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ORIGINAL RESEARCH ARTICLE

Renal lithiasis in children

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ABSTRACT

Justification and objective: Renal lithiasis is due to the precipitation of crystals due to an imbalance in the urine between promoting substances and inhibitory substances. It is a pathology with a prevalence between 2–10% in the pediatric population, with an incidence that has increased in the last 25 years; for this reason this study aims to know the prevalence, clinical and metabolic manifestations of renal lithiasis in the pediatric population of the National Children's Hospital of Costa Rica. **Methods**: Tthis is a retrospective, descriptive and observational study, through the review of records of patients under 18 years of age with the diagnosis of renal lithiasis, attended at the National Children's Hospital, in the period from January 2000 to 2018. **Results**: A total of 106 patients were included. The average age at diagnosis was 6.6 ± 3.8 years; the frequency of cases has increased 5.5 times in the last 5 years. Risk factors detected: urinary tract abnormalities 22.6% and family history of lithiasis 17.9%. Metabolic analysis showed low urine output in 74.3%, hyperphosphaturia in 43.2%, hypomagnesuria 39.2% and hypercalciuria 37.8%. Etiologies determined: metabolic 54.7%, urinary tract malformations 16% and idiopathic in 30.9%. Intracorporeal lithotripsy was applied in 61.2%. Recurrence was observed in 28.5% of cases, and a relationship was found between the incidence of recurrence and the size of the lithotripsy ($p = 0.001$) and surgical treatment ($p = 0.010$). **Conclusions**: There is an increase in the frequency of cases of pediatric lithiasis with a multifactorial etiology at the National Children's Hospital of Costa Rica.

Keywords: nephrolithiasis; urinary tract, hypercalciuria; lithotripsy; metabolic

1. Introduction

Renal lithiasis is due to the precipitation of crystals due to an imbalance in the urine between promoting substances (calcium, oxalate) and inhibiting substances (citrate, phosphate and magnesium), also involving changes in urinary pH and urine concentration associated with low fluid intake.[1–3]

A prevalence between 2–10% is observed in the pediatric population, with an increasing incidence in the last 25 years.[1–3–5] Family hereditary history, structural deformities, urological surgeries, dehydration and the use of certain drugs are some of the related risk factors.[4–6]

In 13% of pediatric patients the diagnosis is accidental.[1–4] The main causes described are metabolic abnormalities in urine, structural alterations of the

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urinary tract, urinary tract infections or idiopathic etiology.[3–4]

Conservative management such as fluid therapy, analgesia, prophylactic antibiotic and pharmacological treatment is recommended. Surgical treatment is indicated in cases of failure of spontaneous expulsion of the stone and/or if it causes obstruction of the urinary tract, recurrent urinary tract infections, the presence of large stones; the surgical techniques used are ureteroscopy with or without laser extraction and extracorporeal shock wave lithotripsy.[1–4]

Recurrence rates are high, approximately 50% in the first 3 years and mostly in patients with metabolic abnormalities.[4]

2. Methods

This is a retrospective, descriptive and observational study. The information was obtained by reviewing the clinical records of the patients attended. All patients under 18 years of age with a diagnosis of renal or urinary tract lithiasis, seen at the National Children's Hospital "Dr. Carlos Sáenz Herrera" (HNN), during the period from January 2000 to December 2018, were included. Patients with incomplete records (with less than 50% of the required information) were excluded.

The epidemiological variables to be analyzed were gender, age at diagnosis, origin and year of diagnosis. The risk factors and comorbidities investigated were: nutritional status, family history of nephrolithiasis, urinary tract abnormalities, neurological disorders, dehydration and drug use. The clinical manifestations presented in the first episode and the diagnostic methods used were described, and the lithoid was also analyzed according to its size, composition, location and number.

For the metabolic analysis of 24h urine, the definitions and values given in these references were considered (Table 1).[5–911]

Table 1. Definitions of 24-hour urine metabolic analysis

Finding	Value
Hypercalciuria	Calcium/creatinine ratio: <12 months: > 0.8 mg/mg, 1–3 years: > 0.53 mg/mg, 3–5 years: > 0.4 mg/mg, 5–7 years: > 0.3 mg/mg, >7 years: > 0.21 mg/mg Urinary excretion > 4 mg/kg body weight at any age
Hyperoxaluria	Oxalate/creatinine ratio: 0–6 months: >260–288 mg/mg, 7–24 months: >110–139 mg/mg, 2–5 years: >80 mg/mg, 5–14 years: >60–65mg/mg, >16 years: >32 mg/mg Urinary excretion >45 mg/1.73 m2/24 h at any age
Cystinuria	Cystine/creatinine ratio: <1 month: >180 mg/mg, 1–6 months: >112mg/mg, >6 months: >38 mg/mg Urinary excretion: <10 years: >13 mg/1.73 m2/24 h, >10 years: >48 mg/1.73 m2/24 h
Hyperuricosuria:	Uric acid/creatinine ratio: <1 year: >2.2 mg/mg, 1–3 years: >1.9 mg/mg, 3–5 years: >1.5 mg/mg, 5–10 years: > 0.9mg/mg, >10 years: > 0.6 mg/mg Urinary excretion < 815 mg/1.73 m2/24 h in >1 year
Hypomagnesuria	Magnesium/creatinine ratio >2 years: < 0.12 mg/mg Urine excretion < 88 mg/1.73 m2/24 h
Hypocitraturia	Citrate/creatinine ratio: 0–5 years: < 0.2 –0.42 mg/mg, >10 years: < 0.14–0.25 mg/mg Urinary excretion < 0.14 mg/1.73 m2/24 h at all ages
Hypernatriuria	Urinary sodium excretion >3 mEq/kg/24 h at any age Fractional sodium excretion >1%. Tubular reabsorption of phosphorus (TPR): it is calculated with the following formula, (1 urinary phosphorus x plasma creatinine x 100 / plasma phosphorus x urinary creatinine), its normal value is greater than 85–95%.
Normal volume of diuresis	Infants 750 cc/24 h, < 5 years 1000 cc/24 h, 5–10 years 1500 cc/24 h, >10 years over 2000 cc/24 h

The study was approved by the HNN Scientific Ethical Committee with code CEC-HNN–031–2018.

The software used for data entry and analysis was StataCorp version 14.2, license serial number 4014040626265114.

3. Results

A total of 113 patients with the diagnosis of renal lithiasis were recruited, 106 remained for the study analysis. 57.5% (n=61) of the patients were male, the mean age at diagnosis was 6.6 ± 3.8 years

(range: 0.3–14.6 years), 47.1% (*n*=50) were from an urban area.

The distribution of the frequency of lithiasis according to the year of presentation is shown in Figure 1.

The risk factors observed were: overweight or obesity in 18.5% (*n*=15), urinary tract abnormalities 22.6% (*n*=24), family history of lithiasis 17.9% (*n*=19), previous urological surgeries 7.5% (*n*=8), neurological disorders, epilepsy and spina bifida were observed in 4.7% (*n*=5) each.

The main urinary tract abnormality detected was double collecting system 46% (*n*=11), followed by vesicoureteral reflux and hydronephrosis in 25% (*n*=6) each. Signs or symptoms were present in 80.2% (*n*=85) of the patients, which are described in Figure 2.

95.2% (*n*=101) were diagnosed by imaging study, of these 89.4% (*n*=90) with ultrasound and 3.3% (*n*=3) by abdominal radiography and/or computed tomography each.

General urine examination in 31.1% (*n*=33) was normal, hematuria was observed in 21.6% (*n*=23), pyuria in 16% (*n*=17), crystalluria in 5.6% (*n*=6), of which 4 cases with calcium oxalate crystals, 1 with uric acid crystals and 1 with triple phosphate crystals.

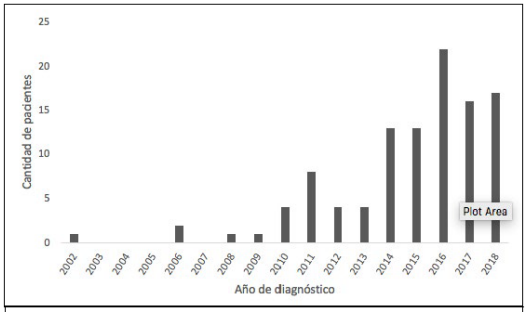

Figure 1. Distribution of the frequency of cases according to year of diagnosis of patients with a diagnosis of renal lithiasis seen at the National Children's Hospital. 2000–2018

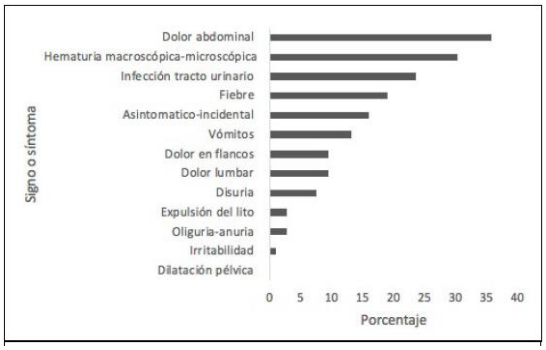

Figure 2. Distribution of the most frequent signs and symptoms in patients with a diagnosis of renal lithiasis seen at the National Children's Hospital. 2000–2018

In 27.9% (*n*=26) of the patients, data of infection were detected in the urine examination and an alkaline urinary pH was found in 65% (*n*=60).

The 24 h urine was performed in 72.5% (*n*=77) of the patients, 74.3% (*n*=57) presented a urine output lower than expected for age. The findings of the metabolic study (*n*=77) are described in Figure 3.

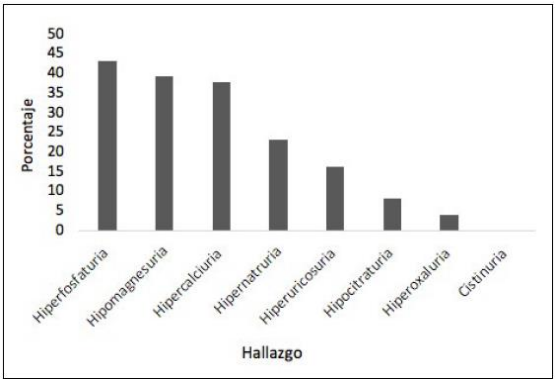

Figure 3. 24-hour urine findings in patients with a diagnosis of renal lithiasis seen at HNN. 2000–2018

A stone composition study was performed on 9.4% (*n*=10), of which 5 had a mixed stone composition, 3 with calcium oxalate, 1 with calcium phosphate and 1 with magnesium ammonium phosphate. The most frequent size of the calculus was between 6–10 mm (39.6%) (*n*=42).

In 56.6% (*n*=60) the lithiasis was located at the pyelocaliceal level, 20.7% (*n*=22) in the distal ureter and 5.6% (*n*=6) in the bladder. In 56.6% (*n*=56) of the patients only one stone was found, 30.8% (*n*=30) from 2 to 5 stones and 13.1% (*n*=13) presented with multiple lithiasis.

Regarding the laterality of the lithoid, it was observed that 82.8% (*n*=77) had a unilateral presentation, with predominance of the right side in 55.8% (*n*=43). No statistically significant difference was found between one side with respect to the other (Z value = 1.450, p value = 0.147).

Among the causes of lithiasis, the following stand out: metabolic cause in 53.7% (*n*=57), urinary tract malformations in 15% (*n*=17), urinary tract infections and previous surgeries in 1.8% (*n*=2) each, and in 30% (*n*=32) were of unknown etiology.

Of these, 57% (*n*=57) required surgical treatment for removal of the lithium and 32% (*n*=32) required expectant management; 11.3% (*n*=11) received concomitant pharmacological and surgical treatment and 6.2% (*n*=6) received exclusive pharmacological therapy.

Intracorporeal lithotripsy was used in 61.2% (*n*=30), open pyelolithotomy 24.5% (*n*=12), pyeloplasty 14.3% (*n*=7) and cystolithotomy 6.1% (*n*=3).

Potassium citrate was administered in 9.1% (*n*=3); tamsulosin, hydrochlorothiazide and sodium citrate were administered in 1 patient respectively.

The 28.5% (*n*=30) of the patients presented recurrence of lithiasis and it was determined that patients with stones between 11 to 15 mm have 4.5 times more risk of relapse (Chi-square = 10.2154, p = 0.001). An association was also found between expectant treatment (Chi-square = 5.4619, p = 0.019) and recurrence, as well as with surgical treatment and relapse (Chi-square = 6.6833, p = 0.010).

4. Discussion

The increase in the incidence of renal lithiasis in children is possibly due to increased diagnostic suspicion, changes in dietary habits, environmental and metabolic factors, as well as the use of more accessible imaging methods.[7–8]

Different studies indicate that the female gender predominates, especially in preadolescents and adolescents (11–17 years old) due to the lithogenic effect of estrogens, the hormonal effect on adipocytes, bone mineralization and a higher sodium intake, as well as a higher incidence of urinary infections (older than 14 years old).[9–12] On the other hand, Yang and Vicedo Cabrera report a higher incidence in favor of males with a lower urinary expenditure in areas with high temperatures.[13–15]

It is difficult to diagnose lithiasis in infants, due to a non-specific clinical picture; the average age at diagnosis ranges from 4.4 to 7.5 years; there is a clear predominance in the adolescent population (12–14 years old) of up to 68–72%.[16–18]

In the Latin American population there are few studies on the frequency of this pathology, Ward and other authors report that 2.5% and 11% of their population were Latinos or Hispanics respectively, this difference may be due to a dietary condition in the consumption of calcium, animal proteins, sodium, oxalate, fluid intake and environmental factors or to an undetermined genetic component.[19–20]

However, the main risk factors found are still urinary tract abnormalities and a family history of lithiasis.[21–22] Urinary tract abnormalities alone do not develop lithiasis; they must be associated with other factors such as urinary stasis, obstruction, urinary tract infections, urine supersaturation, pH alterations and low urinary volume.[10–11]

Family history as a risk factor varies from one series to another (Issler 30%, Dwyer 40%, Velásquez 48–50%), some authors do not find a direct relationship with lithiasis, but they do relate it to environmental, social and dietary factors of the family component.[8, 17, 21, 23, 24]

In pediatrics, the clinical manifestations are very variable and nonspecific, more so in young patients, due to the difficulty of localizing and describing the symptoms or because they are asymptomatic.[25–26] General urine examination may show hematuria, leukocyturia, nitrites, proteinuria, crystalluria, increased osmolarity and alterations in urinary pH due to urinary tract infection or due to the inflammatory reaction produced by the lithoid (4%–23%),

making it difficult to differentiate it from lithiasis.[22, 27, 28] Incident diagnosis is reported in up to 13% of cases.[8, 29]

The main diagnostic method is still urinary tract ultrasound. However, there are centers that use computed axial tomography (CT) given the possibility of detecting smaller size lithoscopies (3.7 mm), frequent in children under 1 year of age; the use of CT can also be justified, since it has a sensitivity and specificity of almost 100%, in addition to providing useful anatomical information in surgical cases.[30–32]

Urinary pH is important in the genesis, if pH < 6 is associated with uric acid, calcium oxalate and cystine lithia formation, pH around 6.5 is associated with phosphate lithia, pH >7 with calcium phosphate lithia, pH>8 correlates with struvite and ammonium urate lithia.[27, 33]

A low urine output for age is one of thd

e factors most associated with childhood lithiasis (52% to 89%), due to a low fluid intake or as a result of a higher output of insensible losses (hot spots), which leads to an increase in the concentration of urinary solutes favoring crystallization.[14, 34]

In the pediatric population the most frequent metabolic causes are hypercalciuria ([50–62]%), hypocitraturia (68%), hyperoxaluria ([20–21]%), cystinuria ([7–22]%) and hyperuricosuria (8%).[7, 8, 21, 22] Hypomagnesuria as a cause of lithiasis is reported in 11.3%–42%; magnesium is an inhibitor of the crystallization of calcium oxalate and calcium phosphate, so its decrease in urine is a lithogenic factor, observed in urine with pH>6.6.[35, 36]

Hyperphosphaturia is observed in 18.4% to 25% of children aged 0 to 5 years, more frequently in children under 12 months, due to a decrease in renal reabsorption of phosphate, increasing the synthesis of vitamin D and the absorption of phosphate and calcium at the intestinal level resulting in hypercalcemia.[16, 36] Hypercalciuria can be associated with distal renal tubular acidosis, tubular dysfunction (Dent or Lowe syndrome), hypervitaminosis D, chronic use of furosemide, dexamethasone, Bartter's syndrome, William's syndrome and primary hyperparathyroidism.[35]

Children show a different metabolic profile than adults; with a higher incidence of hypocitraturia and hypomagnesuria, no alterations in urine uric acid levels are found, suggesting that obesity is not related to the pathogenesis of lithiasis.[37]

According to the location of the lithiasis, there is a higher incidence in the upper urinary tract (65–82%) at the level of the kidney and ureter, this is associated with the size of the lithiasis and the shape of the renal pelvis, which narrows as it passes through the renal hilum at the ureteropelvic junction.11, 25 According to the number of lithiasis reported per patient there is a higher frequency of single lithiasis (Vandervoot (69%), Edvardsson (53%), Sarkissian (80%), Issler 68%), several authors agree that genetic metabolic causes should be suspected in the presence of multiple lithiasis.[8, 10, 11, 22, 23]

Urinary tract malformations, both functional and anatomical, generate lithiasis due to urine stasis, preventing the elimination of crystals already formed, in addition to presenting a greater risk of infections.[35] Urinary tract infections predispose to lithiasis due to the presence of urease-producing bacteria (Proteus, Morganella, Providencia spp and Klebsiella), an enzyme that facilitates the formation of struvite or triple phosphate lithium by alkalinization of the urine; the bacteria also produce substances that form part of the matrix of the lithium, causing hypocitraturia and increasing calcium oxalate deposits.[35–38]

The most commonly used treatment methods are lithotripsy and surgery by ureteroscopy. Extracorporeal lithotripsy is recommended in stones smaller than 2 cm located in the renal region, pyelocaliceal and proximal ureter.[18, 23, 25, 31] As for pharmacological treatment, citrate is used in cases of hypercalciuria and hypocitraturia; it is an inhibitor of the crystallization of calcium salts and prevents recurrence.[13, 39] Thiazide-type diuretics (hydrochlorothiazide) are also used in hypercalciuria; they induce water and salt loss with reduction of extracellular

volume, causing a compensatory mechanism, where calcium is reabsorbed and sodium is excreted, causing hypocalciuria.39 Tamsulosin is an alpha adrenergic antagonist, indicated in children over 5 years of age with ureteral and bladder stones that are symptomatic. Its mechanism of action is to dilate the distal ureter and promote passage of the stone (<10 mm).[17, 18, 39]

Recurrence occurs in a high percentage (44%–47%), some authors report that asymptomatic patients have a lower risk of recurrence and patients who require surgery in their first episode have a higher risk.[7, 9, 21]

The variability of renal lithiasis in the pediatric population is notorious; for prevention, fluid, magnesium and citrate intake should be improved, as well as reducing sodium intake (<2300 mg/day), animal protein and not exceeding calcium intake.[35]

It is concluded that in our environment there is a clear increase in the incidence of cases of renal lithiasis in the pediatric population and often underdiagnosed because this pathology is not considered as a possibility in the child. Unfortunately, there are no genetic studies to rule out a monogenic disease, but a multifactorial etiology is observed, where fluid intake plays an important role in the genesis, as well as variations in the diet of the child population.

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