Comparing Nephrolithiasis with Nephrocalcinosis in Children; A Study From Two Tertiary Centers in Saudi Arabia

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Research Article

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Abstract

Background: Nephrolithiasis and nephrocalcinosis is uncommon in children; however, its incidence is increasing.

Patients and Methods: A multicenter retrospective study of the clinical presentation, etiology, and outcome of childhood nephrolithiasis and compare it with nephrocalcinosis.

Results: The study included 144 children; 93 with nephrolithiasis (formation of stones within renal pelvis or tubular lumen) and 51 with nephrocalcinosis. (deposition of calcium in the renal parenchyma) Mean age at presentation were 72 months and 54 months for nephrolithiasis and nephrocalcinosis, respectively. In 64.8% of the nephrolithiasis and 76% of nephrocalcinosis cases, a history of consanguinity was found. Congenital anomalies of the kidneys and urinary tract were present in 28% and 9.8% of those with nephrolithiasis and nephrocalcinosis, respectively. The most common symptoms of nephrolithiasis were flank pain (29%), hematuria (15%), and dysuria (11%). Urinary tract infection was the primary presentation in the nephrocalcinosis group (18%) followed by failure to thrive (16%), polyuria (12%), and dehydration (12%).

The majority of nephrolithiasis cases were caused by metabolic disorders. In contrast, the most common underlying disorders for nephrocalcinosis were familial hypomagnesemia hypercalciuria nephrocalcinosis (35%), distal renal tubular acidosis (23%), and Bartter syndrome (6%).

Clinical outcomes were significantly better in children with nephrolithiasis than those with nephrocalcinosis who had radiological evidence of worsening/persistent calcinosis and progressed more frequently to chronic kidney disease (stage II-IV) and end stage kidney disease.

Conclusion: The etiology of nephrolithiasis can be identified in many children. Nephrocalcinosis is associated with worse clinical outcomes related to kidney function and disease resolution as compared to nephrolithiasis.

Introduction

Nephrolithiasis is relatively uncommon in the pediatric population; however, cases in children are increasing [1]. It is associated with significant long-term sequelae, including the morbidity caused by recurrent stones as well as the development of chronic kidney disease (CKD) and renal impairment.

The annual incidence of pediatric nephrolithiasis has increased from 6–10% over the past 20 years in the United States [1], with an observation of a greatest increase among adolescent black girls [2].

The etiology is metabolic in most children, with hematuria and urinary tract infections as the most common presentations [3]. However, the clinical presentation varies with age, as flank pain may be seen in older children or adolescents whereas vague symptoms such as nausea, vomiting, and irritability are
typical in younger children. Incidental findings on imaging studies have also been reported in a considerable proportion of affected children [4].

Kidney stone formation requires urine that has a higher solute concentration than its solubility [1]. Crystallization occurs due to an imbalance of promoters and inhibitors, and the attachment and growth of crystals into nephroliths due to epithelial abnormalities [5].

The management of pediatric nephrolithiasis includes urinary decompression, medical treatment of specific risk factors, and surgical intervention [6].

In this study, we report the epidemiology, etiology and outcome of childhood nephrolithiasis from two tertiary centers in the Kingdom of Saudi Arabia (KSA) and compare it with nephrocalcinosis.

**Study Design**

This multicenter retrospective study was conducted at two tertiary centers in KSA (King Abdulaziz University Hospital and King Saud University Medical City).

**Patients And Methods**

Children diagnosed with renal stones or nephrocalcinosis were included and followed in the recruiting pediatric nephrology units during a period of eight years (between January 2010 and December 2018).

The inclusion criteria included children (defined as those aged 14 years or younger) with a radiologic diagnosis of renal stones or nephrocalcinosis.

Renal stone (nephrolithiasis) was defined as the presence of a stone in two images excluding artifacts. Children who had spontaneous passage of a stone or had a stone removed by surgical intervention were included if the stone analysis was available. Nephrocalcinosis was defined as medullary calcification in a portion of the renal medulla without shadowing. We used either ultrasound or computerized tomography (CT) in detecting faint calcifications. Nephrocalcinosis was classified based on renal ultrasound findings as follows: mild (early hyper echogenicity in the periphery of the pyramids), moderate (diffuse hyperechoic pyramids), and severe (clumps of renal pyramids)[7].

All demographic and clinical data were collected from the patients’ electronic hospital records and included age at presentation, gender, creatinine level, estimated glomerular filtration rate (eGFR) at presentation, medical and surgical history, presence of a family history of nephrolithiasis or CKD, consanguinity, symptoms and signs at presentation, number and localization of stones as well as grades of nephrocalcinosis. All patients presenting with symptoms and/or signs of urinary tract infection (UTI) were screened using urine analysis and urine culture. Urine samples were collected either via transurethral catheterization for children younger than 3 years old or clean catch samples if more than 3 years old. We defined UTI as the presence of more than 5 white blood cells per high power field (hpf) and a positive
urine culture with more than 1,000,000 bacterial colony counts per ml. Urine collection was obtained from midstream urine or through a transient clean catheter for younger children.

To reach the diagnosis of metabolic renal stones or nephrocalcinosis, we combined the data of urine metabolic workup, genetic tests with the relevant clinical data, and stone analysis. The metabolic workup of nephrolithiasis was done using a spot urine sample and was interpreted as solute/creatinine ratio [8]. The test was repeated twice as a confirmatory method for hypercalciuria, hyperoxaluria, cystinuria, hypocitraturia, and hyperuricosuria. Hypercalciuria, hyperoxaluria, and hyperuricosuria were defined as a urinary solute: creatinine ratio greater than the 95th percentile as a function of age (Table 2). We also examined the associated acid-base and electrolytes disturbances such as metabolic acidosis and alkalosis, hypo- or hypernatremia, hypo- or hyperkalemia, hypo- or hyperchloremia, hypo- or hypercalcemia, and hypo- or hyperphosphatemia. Hypernatremia and hyponatremia were defined as a serum sodium level greater than 145 mmol or less than 135 mmol, respectively. Hyperkalemia was defined as a serum potassium greater than 5.5 meq/L in children and greater than 6 meq/L in neonates, and hypokalemia was defined as potassium level less than 3.5 meq/L. Hypercalcemia was defined as a serum calcium level greater than 2.6 mmol/L, and hyperphosphatemia as a serum phosphate level greater than 1.58 mmol/L. Metabolic acidosis was defined as a pH level less than 7.35 and a serum bicarbonate level less than 18 meq/L, whereas metabolic alkalosis was defined as a pH level greater than 7.45 and a serum bicarbonate level greater than 25 meq/L.

Renal imaging (renal ultrasound, X-ray, and CT) was reviewed and used for classification, as previously mentioned. Genetic tests and stone analysis were performed when possible and were used as confirmatory tests to diagnose the underlying cause of kidney disease. All confirmed cases of renal stones or nephrocalcinosis were followed-up, and serial imaging studies (renal ultrasound and/or X-ray and/or helical CT) were performed to evaluate the outcome. eGFR was calculated using the Schwartz formula [7][9]. All clinical data about the stones such as the number, location, laterality, and grades of nephrocalcinosis were collected. All associated congenital anomalies of the kidney and urinary tract were reported. Stone analysis was performed for those who spontaneously passed their stones. We documented the used treatment modalities, which included conservative, extracorporeal shock wave lithotripsy (ECSL), or surgical therapies.

The outcomes of nephrolithiasis or nephrocalcinosis were monitored and categorized as follows: spontaneous resolution, post intervention resolution, persistence, worsening or with new stone formation, or nephrocalcinosis. Cases that were missed during the follow-up were identified and documented. Spontaneous remission was defined as the disappearance of stones and/or nephrocalcinosis in two or more serial imaging studies. Renal outcome was used as an indicator of morbidity and was assessed by measuring the reduction in eGFR compared with the initial GFR and determining the presence and severity of proteinuria. The incidence of mortality was reported.

**Statistical analysis:**
All analyses were performed using STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) software. The proportion and mean for dichotomous and continuous variables, respectively, were measured to describe patients’ characteristics. Comparative analyses were performed using chi-square test for categorical variables and student $t$ test for continuous variables. Statistical significance was determined using the 95% confidence interval and $p$-value of 0.05.

**Results**

We have identified 144 patients who met the inclusion criteria (93 presented mainly with nephrolithiasis and 51 with nephrocalcinosis).

The average age at presentation for children with nephrolithiasis was greater than that of those with nephrocalcinosis (mean of 72 months versus 54 months). Most patients with nephrolithiasis were male (66.7%), representing a male-to-female ratio of 2:1. On the contrary, nephrocalcinosis occurred mainly in females (60.4%), representing a male-to-female ratio of 0.66. Furthermore, a greater proportion of children with nephrolithiasis had normal kidney function at the time of presentation. The mean eGFR at time of presentation was higher in children with nephrolithiasis (148.4 versus 122.7 ml/min/1.73 m$^2$) (Table 1). A history of consanguinity was found in 64.8% of the patients with nephrolithiasis (56% of the patients had parents who were first degree cousins). A quarter of this group had a family history of nephrolithiasis and a third had a family history of CKD (Table 1). In the nephrocalcinosis group, consanguinity was found in 76% of the cases. Of these, 35% had a family history of nephrolithiasis and 23.7% had a family history of CKD (Table 1).

Congenital anomalies of the kidney and urinary tract were reported in 28% of children with renal stones and in 9.8% of those with nephrocalcinosis (Table 1).

The most frequent presenting symptom of nephrolithiasis was flank pain (29%), followed by hematuria (15%) and dysuria (11%). Approximately 19% of the children presented with signs and symptoms of UTI, which was confirmed with a urine culture in 15% of the cases. Nephrolithiasis were incidentally discovered during routine investigations in 14% of the patients. Other symptoms such as failure to thrive, dehydration, and polyuria were reported less frequently (Fig. 1). UTI symptoms and signs were the main presentation in the nephrocalcinosis group (31%); however, UTI was confirmed with a urine culture in only 18% of the cases.

Failure to thrive, polyuria, and dehydration were the presentation in 16%, 12%, and 12%, respectively, of the children with tubulopathy with nephrocalcinosis (Bartter syndrome and distal renal tubular acidosis). Nephrocalcinosis was incidentally diagnosed during routine investigations in 18% of the children. Other less frequent presentations included rickets, dysuria, and hematuria (Fig. 1).

The etiology of nephrolithiasis was determined in 78% of the cases, whereas it was idiopathic in 22% of the children. Metabolic disorders were observed in 69% of the cases and included the following conditions: hyperoxaluria (18%), cystinuria (18%), hypercalciuria (12%), and hyperuricosuria (2%). A UTI
was documented in 20% of the cases. Distal renal tubular acidosis and the use of diuretics were reported in less than 5% of the children in this group. On the other hand, the underlying cause of nephrocalcinosis was determined in 86% of the cases (familial hypomagnesemia hypercalciuria nephrocalcinosis [FHHNC] 35%), distal renal tubular acidosis (23%), and Bartter's syndrome (7%) (Fig. 2).

The results of urinary metabolites (solute/creatinine ratio) and serum electrolytes for both the renal stone and nephrocalcinosis groups were represented as mean of solute/creatinine ratio and 95% confidence interval (CI), which are summarized in Tables 3 and 4.

The high frequency of FHHNC explains the higher incidence of hypermagnesuria represented as fractional excretion of magnesium (FEMg%) and hypercalciuria in the nephrocalcinosis group as compared to those with the nephrolithiasis group (p-value ≤ 0.001; Fig. 3A). Similarly, the incidence of hypokalemia, hypomagnesemia, and acid-base disturbance were significantly higher in the nephrocalcinosis group (p-value < 0.001, Fig. 3B).

The clinical outcomes were significantly better in children with nephrolithiasis; among those a greater proportion showed spontaneous or post intervention improvement. In contrast, a greater proportion of patients with nephrocalcinosis had a radiological evidence of worsening or persistent calcinosis (Fig. 4A). In addition, patients with nephrocalcinosis progressed more frequently to CKD (stage II-IV) and end stage kidney disease compared to those with renal stone (Fig. 4B).

**Discussion**

Although the regional incidence of kidney stones is high in Saudi Arabia [8], pediatric nephrolithiasis is uncommon. However, in a country where children constitute approximately 40% of the population [9], it is essential to study the epidemiological and clinical features of this disease. Moreover, pediatric nephrolithiasis is associated with significant morbidity, mainly due to the potential of stone recurrence and, consequently, it should not be overlooked. Unfortunately, a paucity of reports has described the epidemiological and clinical features of nephrolithiasis in Saudi pediatric patients. This report attempts to describe the epidemiology and underlying causes of pediatric nephrolithiasis and nephrocalcinosis.

According to a study that evaluated urolithiasis in the Middle East, there has been a change in the pattern and etiology of pediatric nephrolithiasis in Saudi Arabia [10]. In one study, it was reported that cases of pediatric nephrolithiasis constitute < 1% of all kidney stones [11, 12]. The mean age at diagnosis was 12 years, with a male-to-female ratio of 2:1. In a single-center study conducted in Jordan, it was reported that pediatric urolithiasis constituted 1.85% of all cases of stones [13].

In our report, the mean age at presentation for children with renal stones was 72 months while that of nephrocalcinosis cases was 54 months. Of note is that the male-to-female ratio among our patients with nephrolithiasis was 2:1, which is consistent with those of other investigators [10, 11]. On the contrary, nephrocalcinosis occurred mainly in females, with a male-to-female ratio of 0.66. In a report from Jordan, the mean age of occurrence of pediatric urolithiasis was 14 years, with a male-to-female ratio at 2:1 [13].
In another hospital-based study conducted in Iraq, the investigators found that kidney stones occurred at an early age, with most cases diagnosed in children less than 5 years old [14]. Similar to our study, the authors reported a higher prevalence among males, with a male-to-female ratio of 2.8:1.

In our study, approximately 19% of the children with nephrolithiasis presented with signs and symptoms of a UTI, which was confirmed with a urine culture in 15% of the cases. A larger proportion of children with nephrocalcinosis presented with symptoms and signs of a UTI, which was confirmed in 18% of the cases. In literature, UTIs were reported in 10 to 17% of children with urolithiasis [11, 12]. The etiology of kidney stones in our study differs from that in a previous report that included 85 children with urolithiasis [11]. A-Rasheed et al., in their study, reported that 60% of the children had formed idiopathic stones, contrary to the 22% in our patients with renal stones[11]. However, they found that approximately 12% of the children in their study had hypercalciuria which is similar to the cases in our study. Additionally, a metabolic etiology was implicated in 10% of the children in their study, mainly in the form of cystinuria and primary hyperoxaluria[11]. While we found that metabolic causes were implicated in 69% of our patients, we also found that these were mainly in the form of hyperoxaluria (18%) and cystinuria (18%). These findings suggest the need to perform a metabolic screening test in all children with nephrolithiasis because a UTI, which is a common finding in these children, can mask an underlying metabolic etiology, which may be the primary cause [4].

A strong family history of urolithiasis has been reported in children with kidney stones [14, 15]. Although consanguinity has been reported in stone formers, these were reported in studies of adult patients [16, 17]. Studies conducted worldwide found that pediatric stone formers had a strong family history of urolithiasis. In a study conducted at a tertiary center in Brazil, the investigators reported 85% of the children in their study has a family history of urolithiasis [18]. Furthermore, the investigators found that 83.3% of the patients with metabolic changes had a family history of kidney stone disease. In other studies, it was reported that about 40% of pediatric stone formers had a family history of urolithiasis [19–21]. In another study conducted in Iran [22], a family history of urolithiasis was reported in 62.7% of the 142 children with kidney stones. We found that 36.3% of children had a family history of nephrolithiasis and 23.1% had a family history of CKD, confirming the importance of family history in the occurrence of pediatric urolithiasis.

The clinical outcome of kidney disease in children is poorly understood. According to a recent report, male and female patients have similar hospitalization rates and frequency of stone episodes [23]. In an older study that attempted to investigate clinical outcomes in children with urolithiasis, the investigators were unable to comment on the outcome of urolithiasis in their patients [21]. Although we found that clinical outcomes were better in children with renal stones, children with nephrocalcinosis showed radiological evidence of worsening of the disease. However, we believe these results only provide preliminary evidence of the disease course in pediatric kidney stone formers.

There are several limitations to this study that merit consideration. One of the main limitations is retrospective nature of the study and relatively small sample size.
Conclusion

The etiology of nephrolithiasis was identified in most of our study population. This was achieved through metabolic screening of all suspected cases of pediatric nephrolithiasis, as metabolic causes are implicated in most of these patients. We also showed that most pediatric stone formers have better clinical outcomes compared to patients with nephrocalcinosis which was associated with worse outcomes related to kidney function and disease resolution.

Declarations

Ethics approval and consent to participate: The study was approved by the Biomedical Ethics Research Committees at college of medicine at King Abdulaziz University and also approved by institutional review board at college of medicine at King Saud University. Consent from participants was not required as this was a retrospective study using data collected for routine clinical practice. All methods were carried out in accordance with relevant guidelines and regulation.

Consent for publication: Not required.

Availability of data and materials: available

Competing interests: The authors report no conflicts of interest.

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Authors' contributions:

KAA: Idea, coordination of the study, writing and editing the manuscript

MAS: Writing and editing the manuscript

ASA: Analysis of the data, writing up the results and revising the manuscript

MHT: Writing and editing the manuscript

ZA: Collecting data and review the manuscript

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ZFZ: Writing and editing the manuscript
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Tables
Table 1
Patients’ baseline demographic and disease characteristics.

| Characteristics                          | Renal Stone                  | Nephrocalcinosis         |
|------------------------------------------|------------------------------|--------------------------|
|                                          | Estimate 95% CI               | Estimate 95% CI          |
| Age at presentation (mean, month)        | 72.22 62.7–84.7               | 54.25 39.1–63.6          |
| Male sex (%)                             | 66.7 56.6–75.7               | 39.2 26.6–53.0           |
| Creatinine (mean, at presentation)       | 60.24 39.6–80.7               | 83.90 41.2–126.5         |
| GFR (mean, at presentation)              | 148.31 136.2–160.3            | 122.72 104.4–140.9       |
| Consanguinity (%)                        | 64.8 54.6–74.1               | 78.7 65.3–88.7           |
| Family history of nephrolithiasis        | 23.1 15.3–32.6               | 59.6 45.2–72.8           |
| Family history of renal disease          | 36.3 26.9–46.5               | 51.1 33.7–60.7           |
| Associated kidney and urinary tract (%)  | 28 23.0–44.6                 | 9.80 0.3–20.3            |
| Initial renal status                     |                              |                          |
| Normal (%)                               | 86 77.0–92.0                 | 72 59.2–82.6             |
| Stage (II-IV) (%)                        | 12 6.40–19.6                 | 24 13.4–36.6             |
| ESRD (%)                                 | 2 0.4–6.90                   | 4 0.7–12.4               |

**Abbreviations:** GFR, ml/min/1.73 m², Creatinine µmol
Table 2
Cut-off level of solute:creatine ratio in relation to age group

| Item                        | Range (Month) | Range (year) | Normal Value |
|-----------------------------|---------------|--------------|--------------|
| Ca/Creatine (mmol/mmol)     | 0–12          | 0–1          | 2.2          |
|                             | 12–36         | 1–3          | 1.5          |
|                             | 36–60         | 3–5          | 1.1          |
|                             | 60–84         | 5–7          | 0.8          |
|                             | >84           | >7           | 0.6          |
| Oxalate/Creatine (mmol/mmol)| 0–12          | 0–1          | 0.17         |
|                             | 12–24         | 1–2          | 0.13         |
|                             | 24–36         | 2–3          | 0.1          |
|                             | 36–60         | 3–5          | 0.08         |
|                             | 60–84         | 5–7          | 0.07         |
|                             | >84           | >7           | 0.06         |
| Cystine/Creatine (mmol/mol) | 0–1           | 0–1          | 85           |
|                             | 1–6           |             | 53           |
|                             | >6            |             | 18           |
| Citrate/Creatine (mmol/mmol)| 0–60          | 0–5          | 0.12         |
|                             | >60           | >5           | 0.08         |
| Uric acid/Creatine (mmol/mmol)| 0–12        | 0–1          | 1.5          |
|                             | 12–36         | 1–3          | 1.3          |
|                             | 36–60         | 3–5          | 1            |
|                             | 60–120        | 5–10         | 0.6          |
|                             | >120          | >10          | 0.4          |
Table 3
Urine chemistry results among patients with nephrolithiasis and nephrocalcinosis

| Characteristics                     | Renal Stone |               | Nephrocalcinosis |               | P-value |
|-------------------------------------|-------------|---------------|------------------|---------------|---------|
|                                     | Estimate    | 95% CI        | Estimate         | 95% CI        |         |
| Recurrent UTI (%)                   | 36.71%      | 25.8–47.6     | 17.24%           | 0.3–20.3      | 0.09    |
| Ca/Creatinine (mean, mmol/mmol)     | 2.07        | 1.0–2.0       | 1.35             | 0.7–2.1       | 0.168   |
| Oxalate/Creatinine (mean, mmol/mmol)| 2.18        | 0–4.9         | 7.12             | 0–19.3        | 0.433   |
| Cystine/Creatinine (mean, mmol/mol) | 29.47       | 17.2–41.6     | 5.28             | 0–11.7        | 0.408   |
| Citrate/Creatinine (mean, mmol/mmol)| 6.86        | 4.7–8.9       | 8.63             | 4.2–13.1      | 0.449   |
| Uric acid/Creatinine (mean, mmol/mmol)| 0.63      | 0.4–0.8       | 0.74             | 0.3–1.1       | 0.718   |
| FEMg% (mean)                        | 2.07        | 1.7–2.3       | 8.78             | 5.7–11.7      | <0.001  |
| TRP% (mean)                         | 91.82       | 90.8–92.0     | 87.76            | 84.4–91.0     | 0.02    |

**Abbreviations:** CI, confidence interval; FEMg%: fraction of excretion of magnesium; TRP: tubular reabsorption of phosphate %; UTI, urinary tract infection.
Table 4
Serum electrolyte results among patients with nephrolithiasis and nephrocalcinosis

| Characteristics   | Renal Stone | Nephrocalcinosis | P-value |
|-------------------|-------------|------------------|---------|
|                   | Estimate    | 95% CI           | Estimate | 95% CI          |         |
| Serum sodium (mean) | 139.04      | 138.2–139.8      | 139.43   | 138.3–140.4      | 0.567   |
| Serum K (mean)    | 4.15        | 4.04–4.25        | 3.78     | 3.58–3.95        | 0.001   |
| Serum chloride (mean) | 103.66    | 102.83–104.46    | 103.18   | 101.37–104.97    | 0.58    |
| pH (mean)         | 7.37        | 7.36–7.37        | 7.38     | 7.33–7.42        | 0.505   |
| Serum HCO₃ (mean) | 23.59       | 23.15–24.16      | 25.06    | 23.53–26.58      | 0.086   |
| Serum Ca (mean)   | 2.38        | 2.35–2.40        | 2.28     | 2.21–2.32        | 0.001   |
| Serum phosphate (mean) | 1.57       | 1.49–1.62        | 1.47     | 1.32–1.59        | 0.184   |
| Serum Mg (mean)   | 0.83        | 0.63–1.02        | 0.73     | 0.67–0.76        | <0.001  |

Figures

![Figure 1](image-url)
Clinical presentations of patients with nephrolithiasis and nephrocalcinosis Abbreviations: FTT: failure to thrive, UTI: urinary tract infection.

Figure 2

Comorbidities associated with renal stones and nephrocalcinosis Abbreviations: FHHNC: familial hypomagnesemia hypercalciuria nephrocalcinosis.