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Infant nephrolithiasis and nephrocalcinosis: Natural history and predictors of surgical intervention

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Summary

Introduction
Renal stone disease diagnosed in the first year of life is relatively uncommon. While risk factors such as low birth weight, furosemide exposure, and metabolic disorders are well established, there exists little information regarding resolution rates and need for surgical intervention. Our study objective was to evaluate urolithiasis and renal calcification resolution rates, time to resolution, and need for surgical intervention in children diagnosed in their first year of life.

Material and methods
REB approved retrospective chart review of children younger than 12 months of age (corrected for prematurity) diagnosed with nephrolithiasis and/or nephrocalcinosis in a tertiary pediatric hospital between April 2000 and August 2015 with a minimum 1-year follow-up period. Exact logistic regression was performed to assess the relationship between size of the largest stone (on either side) and the need for surgical intervention. Kaplan–Meier curves were constructed to examine time to stone resolution among those not requiring surgical intervention.

Results
62 patients (61% male) were diagnosed with stones or nephrocalcinosis by ultrasound at a median age of 2.9 months. Of these, 37% had been admitted to the NICU because of prematurity, low birth weight or comorbidities. A total of 45 patients were found to have stones (Table); 35 of these had a stone at initial ultrasound and 10 initially diagnosed as nephrocalcinosis were later confirmed to have a stone. 67% of all stones were asymptomatic on presentation. Metabolic anomalies were present in 56% (35/62), and 16% (10/62) required medical treatment. Seven patients ultimately required surgical intervention. Stone size was found to predict the eventual need for surgical intervention (OR 3.52, 95% CI 1.47–12.78) for each 0.1 mm increase in diameter). Among patients not requiring surgical intervention (n = 38), the estimated median time to spontaneous resolution of urolithiasis was 1.1 years (95% CI 0.89–1.53, range 2 months–6 years) and 1.2 years for nephrocalcinosis (95% CI 0.59–2.13).

Conclusions
Spontaneous resolution was a common outcome for newborns and infants diagnosed with urolithiasis in the first year of life, but high variability in time-to-resolution was observed. Only a small proportion who had confirmed stones on ultrasound required surgical intervention (15%), and large stone size was a predictive factor for surgery.

Table Clinical, radiographic, and renal stone or nephrocalcinosis outcomes of children younger than 12 months.

	Stones (n = 45)	Nephrocalcinosis (n = 17)
Sex, n male (%)	28 (62%)	10 (59%)
Age at presentation, months, median (IQR)	2.9 (3.3)	2.1 (2.1)
Symptomatic presentation, n (%)	15 (33%)	6 (36%)
Premature, n (%)	26 (58%)	14 (82%)
Metabolic anomalies (%)	22 (49%)	13 (76%)
Stone size		
Under 3 mm	24 (53%)	
3–5 mm	13 (29%)	–
Larger than 5 mm	8 (18%)	
Spontaneous resolution, n (%)	35 (78%)	16 (94%)
Median time to resolution, years (CI)	1.1 (0.2–6)	1.2 (0.6–2.1)
Required surgery/ESWL, n (%)	7 (15%)	–

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Introduction

Incidence of nephrolithiaisis in adults is increasing with 1 in 11 American adults having stones [1]. There has been a corresponding increase seen in the pediatric population with pediatric urolithiasis rates increasing from 18.4 per 100,000 in 1999 to 57 per 100,000 in 2008 (10.6% increase) [1–3].

Despite these rising trends, there is a paucity of information regarding urolithiasis incidence in newborns or infants. Recent institutional case series report that urolithiasis rates of children under 1 or 5 years represent as much as 13–23% of the pediatric stone population [2,4–6]. In extreme low birth weight babies with prolonged NICU admission, the rates of renal calcifications, albeit conflicting, were considerable and found in 10–65% with an estimated 5000 cases per year in the USA [7]. Currently, there are no available studies evaluating a newborn's likelihood of stone resolution or need for intervention. This younger population may have very different stone characteristics from their older counterparts and also have unique surgical challenges given their small size.

The goal of our study was to assess urolithiasis and nephrocalcinosis resolution rates, time to resolution based on ultrasound, and need for surgical intervention in patients under 1 year of age.

Patients and methods

We conducted a retrospective chart review of patients younger than 1 year of age (corrected for prematurity) diagnosed with renal calcifications (stones and/nephrocalcinoses) on imaging who were followed for a minimum period of 1 year at our institution between April 2000 and August 2015. Patients followed for longer than 1 year were included for the entire follow-up period. Patients who received medical or surgical treatment outside our center or did not have ultrasound (US) images available were excluded.

Data were collected on patient characteristics including gender, prematurity, birth weight, and neonatal intensive critical care unity (NICU) admissions. Patients were considered premature when born at 37 weeks or less of pregnancy. The post-natal age at diagnosis was determined for all patients, and symptoms leading to diagnosis were examined. Of note, children with symptoms such as irritability, jaundice, oxygen desaturations, or vomiting found to have non-obstructing stones without hydronephrosis were coded as incidental stones if another cause for their symptoms was found (i.e. pleural effusion, abdominal hernia). Symptomatic stones are defined as stones presenting with gross hematuria, urinary tract infection, abdominal pain, or renal failure. Finally, data were extracted on treatment for underlying conditions (i.e. furosemide) or treatment for stone disease (i.e. magnesium citrate) and need for surgery. Patients with identified genitourinary anomalies were included and the anomaly, it's treatment, and the ipsilaterality to the stone was documented. Patients with ipsilateral hydronephrosis during an active stone passage event were not considered to have an underlying anatomic defect, unless this persisted following the stone passage event. Comorbidities, spot urine analyses, and serum studies were documented. We reviewed which patients underwent a surgical intervention, including the type (ureteroscopy, ESWL, PCNL), time to surgery, and indication for surgery and stone outcome.

Newborns diagnosed with nephrolithiasis in our institution undergo follow-up US between 3 and 6 months after initial diagnosis depending on presence of other genitourinary anomalies such as hydroureteronephrosis, vesicoureteral reflux (VUR), neurogenic bladder, and ureterocele. Metabolic evaluations include urinalysis, urine osmolarity, and spot urine ratios in relation to creatinine for the following: sodium, potassium, chloride, calcium, magnesium, phosphate, oxalate, citrate, and uric acid. A urine amino acid profile is also done to evaluate cysteine levels. Serum testing includes creatinine, urea, electrolytes, calcium, magnesium, phosphate, uric acid, alkaline phosphatase, parathyroid hormone, venous blood gas, and vitamin D 25-OH level. Abnormal laboratory results in the initial metabolic evaluation were documented. Diagnoses of metabolic anomalies are defined as persistent abnormal laboratory results on repeat testing despite appropriate changes in fluid intake or dietary changes.

Diagnosis of stones or nephrocalcinosis (medullary or cortical) was confirmed through careful examination of US imaging. A multidisciplinary meeting between urologists (VA and MK), radiologists (KH), and nephrologists (JV) was conducted to establish a standardized sonographic classification, which allowed for consistent classification of patient diagnosis (Table 1). Patients with Tamm–Horsfall proteinuria (also known as transient neonatal renal medullary hyperechogenicity) were excluded as this is considered a normal finding that can mimic non-obstructing stones [8,9]. Our final standardized radiological classification criteria were developed by a multi-disciplinary panel comprising urologists, radiologists, and nephrologists who appraised the available literature on the subject and subsequently reviewed included complete ultrasound studies [10] (Table 1).

Exact logistic regression was performed to assess the relationship between stone size and need for surgical intervention. Kaplan–Meier curves were constructed to examine time to stone resolution for nephrocalcinosis and for stones that did not require surgical intervention, and receiver operating characteristic (ROC) curves were conducted to estimate a cut off stone size for patients that required invasive procedures as ureteroscopy, external shock wave lithotripsies (ESWL), percutaneous nephrolithotomy (PCNL), or open pyelolithotomy.

This study was approved by our institutional research ethics board.

Results

A total of 186 charts and ultrasound studies were reviewed and 62 patients met inclusion criteria. The majority of patients were male ($n = 38$, 61%). Of 62 patients, 40 (65%) were premature (born prior to 37 weeks of gestation) and 37% (23/62) were admitted to the NICU because of prematurity, low birth weight, or comorbidities. A total of 44% (27/62) children were treated with furosemide; of note, 11