed by fever (45.2%), and dysuria (19.6%), respectively. Results showed that UTI increased the risk of urinary reflux in 32.4% of the children ($P=0.005$). The prevalence of UTI in female children was more than male ones (27.4% vs. 8.6%, $P=0.001$).

Conclusion

In the present study we concluded that UTI and also pyuria can significantly have decreased the prevalence of VUR. However, based upon our results, there was no significant correlation between urinary stone and VUR.

Key Words: Children, Nephrolithiasis, Urinary tract infection, Vesicoureteral reflux.

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1- INTRODUCTION

Urinary stone in children is a painful and costly experience. It can have long-term effects on the function of kidney. The incidence of this disease has increased steadily in recent decades (1). Enough information about the prevalence of this problem does not exist in Iran. However, the overall prevalence of the disease is 1-15% over the world (2). The prevalence of nephrolithiasis varies geographically and also depended on variable etiologies. However, urinary stone was recognized as a curious medical problem in developed countries in contrast to developing countries (3-6). Iran is in the "belt stone" and the prevalence of kidney stone in Iran is about 2-3% (7). It has been reported that patients mostly suffer from urinary metabolism disorders (6, 8-11).

Urinary stones are polycrystalline aggregates and the combination of different amounts of crystalloid and organic matrix. The formation of urinary stone needs supersaturated urine (12), which depends on urinary PH, ionic strength, as well as urine composition. In addition, the formation of kidney stone is related to factors including metabolic disorders, urinary tract structural problems, nutrition, heredity, age, gender, and climate (13). Metabolic abnormalities such as hypercalciuria, ystinuria, hyperoxaluria, and hyperuricosuria are some common causes of kidney stones in children (14).

A proper evaluation of kidney stone in children encompasses assessments of the type of stone and predisposing factors for its formation. The hereditary and environmental factors should be also considered during the evaluation of kidney stones (15). Structural abnormalities have been reported to be available in 10 to 25 percent of children with nephrolithiasis (12). Congenital and structural abnormalities are also associated with nephrolithiasis. Urinary saturation can predispose children to the formation of

crystals and stones (12). In this regard, urinary reflux can be a probable reason of nephrolithiasis in children. Urinary reflux in children is mainly congenital with the overall prevalence of 1% (16). The role of reflux as a risk factor for pyelonephritis leading to serious kidney damages has been confirmed (17). In some studies, a significant association has been reported between vesicoureteral reflux and urolithiasis (18). It has been manifested by an increased prevalence of hypercalciuria in children and their family members (19, 20). Generally, some risk factors for the formation of kidney stone included metabolic abnormalities (50%), followed by urinary tract infection (UTI) (20 to 35%), and structural anomalies (20%) such as urethral duplication (16,21,22). Urethral reflux is a major cause for UTI that is also a considerable risk factor for urolithiasis (18, 23, 24). This study aimed to assess the relationship between urinary reflux and its related stasis with kidney stone formation in children. The findings of this study can be useful to recognize urinary saturation as a major cause of childhood nephrolithiasis.

2- MATERIALS AND METHODS

2-1. Design and setting

This cross-sectional study was carried out between February 2014 and September 2016 (19 months) with 199 children diagnosed with nephrolithiasis. They were hospitalized in the nephrology ward of a referral children hospital in Hazrate Masumeh Pediatrics Hospital, Qom, Iran. The inclusion criteria were those children who had an ultrasound evidence of kidney stone. The exclusion criteria were those children with the size of stone less than 2mm, congenital diseases of kidney and cyst or tumor lesions in kidney, other disorders with similar ultrasound evidence of kidney stone, the use of ceftriaxone during the last 3 months, and incomplete data in patients' files.

2-2. Data collection

The grading of the Vesicoureteral Reflux (VUR) was standardized with the voiding cystourethrogram (VCUG) by the International Reflux Study Research (IRSC), which was divided into five grades. The grades consist of Grade *I*. The non-dilated ureter was filled by the contrast. Grade *II*. The non-dilated ureter and renal pelvis was filled by the contrast. Grade *III*. The ureter was mildly dilated and renal pelvis was minimally blunted. Grade *IV*. The ureter had moderate tortuosity and the renal pelvis and calyces were dilated. Grade *V*. the renal pelvis and the calyces were grossly dilated with the significant tortuosity of the ureter (25).

A questionnaire was developed to collect data regarding: baseline characteristics of the samples, the presence of hematuria (defined as more than five red blood cells per microliter in high power field), pyuria (defined as ≥ 10 white blood cells per microliter in high power field), UTI (defined as bacterial growth of $\geq 10^5$ CFU) (36), size of stone, and the findings of ultrasonography and the VCUG (25). The related data was recorded using the patient's files in the hospital. It is noted that those children with the ultrasonography evidence of kidney stone was referred back to the radiology department to be assessed the same radiologist for urinary reflux using VCUG.

2-3. Sampling

The sample was chosen using convenient sampling method. Therefore, all children referred to the study setting for kidney stone were recruited in this study. During the study process between February 2014 and September 2016, 199 children were recruited. In our 19 months` experiences, pre-specified data extracting forms were completed, according to patients` hospital records.

2-4. Ethical considerations

The study research proposal was approved and supported financially by research

council of Qom University of Medical Sciences, Qom, Iran. Also, this university's ethics committee supervised and corroborated the study in terms of ethical considerations. To comply with the principle of anonymity, the samples' identities were kept confidential. Moreover, the samples' guardian was informed of the study process and gave consent for the children' data to be used in this study for research purposes.

2-5. Data analysis

The statistical software of SPSS version 19.0 for windows (SPSS Inc., Chicago, IL) was used for data analysis. Results were presented as mean \pm standard deviation (SD) and were summarized by using absolute frequencies and percentages for categorical variables. Categorical variables were compared using Chi-square test or Fisher's exact test. P-value of 0.05 or less were considered statistically significant.

3- RESULTS

In total, 199 children younger than 14 years old were included in this study. Their mean age was 27.7 ± 27.9 months and 53.3% were female. Also, 43.7% aged lower than one year, 45.7% aged 1 to 5 years, and only 10.5% aged higher than 5 years.

Overall, 83.9% had normal conditions regarding urinary reflux, while 1.5% had reflux grade I, 5.5% reflux grade II, 8.1% reflux grade III, and 1% reflux grade IV with the total urinary reflux rate of 16.1% (**Figure.1**).

Hematuria was found in 38.7% of the children. The average sizes of kidney stone in the left and right kidneys were 3.0 ± 1.5 mm (ranged 2-10 mm) and 3.25 ± 1.26 mm (ranged 2-13 mm), respectively without any significant statistical difference ($P = 0.470$). The most prevalent clinical manifestation of nephrolithiasis was irritability (45.2%) followed by fever (45.2%), and dysuria (19.6%).

While malaise was more dominant in children younger than 1 year old, fever was more observed in the children lower than 5 years and dysuria and abdominal pain in the children older than 5 years (**Figure.2**). The prevalence of UTI increased the probability of urinary reflux (**Table.1**). It meant that UTI increased the risk of urinary reflux in 32.4% of the children ($P=0.005$). A statically significant relationship was found between the children's gender and UTI ($P=0.005$) (**Table.2, Figure.3**).

The prevalence of UTI in female children was more than male ones (27.4% vs. 8.6%, $P =0.001$). Also, 18.6% of the children suffered from UTI. Comparing baseline variables between the children with and without urinary reflux showed no statistical difference between the male and female children (14% vs. 18%, $P = 0.288$).

The presence of pyuria increased the rate of reflux from 11.0% to 27.9% ($P = 0.004$). Also the presence of UTI increased the risk of reflux from 12.3% to 32.4% ($P = 0.005$). The prevalence rate of UTI was significantly higher in the female children than in male children (78.4% vs. 21.6%, $P < 0.001$). Nevertheless, no statistical difference was revealed in the rate of UTI between the age subgroups ($P = 0.151$).

Additionally, the rate of UTI was 33.3% in reflux grade I, 54.5% in reflux grade II, and 27.8% in reflux grade III without any significant difference ($P = 0.348$). No relationship was found between the size of kidney stones in both kidneys and the presence of reflux and its grade. The size of kidney stones in left and right kidneys was not related to hematuria, pyuria, and UTI (**Table.3**).

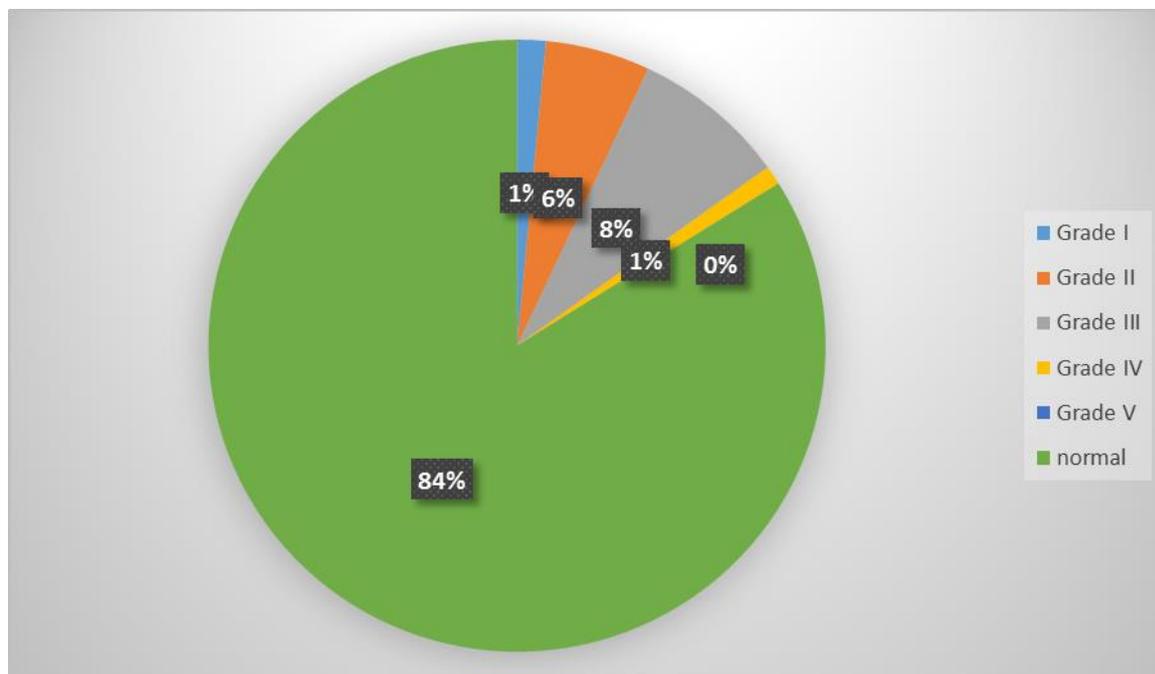


Fig.1: The prevalence of the patients by VUR grading (n=199).

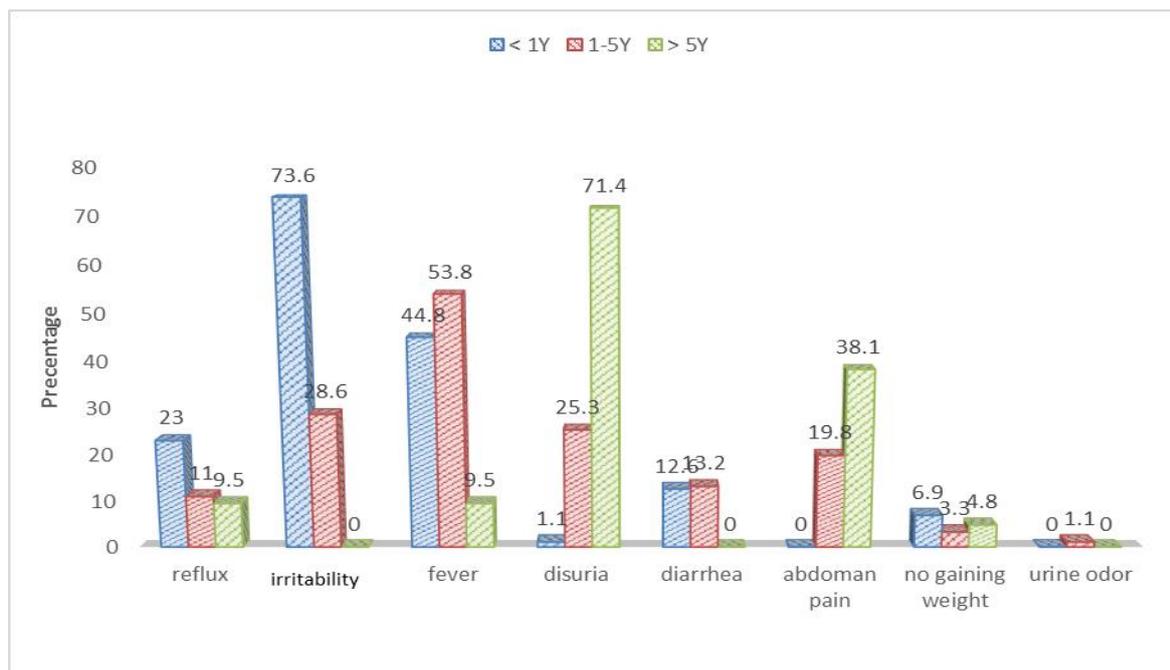


Fig.2: The prevalence of clinical symptoms in different age subgroups (n=199).

Table-1: The frequency of reflux in children suffering from UTI

Urinary reflux	UTI		P-value
	Yes (n %)	NO (n %)	
Yes	12 (32.4)	25 (67.6)	0.005
No	20 (12.3)	142 (87.7)	

UTI: Urinary Tract Infection.

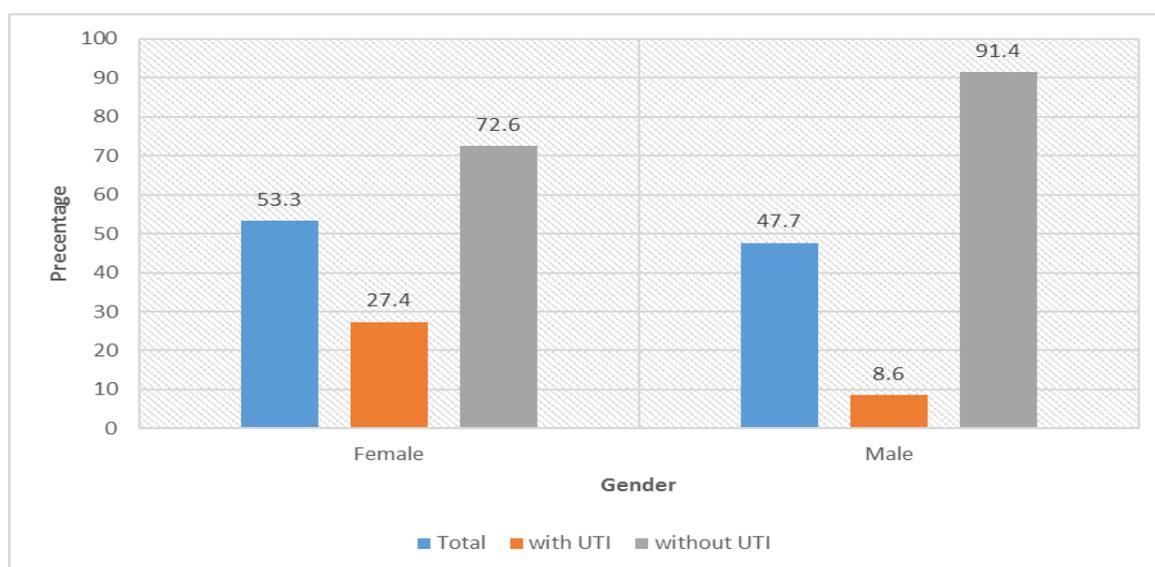


Fig.3: The prevalence of the UTI by the gender (boys=93, girls=106).

Table-2: The frequency of UTI between genders

Gender	UTI		P-value
	Yes (n %)	No (n %)	
Female	29 (27.4)	77 (72.6)	0.005
Male	8 (8.6)	85 (91.4)	

UTI: Urinary Tract Infection.

Table-3: The relationship between the size of kidney stone and data

Variables	Left kidney Mean ± SD	Right kidney Mean ± SD
Hematuria		
Presence	2.8 ± 1.6	3.9 ± 2.9
Absence	3.1 ± 1.6	4.7 ± 1.4
p-value	0.205	0.164
Pyuria		
Presence	3.3 ± 1.7	3.4 ± 2.6
Absence	2.9 ± 1.4	3.1 ± 2.0
p-value	0.077	0.655
UTI		
Presence	3.0 ± 1.6	3.5 ± 2.3
Absence	3.0 ± 1.5	3.2 ± 2.3
p-value	0.850	0.660
Reflux		
Presence	2.9 ± 1.7	2.8 ± 1.1
Absence	3.1 ± 1.5	3.3 ± 2.4
P-value	0.716	0.459
Reflux Grade		
II	3.5 ± 2.3	2.2 ± 0.2
III	2.6 ± 1.3	3.0 ± 1.4
P-value	0.238	0.347

UTI: Urinary Tract Infection; SD: Standard deviation.

4- DISCUSSION

This study presented the answer to the question regarding the relationship between urinary reflux and other reason of stone formation in children. There is a wide variation in prevalence of urolithiasis in different countries (27 -29). However, the incidence of nephrolithiasis was estimated approximately 0.001 to 0.1% in the United State and 7% in Asia (6).

The formation of the urinary tract stone is the complex process. Several factors consist of biochemical and anatomical factors had been explained for this process. These factors were including urinary

supersaturation, pH, biochemical composition, and anatomical malformation of urinary tract (6, 30). The lifetime prevalence of kidney stones is estimated between 1% and 15%. Similar to other developed and transitional countries, the prevalence of urolithiasis in Iran has increased due to changes in people's lifestyle (2). The findings of this study showed that fever and malaise were the dominant clinical manifestations of nephrolithiasis in children compared with adults that abdominal pain might be the pathognomonic symptom. In fact, suspicion to nephrolithiasis should be considered in children with fever, malaise, and dysuria. The signs and symptoms of

childhood nephrolithiasis are considerably different from those in adults. In other words, vague abdominal pain, hematuria, and UTI are more common in children in comparison with the classic colicky flank pain in adults. In our study, abdominal pain only occurred in 13% of the children, while UTI appeared in 18.6% and hematuria in 38.7%. The classic unilateral colicky flank pain occurs in 7% of patients. Instead, abdominal pain is the most common symptom occurring in 53-75% and gross hematuria in 14-33% (27 - 29, 31-34). In this study, 18.6% of the children suffered from UTI. It is reported that UTI affects 8-45.9% of children with nephrolithiasis (35-37). In children less than five years old, UTI most often lead to the diagnosis of nephrolithiasis that occurs in 62% of this age group (36, 37).

Furthermore, if one considers only infants, UTI may be the presenting sign in up to 75% of patients (37). Therefore, it seems that such a finding may be paradoxical due to the different rates of symptoms and signs in different age subgroups. Although all study samples in this study suffered from nephrolithiasis based on the findings of ultrasonography, only 16.1% showed urinary reflux according to the VCUG. This finding should be highlighted from two main aspects (i), nephrolithiasis in most patients may not have any association with urinary reflux and in fact the pathological features of urinary stone may not be dependent to urine reflux in the most cases; (ii), the frequency of urinary reflux may reflect partial agreement between the two diagnostic modalities including ultrasonography for assessing kidney stone and the VCUG for assessing urinary reflux. According to the literature, the accuracy of Computed Tomography (CT) scan for assessing kidney stones has been confirmed. However, it also has been shown that ultrasonography is the modality of choice for initial imaging in pediatric patients who have findings consistent with

nephrolithiasis. Ultrasonography has a high sensitivity (up to 90%) for the detection of kidney stones, though sensitivity for ureteral stones is lower (44-90%) (35-39). Despite such a limitation, this modality is a useful test in those children in whom kidney stones are suspected. If kidney stones are not observed in ultrasonography, suspicion remains high due the possibility of hydronephrosis, therefore, proceeding to CT is reasonable.

Regarding the association between vesicoureteral reflux and kidney stone in children, it seems that these two pathologic features are not interdependent. As shown by Roberts and Atwell (40), in 80% of children with reflux, vesicoureteral reflux was probably primary and only in 20%, it can be secondary to kidney stone. In this regard, the incidence of kidney stone with reflux is approximately 0.5% whereas the incidence of reflux with kidney stone is approximately 8%. Therefore, the presence of reflux is not a decisive reason for the diagnosis of kidney stone in children.

4-1. Limitations of the study

Some limitation was restricted our study. As in all similar studies, retrospective data collection may increase the chance of bias in medical records. However, it would be better if the data analyzed in the large sample size and prospectively.

5- CONCLUSION

Overall, in the present study, data demonstrated that urinary tract infection and also pyuria can significantly increase the risk of vesicoureteral reflux. However, the risk of VUR was significantly higher in the female. Furthermore, we concluded that there was no significant correlation between prevalence of nephrolithiasis and occurrence of vesicoureteral reflux.

6- CONFLICT OF INTEREST

No conflict of interest is declared by the authors.

7- ACKNOWLEDGMENT

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