Metabolic evaluation of children with urolithiasis

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Aim: The aim of the study is to identify the prevalence of metabolic abnormalities in children with urolithiasis.

Materials and Methods: This is a prospective study; all children below 15 years who are found to have urolithiasis were prospectively evaluated with relevant history, clinical examination, and urine and serum testing. Metabolic workup includes complete urine examination, urine culture and sensitivity, and 24-h urinary analysis (lithorisk profile).

Results: A total of 55 patients are included in the study. Forty-two are boys and 13 are girls aged between from 8 months to 15 years. Thirty-three patients underwent stone analysis, primary composition of calcium oxalate stones in 19 (58%), ammonium urate in 4, dahlite in 3 and uric acid in 3, silicon oxide in 2, and struvite in 2 cases. Lithorisk profile was performed in 40 cases (72.7%). The pH range is 5.6–6.2. We noted hypercalciuria in 20 patients (50%), hyperuricosuria in 23 (57.5%), hyperoxaluria in 20 (50%), hypernatriuria in 26 (65%), hypochitraturia in 9 (23%), and hypomagnesuria in 3 (7.5%). Urine calcium-to-creatinine ratio >0.2 was found in 22 (55%) patients. Statistically significant association between hyperoxaluria and hyperuricosuria (P < 0.04, r = 0.32) and hypercalciuria and hyperuricosuria (P < 0.001, r = 0.51) found in this study. Hyperuricosuria is seen in 75% and 73% of patients with hypercalciuria and hyperoxaluria, respectively. Twenty-five children have both lithorisk profile and stone analysis. Hypercalciuria and hyperoxaluria were noted in 60% of calcium oxalate stone formers each. Elevated urinary calcium/creatinine ratio (>0.2) was seen in 73% of calcium oxalate stone formers.

Conclusion: Because of high prevalence of metabolic risk factors and the significant risk of lifelong recurrence, all children with urolithiasis need complete evaluation with metabolic workup.

Keywords: Calcium oxalate stones, lithorisk profile, metabolic workup, pediatric calculi, stone analysis

INTRODUCTION

Urinary calculus disease has afflicted humankind for millennia. The lifetime prevalence of stone disease was found to be 10% for men and 4% for women with the probability of having a stone varying according to age, gender, race, and geographic location.[1] The prevalence of nephrolithiasis in North American children varies widely and accounts for 1 per 1000–1 per 7600 pediatric hospital admissions, a rate one-tenth of that seen in adults.[2] The rate of recurrent stones in childhood has been reported...
to be 6.5%–54% with a mean interval to recurrence of 3–6 years. Only 1%–5% of children with urologic abnormalities develop calculi, suggesting a concomitant metabolic abnormality in patients that predisposes to calculus formation.

Children need comprehensive metabolic evaluation for any abnormality rather than only clearance of stone. The evaluation includes serum chemistries, 24-h urinary parameters, and stone analysis which help in identifying metabolic abnormalities predisposing to stone formation. High levels of oxalate and calcium contribute to kidney stones recurrences and therapy to reduce these two substances in the urine can reduce recurrence rates. Low levels of citrate also increase the risk for forming stones. The aim of the study is to identify the prevalence of metabolic abnormalities in children with urolithiasis.

MATERIALS AND METHODS

Study design

This is an observational study conducted in Department of Urology, Nellore, India, during period August 2012 to January 2015. This clinical study was evaluated and approved by the Institutional Ethics Committee.

Inclusion criteria

All children below 15 years who are found to have urolithiasis were prospectively evaluated with a relevant history, clinical examination, and urine and serum testing. Metabolic workup includes complete urine examination, urine culture, and sensitivity; Serum chemistries include creatinine, calcium, phosphorus, uric acid, stone analysis by Fourier transform infrared (FTIR) spectroscopy method, and 24-h urinary analysis (lithorisk profile).

24-h urinary analysis (lithorisk profile)

Method of collection

24-h urine was collected in a plastic container with 20 ml 6N HCl as a preservative from 6:00 a.m. to next day 6:00 a.m. either at home or as an inpatient. A volume of 10 ml of freshly voided spot urine was also collected from each patient to measure pH. All patients were on a regular diet with no special instruction regarding diet and fluid intake. Patients who underwent intervention and 24-h urine samples were taken 1 month after complete stone clearance. Data were obtained and recorded in Excel sheet. There are no standard reference values for 24-h urine analysis in children. We have taken into consideration of Rizvi et al. 2007 study as it was performed in our subcontinent with similar climatic conditions and dietary habits.

Data analysis

All data collected were entered in the case record form and Excel sheet was prepared. Data analysis was done by SPSS 21 software (IBM Corp., 2012 released, Armonk, NY, USA). For comparison between means, “independent sample and t-test” were used. Correlation between numerical values was assessed by Spearman’s rank correlation analysis. \( P < 0.05 \) was considered statistically significant.

RESULTS

A total of 55 patients are included in the study. Forty-one are boys and 13 are girls aged between from 8 months to 15 years. The mean age is 7.8 years. Fourteen children were <5 years, 26 between 6 and 10 years, and 15 between 11 and 15 years. The abdominal or flank pain was the presenting symptom in 91% (50/55) of the cases. Fever and vomiting are present in 44% and 33%, respectively. Dysuria, frequency, and hematuria are seen in 40%, 31%, and 51%, respectively. They are more commonly seen with vesical calculi than renal and ureteric calculi. Two patients presented with sepsis. Family history was positive for urolithiasis in 5 patients (9.1%). Of the 55 patients, 44 (80%) were first-time stone formers and the remaining 11 (20%) were recurrent stone formers. Multiple calculi were noted in 14 cases (25%) and staghorn in 3 patients (5.5%) in 4 renal units. Three patients with 4 renal units had staghorn calculi. Urine culture was positive in all cases. Among them, two presented with sepsis. Six cases presented with raised creatinine. One child required dialysis preoperatively.

A spontaneous stone passage was observed in 7 (13%) patients and surgical stone removal was necessary for 41 (74%) patients [Table 1]. Conservative management was advised in seven children (13%) who were asymptomatic with calculi <5 mm. Of the 33 patients for whom stone analysis was available, primary composition

| Name of procedure              | n  |
|--------------------------------|----|
| PCNL                           | 17 |
| PCCL                           | 6  |
| URSU                          | 5  |
| Cystolithotomy                 | 4  |
| ESWL                           | 2  |
| URSU + PCCL                    | 2  |
| Laparoscopic ureterolithotomy   | 1  |
| RIRS                           | 1  |
| Meatotomy                      | 1  |
| URSU + PCNL                    | 1  |
| ESWL + PCNL                    | 1  |

PCNL: Percutaneous nephrolithotomy, PCCL: Percutaneous cystolithotomy, URSU: Ureteroscopic lithotripsy, ESWL: Extracorporeal shock wave lithotripsy, RIRS: Retrograde intrarenal surgery
of calcium oxalate stones was found in 19 (58%), ammonium urate in 4, dahlite in 3 and uric acid in 3, silicon oxide in 2, and struvite in 2 cases [Figure 1]. The mean stone burden is 15.8 ± 8.89 mm. Stone samples were not available in 22 patients (40%). The lithorisk profile was performed in 40 cases (72.7%) [Table 2]. All had adequate urine output. The pH range is 5.6–6.2. We noted hypercalciuria in 20 patients (50%), hyperuricosuria in 23 (57.5%), hyperoxaluria in 20 (50%), hypernatruria 9 (23%), and hypomagnesuria in 3 (7.5%) [Table 3]. Urine calcium-to-creatinine ratio >0.2 was found in 22 (55%) patients. Eleven patients (25%) had at least two abnormalities, 13 (29.5%) had three, and 7 (17.5%) had >3 abnormalities.

On performing Spearman’s rank correlation analysis among various urinary abnormal parameters, we found statistically significant association between hyperoxaluria and hyperuricosuria ($P < 0.04, r = 0.32$) and hypercalciuria and hyperuricosuria ($P < 0.001, r = 0.51$). Hyperuricosuria is seen in 75% and 73% of patients with hypercalciuria and hyperoxaluria, respectively. There were no significant differences regarding the frequency and types of metabolic abnormalities between the male and female children, recurrent and first-time stone formers, with and without a positive family history of urinary calculi. Twenty-five children have both lithorisk profile and stone analysis. Hypercalciuria and hyperoxaluria were noted in 60% of calcium oxalate stone formers each. Elevated urine calcium-to-creatinine ratio (>0.2) was seen in 73% of calcium oxalate stone formers.

**DISCUSSION**

Urolithiasis in pediatric age group is an important cause of morbidity worldwide. The evaluation of a child who presents with urolithiasis should be directed toward identifying physicochemical, anatomic, metabolic, and genetic factors predisposing to urolithiasis. Because of potential morbidity and risk of recurrence, metabolic evaluation is indicated in all children with urolithiasis. Etiology of pediatric urolithiasis remains largely unknown. Several studies show that anatomical abnormalities, recurrent infection, lithogenic dietary habits, and metabolic factors predispose to stones formation. Overall predisposing factors can be identified in 30%–80% of the patients. In developing countries, an idiopathic cause is reported in up to 50% of cases compared with <20% in developed nations. Anatomical abnormalities as a cause of calculus disease in a pediatric group were low in our series (3.6%, 1 ureterocele and 1 neurogenic bladder) and in other developing countries compared with 20%–30% in developed countries. The rate of recurrent stones in childhood has been reported to be 6.5%–54% with a mean interval of 3–6 years. Children with an identifiable metabolic disorder are nearly fivefold more likely to have recurrent stones than those with no identifiable metabolic disorder.

**Clinical presentations**

Clinical presentation of stone disease is usually subtle, particularly in younger age group. Nonspecific abdominal/flank pain occurs as the initial clinical feature in approximately in 50% of children as reported in the literature and in 90% in our study. The incidence of urinary tract infection (UTI) in children with urolithiasis has been reported to be 8%–70% in the literature. Bacteria, pyuria, and positive urine culture are noted in 29%, 51%, and 27.3%, respectively, in our study. Birikilik et al. demonstrated a high incidence of hypercalciuria (43%) in patients with recurrent UTI. In the literature, family history of calculus disease varies from 12 to 50% in the different studies. In our study, it is about 9.1% of cases. Familial recurrence does not only mean inherited transmission but also indicate sharing of same environmental factors, dietary habits by family members. Microscopic or macroscopic hematuria has been reported in 50% in our study, and Milliner and Murphy reported hematuria in 33% to 90% of children with stones. Renal and ureteric calculi constituted for 78% location and 22% are bladder and urethral in our study. In the United States, three-fourths of pediatric stones are renal, 10% being ureteral, and remaining 10% located in the bladder.

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**Table 2: 24-h urinary analysis**

| 24-h urinary abnormality       | n (%)     |
|-------------------------------|-----------|
| Hypernatruria                 | 20 (50%)  |
| Hyperuricosuria               | 23 (57.5) |
| Hyperoxaluria                 | 20 (50%)  |
| Hydrocalciuria                | 20 (50%)  |
| Hypomagnesuria                | 3 (7.5%)  |
| Urinary calcium/creatinine ratio | 22 (55%)  |

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**Figure 1: Stone analysis**

- Uric acid, 3
- Dahlite, 3
- Ammonium urate, 4
- Struvite, 2
- Silicon oxide, 2
- Calcium oxalate, 19

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Serum chemistries
Serum studies are typically not as informative as urine studies but provide useful information and are necessary for interpretation of urine test results. The registry of the Turkish Society of Nephrology in 2003 revealed that urolithiasis formed the etiology of 3.8% of children with chronic renal failure. We had 6 (11%) patients with raised creatinine ranging from 1.35 to 3.4 mg/dl. One patient required dialysis preoperatively and remaining five patients recovered after clearance of stone. Serum calcium, phosphate, and uric levels are measured, and their levels were normal in all children in our series.

Stone analysis
We performed infrared spectroscopy stone analysis in 33 patients. The majority of stones are formed from a mixture of substances and that primary composition is calcium oxalate in 58% of cases. The most common type of upper urinary tract stone in children is calcium oxalate, which comprises about 60%–70% of all upper tract calculi. Calcium oxalate stones are found in many conditions, including hypercalciumia, hypocitraturia, hyperuricosuria, and hyperoxaluria. Pak et al. showed that the most significant metabolic abnormality contributing to the development of calcium oxalate stones was hypocitraturia in their study.

In our study, we had 2 cases of silicate renal calculi and the composition is purely silicon dioxide (100%). The cause is unknown in both cases. Renal silicate calculi are rare, with an incidence of 0.2% of all urinary calculi in humans. There are several reports showing that the long-term administration of magnesium trisilicate antacid in patients with gastric and duodenal ulcers induces silica urinary calculi. Stone analysis and characteristic wave pattern on FTIR at 1000–1200 cm⁻¹ established the diagnosis. Silicate renal calculi in children without any predisposing causes are extremely rare.

Lithorisk profile (24-h urine analysis)
Urine is a complex solution containing ions that interact with other constituents. The generation of crystals is promoted or inhibited by several physicochemical or anatomic factors. These factors include the solute excretion rate, urinary supersaturation, urinary ionic strength, urinary flow rate, urine pH, and urinary tract developmental anomalies. The standard reference values for 24-h urinary parameters have not been established that can be uniformly applied to all children. It varies depending on climatic conditions, dietary habits, and age of a child. Various studies have taken different reference range values into consideration. We have taken into consideration, reference ranges of Rizvi et al. because this study as it was performed in our subcontinent with similar climatic conditions and dietary habits. A collection of 24-h urine is a challenge, especially for younger children. A metabolic abnormality was identified in 90% of children with the stone disease, and it was comparable with various other studies [Table 3]. Hypernatriuria (65%) was the most common abnormality, hyperuricosuria in 57.5% of children. Hyperoxaluria and hypercalciuria were found in nearly 50% of the patients. Hypocitraturia and hypomagnesuria are found in 23% and 7.5% of patients, respectively. The presented study is compared with various other studies that evaluated 24 hour urinary metabolic abnormalities [Table 4].

Hypernatriuria (65%) was the most common abnormality in our study. Dietary sodium intake influences urinary calcium excretion in children with and without hypercalciuria. This is attributed to increasing intake of salt in the routine diet in the subcontinent. This is evident from the mean values of sodium excretion are high from our study and Rizvi et al. study in Pakistan when compared to Tekin et al. study in Turkey. A highly significant correlation between urinary calcium and sodium excretion was observed during Aladjem et al. study.

Total urate excretion, excretion per unit body weight, and fractional excretion of uric acid, all vary with age. Uric acid excretion is extremely high in the neonatal period and remains substantially higher than adult values throughout early childhood. Hyperuricosuria is associated in 57% of children in our study. Most patients with hyperuricosuria also have hypercalciuria (75%) and hyperoxaluria (73%) in our study, and there exists a significant positive correlation between them. Dursun et al. stated that hypercalciuria and hyperuricosuria were detected in 42.3% and 54.8% of patients, respectively. Worldwide, hypercalciuria is seen as the most prevalent risk factor in the formation of calcium oxalate stones, representing up to 50% of the metabolic risk factors. Hypercalciuria was noted in 50% of children in our study. Scheinman reported hypercalciuria in as many as 66% of pediatric calculus cases.

The majority of children with hypercalciuria had normocalcemia, the cause is idiopathic. The pathogenesis of idiopathic hypercalciuria can be explained by increased

| Study                  | Country    | Percentage metabolic abnormality |
|------------------------|------------|----------------------------------|
| Rizvi et al., 2007     | Pakistan   | 87                               |
| Alpay et al., 2009     | Turkey     | 87                               |
| Gürgüze and Sari, 2011 | Turkey     | 92                               |
| Rellum et al., 2014    | Netherlands| 78                               |
| Elmaci et al., 2014    | Turkey     | 79.2                             |
| Our study 2015         | India      | 90                               |

Table 3: Prevalence of metabolic abnormalities in various studies
renal calcium excretion, increased gastrointestinal absorption, and occasionally increased bone resorption.[23] In a multicenter study, Stapleton reported a significant association of idiopathic hypercalciuria with a high risk of future urolithiasis in children with hematuria.[31] Perrone et al. reported hypercalciuria in as many as 66% of pediatric stone cases.[8] A simple screening test for hypercalciuria can be performed by determining the ratio of urinary calcium to creatinine concentrations in a random specimen. Values >0.2 in a 24-h urine sample[36,37] are considered elevated. Elevated urinary calcium-to-creatinine ratio (>0.2) is noted in 73% of the calcium oxalate stone formers in our study.

Hyperoxaluria is seen in 50% of children in our study. Nicoletta and Lande stated that 20% of children with nephrolithiasis and hyperoxaluria most commonly caused by idiopathic hyperoxaluria with mild elevations of urinary oxalate levels.[38] In the comparative study, Takin et al.[29] found that median urinary oxalate in stone formers was significantly higher than in controls. Hypocitraturia was coexisting with hyperoxaluria in many stone formers in their studies.[29] In our study group, hypocitraturia is noted in 23% of children. Miller and Stapleton found that hypocitraturia has been found in only 10% of children with urolithiasis.[39] Hypocitraturia (87%) was the most common finding in Rizvi et al.[23] study due to low citrate in the diet. Hypocitraturia is seen routinely in children ingesting a ketogenic diet. Magnesium is a well-documented inhibitor of urinary calcium oxalate supersaturation and thus the nucleation of calcium oxalate crystals.[40] Hypomagnesuria has gained little attention in pediatric stone disease, mainly because of its low frequency. We had 7.5% children with hypomagnesuria. Tekin et al.[29] detected hypomagnesuria always accompanied hypocitraturia and no correlation demonstrated in our study. The majority of our patients had normal to high urine volume. Decreased urine output <1 L is seen in 31% in Rizvi et al. study.[23] This might be due to patient biased to take plenty of water in spite of our instructions to take normally. Our study group represents a pediatric population from a geographical region with a high incidence of calculus disease in both children and adults; the 24-h urinary excretion of lithogenic substances, such as calcium, oxalate, sodium, and uric acid, was in higher amounts than inhibitory solutes such as citrate and magnesium in children promoting supersaturation, heterogeneous nucleation, crystallization, and finally stone formation.

In countries where pediatric urinary calculus is considered to be endemic, the etiology remains idiopathic in the majority of cases.[40] Metabolic abnormalities have been reported in 30%–86% of children with urolithiasis, depending on the geographic location of the studies.[3,38] Although our study has a small number of participants, which could be a limitation, we observed significant metabolic abnormalities in children with urolithiasis. Hypernatuira along with hyperuricosuria, hypercalciuria, and hyperoxaluria was observed in our study population. Hence, we recommend dietary sodium restriction and maintenance of calcium intake consistent with the recommended daily allowance for children. In addition, a high-potassium, low-oxalate diet is recommended for children. A low-calcium diet is not effective in reducing the risk of stone recurrence and poses a substantial risk to maintenance of bone health.

CONCLUSION

In our study of children with urolithiasis, we found a very high percentage of metabolic abnormalities (90%), which is similar to abnormalities found in high calculus endemic areas. There are differences in 24-h urine analysis depending on geographical region and dietary habits. Hypernatuira (65%) is the most common abnormality, and hyperuricosuria (57.5%), hypercalciuria (50%), and hyperoxaluria (50%) were also found in our study. Calcium oxalate is the most common primary composition of stones. Most of the stones formed were of mixed composition. The 24-h urinary calcium-to-creatinine ratio >0.2 is correlating with hypercalciuria and is found in 73% of calcium oxalate stone formers. The 24-h urinary excretion of lithogenic substances, such as calcium, oxalate, sodium, and uric acid, was in higher concentration than inhibitory solutes such as citrate and magnesium in children promoting
supersaturation, heterogeneous nucleation, crystallization, and finally stone formation. Serum calcium, phosphorus, and uric acid are in normal range in spite of having urinary abnormalities. Because of the high prevalence of metabolic risk factors and the significant risk of lifelong recurrence in this population, all children with urolithiasis require a complete evaluation with metabolic workup.

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Conflicts of interest
There are no conflicts of interest.

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