Journal of Pediatric Urology (2017) 13, 357.e1–357.e7

Stone growth patterns and risk for surgery among children presenting with hypercalciuria, hypocitraturia and cystinuria as underlying metabolic causes of urolithiasis

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Keywords
Urinary stones; Metabolic study; Risk; Stone burden; Children; Stone growth

Received 7 January 2017
Accepted 29 June 2017
Available online 4 August 2017

Summary

Introduction
Hypercalciuria, hypocitraturia and cystinuria are the most common underlying metabolic stone abnormalities in children. The present study compared stone growth patterns, stone burden, and the risk of stone-related surgery among these underlying metabolic conditions.

Methods
A retrospective cohort of 356 children with renal stones, followed from 2000 to 2015, was studied. Differences among metabolic groups were determined using Kruskal–Wallis test; the Scheffé-test was used for multiple comparisons to determine differences among single groups. Independent sample *t*-test was used when adequate, given the sample size, and Chi-squared test was used for categorical variables. Stone growth rates were calculated as differences in diameter divided by time elapsed between U/Ss (mm/year). Logistic regression was performed to assess the effect of initial stone size on the likelihood of surgery.

Results
Median stone size at presentation was significantly different among groups, with cystinuria being the group with the largest proportion of stones >10 mm, while patients with stones <5 mm were likely to have a normal metabolic workup ($P < 0.05$). Stones with a higher growth rate were found in the operative group, while slower growing stones were mostly managed conservatively (3.4 mm/year vs 0.8 mm/year, respectively; $P = 0.014$). However, stone growth rates were not significantly different among metabolic groups. On the other hand, the rate of new stone formation in cystinuric patients at their first follow-up was 30.4%, which was significantly higher than in patients with hypercalciuria (16.3%) or with a normal metabolic workup (17.2%; $P < 0.05$). Compared with stones <5 mm, stones measuring 5–10 mm were more than four times more likely to result in surgery, whereas the likelihood of surgery for 10–20 mm or >20 mm stones was almost 16 or 34 times, respectively ($P < 0.001$).

Conclusions
It is believed that this is the first study to evaluate stone growth patterns, stone burden and surgical risk among children with hypercalciuria, hypocitraturia and cystinuria. Cystinuric patients presented with larger stones at the time of diagnosis, higher new stone formation rates, and were at higher risk of surgery. While no significant difference of growth rate was found among metabolic groups, stones with a higher growth rate were significantly more likely to result in surgical treatment than slower growing stones. Initial stone size, location of largest stone, previous urinary tract infection, and patient's metabolic type significantly influenced the likelihood of a surgical intervention. Better understanding of the natural history ultimately helps surgeons and clinicians defining prognosis, treatment, and prevention plans for pediatric urolithiasis.

Summary table Stone-characteristics of metabolic groups.

Metabolic type (*N* of patients)	Normal (126)	Hypercalciuria (86)	Hypocitraturia (20)	Cystinuria (24)
Median initial stone size (IQR, mm)*	6.0* (4.0–10.5)	7.0 (5.0–11.5)	6.0 (2.7–10.8)	10.0* (6.0–14.0)
Median stone growth rate (IQR, mm/year)[a]	0.30 (0.0–2.40)	0.15 (0.00–1.90)	0.0 (0.0–0.20)	1.1.41 (0–6.57)
% of new stone formation from baseline to first follow-up#	17.2%	16.3%	11.1%	30.4%#

*Cystinuric patients had the highest ratio of stones >10 mm, while patients with stones <5 mm were most likely to have a normal metabolic workup ($P < 0.05$, Chi-squared test with Bonferroni correction). Moreover, metabolic groups were significantly different from each other, while pairwise comparison did not reach statistical significance.
#Cystinuric patients had significantly higher rate of new stone formation compared to other metabolic groups ($P < 0.05$, Chi-squared test with Bonferroni correction).
[a] Difference in median stone growth rate was not significantly different across metabolic groups (Kruskal–Wallis test).

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http://dx.doi.org/10.1016/j.jpurol.2017.06.022

Introduction

Pediatric urolithiasis is common, has significant morbidity and high rates of recurrence [1]. Although more common in adults, an increased incidence of childhood renal stones has been reported over the last two decades [1,2].

Metabolic abnormalities are present in a large number of children with stones [1,3]. Hypercalciuria, hypocitraturia and cystinuria are the most commonly identified underlying metabolic stone abnormalities. However, not much is known about the natural history of stone disease associated with underlying metabolic conditions in the pediatric population.

Distinct pathophysiological mechanisms for stone formation occur in the presence of specific underlying metabolic abnormalities [4]; thus, it has been hypothesized that stone growth patterns and risk for stone-related surgery may vary according to the underlying metabolic condition. The present study aimed to predict stone burden according to the metabolic underlying condition, instead of the type of stone, because those abnormalities are potentially identifiable with urine metabolic workup prior to spontaneous passage or surgical stone removal, allowing early treatment and specific preventive strategies for stone formation. Although the initial goal was to analyze stone growth patterns associated with all underlying metabolic abnormalities, the numbers were too small in this retrospective cohort for rare metabolic conditions such as primary and secondary hyperoxaluria, hyperuricosuria, Dent's disease or hypercalciuria hypomagnesemia syndrome (summarized as mixed group); analysis was therefore limited to the most commonly identified underlying conditions: hypercalciuria, hypocitraturia and cystinuria. The study compared the stone growth patterns, stone burden and surgical risk of children presenting with hypercalciuria, hypocitraturia and cystinuria as an underlying cause of urolithiasis.

Materials and methods

After Research Ethics Board approval, a retrospective chart review was conducted of children aged 0—18 years and who presented with urolithiasis to either the Pediatric Nephrology or Urology Clinic at the Hospital for Sick Children between 2000 and 2015. Patients were followed from date of diagnosis until stone elimination, transfer to adult care, or until their last follow-up visit.

Collected data included age, sex, date of diagnosis, number, size (mm), and location of stones, and prior UTI. The following were recorded: results of ultrasound (U/S), the presence of stone-related and non-stone-related hydronephrosis, and results of metabolic workup. The latter consisted of either 24-h urine collection for toilet trained, or spot urine sample for non-toilet trained children. Metabolic parameters measured included urine volume (ml), and concentrations of creatinine, calcium, oxalate, cystine, citrate, uric acid, phosphate, magnesium, and pH. Absolute mineral excretions were calculated on timed urine samples, and ratios to creatinine were calculated on spot samples and compared to age-related normative data. Additionally, serum was analyzed for creatinine and electrolytes. Patients were assigned to a metabolic group, namely: hypercalciuria, hypocitraturia, cystinuria, and normal metabolic workup. There were also patients with mixed abnormalities, such as hypercalciuria and hypocitraturia, or rare diseases such as primary and secondary hyperoxaluria, hyperuricosuria, hypercalciuria hypomagnesemia, Dent's disease, and Bartter syndrome. These patients were summarized as a mixed group. Number of episodes was defined as the number of times medical attention was sought for a problem attributed to stone disease such as renal colic, hematuria, or UTI. Based on imaging, new stone formation was recorded and, if available, the type of stone (calcium oxalate, calcium phosphate, uric acid, struvite, cystine or others) was also recorded. Stone growth rates were calculated as difference in diameter divided by time elapsed between U/S; growth rates were expressed in mm/year. For patients undergoing surgery, size difference and time elapsed from baseline U/S to the U/S performed immediately before surgery was determined. For patients treated conservatively, growth rate was calculated from baseline U/S to last follow-up U/S. Stone size recorded during follow-up U/S referred to a stone in the identical location as the largest stone was seen on baseline U/S. Negative growth rates were excluded, as they reflected the result of treatment, stone movement, or stone passage, and not spontaneous reduction in stone size.

Statistical analysis was performed using IBM SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA). Differences among metabolic groups were determined using Kruskal—Wallis test; Scheffé test was used for multiple comparisons to determine differences among a single group. Independent samples *t*-test was used to compare normally distributed continuous variables or variables with sample sizes >50. Chi-squared test was used to compare categorical variables, including Bonferroni correction to account for multiple comparisons where appropriate. Statistical significance was determined as $P < 0.05$. Event-free interval among metabolic groups was visualized using a Kaplan—Meier graph. Statistical comparison was performed by a log-rank test. Logistic regression was used to investigate the relationship of stone size and surgical rates. Since stone size and the likelihood of surgery cannot be considered a linear correlation, stone size was categorized into <5 mm, 5—10 mm, 10—20 mm, and >20 mm [4]. Variables were added into the model using purposeful selection. They were initially included if through the univariate screen the *P*-value was <0.2; at this point, collinearity was ruled out using the selected variables in a linear regression model. Then these covariates were included in the model if during multivariate regression the *P*-value was <0.10, and age and sex were forced into the model.

Results

During the study period, 356 children were seen with renal stones in the Nephrology and/or Urology clinics. Patients' demographics and clinical characteristics are summarized in Table 1A. A total of 280 (78.7%) children underwent metabolic workup at baseline or first follow-up visit. Among these 280 patients, metabolic abnormality was identified in 154 (55%) children (Fig. 1A). Differences among metabolic