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Urinary lithiasis in pediatrics

ABSTRACT

Renal lithiasis is an infrequent entity in childhood and its incidence is increasing in developed countries. It affects white individuals more than African-Americans in a 4:1 ratio, with male predominance. There are geographical, racial and genetic factors involved in its pathogenesis, which also depends on physicochemical factors (renal elimination of water and solutes, urinary pH, balance between factors that stimulate/inhibit crystallization), anatomical alterations, infections and socioeconomic changes; which over time have produced changes in dietary habits, which have modified the frequency, chemical composition and location of calculi. Despite its rarity, lithiasis should be considered in order to avoid irreversible renal damage. The availability of less aggressive therapy has reduced surgical indications to 5%, opening new perspectives in the treatment of urolithiasis in childhood.

Key words: renal calculi, hematuria, ultrasonography, calcium oxalate, lithotripsy.

INTRODUCTION

Since ancient times there is evidence that humans have suffered from urolithiasis, with cases reported in mummies of Egyptian children (1). Urolithiasis in children is multifactorial, occurs worldwide and tends to recur (2,3). Its incidence in the pediatric population is 1-3% in developed countries, being small when compared to the adult population (510%). Recent studies in the United States suggest an increase in incidence ranging from 1/1,000 to 1/7,500 (4). The probability of suffering symptomatic calculi is 10 times higher in adolescents compared to children aged 0-3 years. Most children with urolithiasis have a metabolic disorder. Exceptions are patients with a neurogenic bladder, who are prone to infectious stone formation, and those who have undergone urinary tract repair using bowel, which predisposes to bladder stone formation (2). A retrospective study indicated a higher incidence between 5-10 years of age. The mean age of presentation was 8.2 years, with 54.4% of males. A family history of lithiasis was found in 50% of the cases. Urinary infections and metabolic disorders (hypercalciuria, tubular acidosis, cystinuria) were the most frequently found etiological factors. Idiopathic lithiasis was considered in 15% of the cases (5). It is a pathology with high morbidity due to the possibility of causing structural lesions in the kidney or urinary tract at very early ages (6). In healthy individuals, urine passes through the urinary tract without crystals forming or these are so small that they are eliminated asymptomatically (asymptomatic crystalluria) (6).

STONE FORMATION

Metabolic alterations predispose to stone formation (2): hypercalciuria is the most recognized metabolic risk factor worldwide, followed by hypocitraturia, less frequently by hyperuricosuria, hyperoxaluria, heterozygous cystinuria, hypomagnesuria, hyperparathyroidism and renal tubular acidosis (2,7).

Approximately 90% of all stones contain calcium as the main component and 60% are composed of calcium oxalate (epidemiological studies suggest genetic influence on hypercalciuria), others are composed of uric acid, cystine, ammonium or phosphate crystals or a combination of these substances (2,7).

The risk of stone formation increases with increasing concentrations of these crystals and decreases with increasing concentrations of urinary inhibitory substances (2).

Factors that favor urinary stone formation are: low urinary volume, low urinary pH, calcium, sodium, oxalate and urate.

Many inorganic (e.g. citrate, magnesium) and organic (e.g. glycosaminoglycans, osteopontin) substances inhibit stone formation. Organic inhibitory compounds bind to the crystal surface, inhibiting crystal growth and nucleation. Stone formation depends on four factors: matrix, precipitation-crystallization, epitaxy and absence of stone inhibitory substances in the urine. The matrix is a mixture of proteins, non-aminated sugars, glucosamine, water and organic ash.

It constitutes 2-9% of the dry weight of urinary calculi and is arranged in their interior forming concentric lamellar structures.

Precipitation-crystallization refers to the supersaturation of urine for the specific ions that make up the crystal.

Increased urinary saturation for ions increases the rate of nucleation, crystal growth, their aggregation, increases the probability of stone formation and growth.

Epitaxy consists of the aggregation of crystals of different compositions, but with a similar lattice structure; thus, stones of heterogeneous nature are formed.

CLINICAL MANIFESTATIONS

The clinical picture of urolithiasis depends on the age of the child, the size and location of the calculus (3,7). Children usually present with macroscopic or

microscopic hematuria and non-specific abdominal pain (2,7). General signs and symptoms such as nausea, vomiting, manifestations of voiding dysfunction characterized by diurnal or nocturnal urinary leakage and voiding urgency may also be found (7).

If the stone causes obstruction, there is significant pain in the lumbar fossa (renal colic) or in the abdomen. The stone typically causes obstruction in areas of urinary tract narrowing: the pyeloureteral junction, in the area where the ureter crosses the iliac vessels, and the ureterovesical junction.

The ureter narrows progressively distally, and its narrowest segment is the ureterovesical junction. Pain usually radiates anteriorly toward the scrotum or labia.

Often the pain is intermittent, corresponding to periods of urinary flow obstruction, which increase the pressure in the collecting system.

If the stone is in the distal ureter, the child may present irritative symptoms such as dysuria, tenesmus and pollakiuria. When the stone passes into the bladder, the child usually remains asymptomatic. If the stone is in the urethra, dysuria and voiding difficulty may occur, especially in boys.

Some children eliminate small amounts of grit-like material (2).

DIAGNOSIS

Urolithiasis is only the manifestation of other underlying diseases, but not the disease itself, so a complete diagnostic evaluation is needed in each case, so that the appropriate treatment can be instituted as early as possible. The medical history should include as much information as possible on family history (50% of patients have a family member with urolithiasis, and this orients us about a possible genetic disorder), prematurity, concomitant diseases (with their medical treatment), daily fluid intake, diet, use of vitamin supplements (1,8).

The diagnosis can be made by chance when performing abdominal ultrasonography in an asymptomatic child, or it can be made in a patient with clinical symptoms in whom lithiasic disease is already suspected (3).

Laboratory tests and imaging studies are necessary for the diagnostic confirmation of urolithiasis. The following examinations are recommended in the acute phase: the study of the metabolic profile in blood and urine to determine the etiopathogenesis of the stone; urine culture (for the identification of stones associated with urinary infections), antibiogram if necessary, simple abdominal X-rays without preparation (for evaluation of the location and size of the stone), in general by ultrasound of the urinary tract and computed tomography of the kidneys/urinary tract is used in selected cases (7). Once the presence of lithiasis is established, the important thing is to determine the metabolic alteration that conditions stone formation (2). Approximately 90% of urinary calculi are more or less calcified, so they are radiopaque on plain abdominal radiography. However, many are only a few millimeters in diameter and may go unnoticed, especially if they are in the ureter. Struvite (magnesium ammonium phosphate) stones are radiopaque. Cystine, xanthine and uric acid stones may be radiolucent, but are often slightly opacified.

Some children present with nephrocalcinosis or calcification of renal tissue. Nephrocalcinosis is seen more often in children.

frequently in preterm infants treated with furosemide, which causes hypercalciuria, and in children with renal medullary spongiosis. There are numerous imaging options in children with suspected renal colic. The most accurate diagnostic study is non-contrast helical CT of the abdomen and pelvis; it delimits the number and also the location of the stones with a sensitivity and specificity of 96%. It also shows whether the affected kidney is hydronephrotic; however, the radioactive exposure is high. Another alternative is to obtain a simple X-ray of the abdomen and pelvis and a renal ultrasound. These studies can demonstrate hydronephrosis and possibly the stone; however, the stone is not visualized on ultrasound unless it is located

adjacent to the bladder. In addition, kidney stones <3 mm are typically not visible. Thus, clinicians need to carefully weigh the risks of CT versus the lower sensitivity of plain abdominal radiography plus ultrasound. In a child with an already diagnosed stone, serial plain radiographs or renal ultrasound can be used to monitor the status of the stone, whether it has increased or decreased in size or become displaced. Any stone-like material should be sent for analysis to a laboratory specializing in the identification of urinary stone components (2). It is very important to warn parents that when testing for lithogenic and stone-inhibiting substances, fluid intake should not be drastically increased. This is because an excessive increase in fluid intake, and therefore urine volume, may mask the true risk factor related to the patient. For example, many young girls have only one identifiable risk factor: low fluid intake. Therefore, an increase in fluid intake right at the time of collection(s) is likely to make it impossible to elucidate the reason for urolithiasis (9).

METABOLIC STUDY

In all children with urolithiasis, a metabolic evaluation of the most frequent predisposing factors should be performed, taking into account that structural, infectious and metabolic factors often coexist. This evaluation should not be initiated in a child in the middle of the process of stone clearance, since the change of diet, the hydration status, as well as the effect of the obstruction on the kidney, may alter the results of the study (2).

Bladder stones associated with childhood malnutrition, preferentially formed with cereal-based diets, are still endemic in Turkey, China, India, and the African continent. In northeastern Thailand, the high endemicity of urolithiasis was associated with the high prevalence of tubular acidosis and hypocitraturia. On the other hand in northern India the absence of an oxalate-degrading intestinal bacterium, oxalobacter formigenes, has been implicated in the high incidence of absorptive hyperoxaluria, with calcium oxalate formation seen in this region of the world. In the USA, the prevalence of urinary calculi rises in a north-south and west-east direction; 75% of these children have an identifiable risk factor and hypercalciuria or hyperuricosuria is identified in 50% of cases (7).

PATHOGENESIS OF DIFFERENT TYPES OF KIDNEY STONES

In calcium oxalate and calcium phosphate stones the most frequent metabolic abnormality in these children is normocalcemic hypercalciuria. Hypercalciuria can be absorptive, renal or resorptive. The primary disorder in absorptive hypercalciuria is intestinal hyperabsorption of calcium. In some children, an increase in 1,25-dihydroxyvitamin D is associated with increased calcium absorption; while in others the process is independent of vitamin D. Renal hypercalciuria consists in the alteration of renal tubular reabsorption of calcium. Renal calcium losses cause moderate hypocalcemia, which induces an increase in parathyroid hormone production, with increased intestinal calcium absorption and mobilization of calcium deposits. Resorptive hypercalciuria is rare and is seen in patients with primary hyperparathyroidism. Excess parathyroid hormone secretion stimulates intestinal calcium absorption and mobilization of calcium stores. Hyperoxaluria is another potentially important cause of calcium stones. Oxalate increases the solubility product in calcium oxalate crystallization 7 to 10 times more than calcium. Therefore, hyperoxaluria significantly increases the likelihood of calcium oxalate precipitation. Oxalate occurs in high concentrations in tea, coffee, spinach and rhubarb. Primary hyperoxaluria is a rare autosomal recessive disorder that can be subdivided into glycolic aciduria and l-glyceric aciduria. Most patients with primary hyperoxaluria have glycolic aciduria; in affected individuals there is an increase of oxalic and glycolic acids in the urine. Both defects lead to increased endogenous oxalate production, with hyperoxaluria, urolithiasis, nephrocalcinosis and renal injury. In untreated patients, death occurs around 20 years of age due to renal failure. Oxalosis, which is

defined as the extrarenal deposition of calcium oxalate, occurs when there is renal insufficiency with an increase in plasma oxalate. Calcium oxalate deposits appear first in the blood vessels, bone marrow, and eventually are seen throughout the body. Secondary hyperoxaluria is more frequent, it can occur in patients with increased intake of oxalates, of their precursors such as vitamin C, in those with pyridoxine deficiency and in children with intestinal malabsorption.

Enteric hyperoxaluria includes disorders such as inflammatory bowel disease, pancreatic insufficiency, biliary diseases, in which there is gastrointestinal malabsorption of fatty acids, which bind intraluminal calcium and form salts that are excreted in the feces. Normally, calcium forms a complex with oxalate and reduces oxalate absorption, but, if calcium is not available, there is an increased absorption of free oxalate. Hypocitraturia consists of a low excretion of citrate, which is an inhibitor of calcium stone formation. Citrate acts as an inhibitor of calcium urolithiasis by forming complexes with calcium, increasing the solubility of calcium in the urine, and inhibiting the aggregation of calcium phosphate and calcium oxalate crystals. Some disorders such as chronic diarrhea, intestinal malabsorption and renal tubular acidosis can cause hypocitraturia. It can also be idiopathic. Renal tubular acidosis (RTA) is a syndrome in which there is a disturbance of renal basic acid balance. It can be classified into 3 types, one of which predisposes to kidney stones, typically calcium phosphate. In type 1 RTA, the distal nephron does not secrete hydrogen ions into the distal tubule. Urinary pH is never lower than 5.8 and hyperchloremic hypokalemic acidosis occurs. Patients present with nephrolithiasis, nephrocalcinosis, muscle weakness and osteomalacia. Type 1 RTA can be an autosomal dominant disorder, but is more often acquired and associated with systemic diseases such as Sjogren's syndrome, Wilson's disease, primary biliary cirrhosis, lymphocytic thyroiditis, or is due to amphotericin B, lithium or toluene (an organic solvent associated with glue inhalation) (2).

Urolithiasis occurs in 5-8% of patients with cystic fibrosis. Typically, the stones are calcium and often occur in adolescents. Microscopic nephrocalcinosis also occurs in young children with this disease. These patients do not have hypercalciuria, and the propensity for urolithiasis is thought to be due to an inability to excrete excess sodium chloride or intestinal malabsorption. There are other disorders that may play some role in calcium stone formation. Hyperuricosuria may be related to epitaxial growth of calcium oxalate crystals around a core of uric acid crystals or to the action of uric acid as a urinary mucopolysaccharide antagonist, which inhibits calcium oxalate crystallization. Heterozygous cystinuria is seen in some patients with calcium stones. The mechanism of action is unknown, but may be similar to that of uric acid. Sarcoidosis causes increased sensitivity to vitamin D3, thereby increasing calcium absorption in the digestive system. In Lesch-Nyhan syndrome there is excessive uric acid synthesis. These patients are more prone to the formation of uric acid stones, although some of these stones may be calcified. In some children, calcium stones are idiopathic. This diagnosis should only be established after a complete metabolic evaluation (2).

- **Cystine stones**

It causes 1% of kidney stones in children. It is a rare autosomal recessive disorder of the epithelial cells of the renal tubule that prevents the absorption of the four dibasic amino acids (cystine, ornithine, arginine and lysine), causing excessive urinary excretion of these products. The only known complication of this

The most common disease is the formation of stones, due to the low solubility of cystine. Patients usually have acidic urine, which increases the rate of precipitation. The sulfur content present in cystine makes these stones weakly radiopaque (2).

- **Struvite stones**

The prevalence of struvite stones associated with infection, high in the past, is nowadays lower in most industrialized countries, probably due to better diagnosis and treatment of obstructive uropathies, including pediatric urinary tract infections (7). Urinary

tract infections caused by urease-producing germs (most frequently Proteus spp., sometimes Klebsiella spp., Escherichia coli, Pseudomonas spp. among others) cause urine alkalinization and excess ammonia production, which can lead to precipitation of magnesium ammonium phosphate (struvite) and calcium phosphate. In the kidney, stones often have a coralliform appearance and occupy the calyces. They act as foreign bodies, cause obstruction, perpetuate infection and cause progressive renal injury. Patients with struvite stones also have metabolic abnormalities that predispose to stone formation. These stones are often seen in children with neurogenic bladder, particularly in those who have undergone urinary tract repair. Struvite stones may also form in the repaired bladder of children who have undergone enlargement cystoplasty or urinary continent diversion.

- **Uric acid stones**

In the USA they represent less than 5%, but in other less developed areas of the world they are more frequent. Hyperuricosuria, with or without hyperuricemia, is the most common underlying factor in most cases. The diagnosis should be suspected when the urine is persistently acidic and contains urate crystals. Hyperuricosuria may be the consequence of different congenital disorders of purine metabolism, which result in excess production of uric acid, the end product of purine metabolism in humans. Children with Lesch-Nyhan syndrome and patients with glucose-6-phosphatase deficiency also form urate stones. In children with short bowel syndrome, especially those who have had an ileostomy, chronic dehydration and acidosis are sometimes complicated by urate stones.

One of the most frequent causes of uric acid lithiasis is the rapid turnover of purines in some tumors and myeloproliferative diseases. The risk of uric acid lithiasis is especially important when treatment of these diseases causes rapid nucleoprotein destruction. Uric acid stones or uric acid mud can occupy the entire upper part of the collecting system and cause renal failure or even anuria. Urates may also occur within calcium-containing stones. In such cases, there may be more than one predisposing factor for stone formation (2). The basis of treatment is alkalinization of the urine, in principle using potassium citrate, it is also advisable to reduce the dietary intake of purines, and in selected cases, to add allopurinol orally 10mg/kg/day once a day or divided in 2 or 3 times (7). Allopurinol is effective in patients with uric acid stones; it is a xanthine oxidase inhibitor that effectively reduces the production of uric acid and 2,8- dihydroxyadenine (2).

If despite biochemical control and alkalinizing an optimal urinary pH the patient continues to produce urinary stones, the presence of xanthine stones, uric acid metabolites due to allopurinol, should be suspected (7).

- **Indinavir stones**

Indinavir sulfate is a protease inhibitor approved for the treatment of HIV infection. Up to 4% of patients treated with indinavir develop symptomatic nephrolithiasis. Most stones are radiolucent and are composed of indinavir monohydrate, although oxalate or calcium phosphate is present in some. After each dose, 12% of the drug is excreted in the urine unchanged. The urine of these patients often contains crystals with a characteristic rectangular, fan or starburst shape. Indinavir is soluble at pH below 5.5.

Therefore, treatment based on its dissolution by acidification of urine with ammonium chloride or ascorbic acid should be considered (2).

- **Nephrocalcinosis**

Nephrocalcinosis consists of calcium deposition in the renal tissue. Nephrocalcinosis is often accompanied by urolithiasis. Its most frequent causes are furosemide, distal renal tubular acidosis, hyperparathyroidism, renal medullary spongiosis, hypophosphatemic rickets, sarcoidosis, cortical necrosis, hyperoxaluria, prolonged immobilization, Cushing's syndrome, hyperuricosuria, monogenetic causes of hypertension and renal candidiasis (2).

- **Stones with infection**

These should be surgically removed once the infectious

episode has been controlled. Prevention of recurrences is achieved by correcting anatomical abnormalities and using chemoprophylaxis with nitrofurantoin or trimethoprim/sulfamethoxazole at usual doses (7). In a retrospective study of 112 pediatric patients with renal lithiasis, there was a history of urinary tract infection in one third of the patients, and positive urine culture in 25% of them at the time of admission. The most frequent germ was Proteus (55%), and it was also the organism most frequently implicated in cases of acute pyelonephritis associated with lithiasis (57%) (5,7).

TREATMENT

Each alteration entails different therapeutic measures (3).

In the acute phase: relief can be achieved with antispasmodic drugs and nonsteroidal anti-inflammatory drugs or opioids (2,7). In this phase, nonsteroidal anti-inflammatory drugs have been shown to be superior even to opioids. Caution should be exercised when using antispasmodics in the expulsive period, since they inhibit ureteral peristalsis and increase intestinal ileus through a vagal reflex (10).

If the acute picture is accompanied by vomiting, antiemetic agents and intravenous hydration are indicated.

Stone migration should be confirmed with periodic imaging, preferably ultrasound of the urinary tract (7).

Small ureteral stones are usually eliminated spontaneously, and may present from painless to intense nephritic colic. Treatment with alpha-adrenergic antagonists, tamsulosin, terazosin or doxazosin, has been shown to facilitate stone clearance by reducing both the ureteral pressure below the stone and the frequency of peristaltic contractions of the obstructed ureter.

In many cases, endoscopic insertion of a ureteral stent past the stone relieves pain and dilates the ureter sufficiently to allow stone clearance. In children with a uric acid stone or in infants with a stone due to furosemide administration, treatment based on stone dissolution may be effective.

If the stone does not pass or is unlikely to pass, or if there is an associated urinary tract infection, its removal is necessary. For bladder stones, ureteral stones and small stones in the renal pelvis, holmium laser lithotripsy through a flexible or rigid ureteroscope is effective. Extracorporeal shock wave lithotripsy (ESWL) has been successfully applied to children with renal and ureteral stones, with a favorable outcome rate of more than 75% (2,7). A retrospective study showed that complications were more frequent with surgical treatment than when lithotripsy could be used, mainly infections and complications inherent to surgery (post-surgical stenosis) (5,7). The treatment of renal lithiasis in children through ESWL is a safe and effective treatment (11).

Another alternative is percutaneous nephrostolithotomy, in which the collecting system is accessed percutaneously, and the stones are broken up by ultrasonic lithotripsy. When these modalities do not achieve the desired effect, an alternative is laparoscopic removal; this procedure can be performed with the da Vinci robot (2). Hydration is the most important measure, whose objective is to decrease the concentration of lithogenic substances in the urine, it must be distributed throughout the day and night, in order to maintain a constant urinary flow. The fluid intake in the child should be sufficient to promote a diuresis of about 1ml/kg/h. It is recommended 2-2.5 L daily in adolescents, increasing this intake during the summer months (2,7). Fluid replacement after physical activity should be systematic, to prevent urine concentration and saturation. It is suggested to preferably ingest liquids with an alkaline pH. The diet should be adequate to the needs of the child or adolescent, especially in the intake of calcium, proteins, carbohydrates, fats and salts. It is recommended that the dietary plan be individualized and carried out by a nutritionist (7).

Excessive sodium intake increases urinary calcium excretion and may result in hypocitraturia.

In addition, increased salt intake induces metabolic acidosis and to compensate for acid overload, the kidneys conserve anions, including urinary citrate, which contributes to hypocitraturia. For these reasons it is indicated to reduce daily sodium intake and increase potassium intake.

Although counterintuitive, low-calcium diets are less effective for the treatment of calcium stones than diets containing normal amounts of calcium, reduced amounts of sodium and animal protein.

Diets low in sodium and protein reduce urinary excretion of calcium and oxalate. Excessive calcium intake should be avoided. However, children need calcium for bone development and recommendations on daily calcium intake vary according to age. Therefore, calcium restriction should be avoided in children. Thiazide diuretics also reduce renal excretion of calcium. Administration of potassium citrate, a calcium stone inhibitor, at doses of 1-2 mEq/kg/24h, is beneficial. Lemonade is an excellent source of citrate, since about 120 ml of lemon juice contains 84 mEq of citric acid. Daily intake of about 120 ml of lemon juice dissolved in 2 liters of water significantly increases the urinary citrate concentration.

Maintaining a high urinary pH (greater than 6.5) can prevent the recurrence of cystine stones. Cystine is much more soluble when urinary pH is above 7.5. D-penicillamine, a chelator, binds to cysteine or homocysteine and increases the solubility of the product. Although poorly tolerated by many patients, it has been reported to be effective in dissolving cystine stones and in preventing recurrences when hydration and urinary alkalinization fail.

The treatment of renal tubular acidosis type 1 requires the correction of metabolic acidosis, the replacement of potassium and sodium losses. Treatment with sodium citrate and/or potassium citrate is necessary. When metabolic acidosis is corrected, urinary citrate excretion returns to normal (2). As mentioned there are many effective treatment options for stone prevention (12).

Lithiasis is indicated for surgery when the pain is intractable, there is obstruction, associated infection or an impossibility of spontaneous elimination of the calculus (7).

CONCLUSIONS

Urolithiasis is a recurrent disease for which there is still no known cure (7). In this review we have tried to bring to the readers the main causes of lithiasis of the urinary tract in children, the preventive measures to avoid the formation of calculi, and the conduct that should be adopted according to the type of metabolic disorder of the patient. Since it is the most frequent cause, emphasis is placed on the diagnosis and treatment of lithiasis caused by idiopathic hypercalciuria (3).

Urinary lithiasis is a relevant health problem in the pediatric population given the role it may play in the etiology of urinary tract infection and in the progressive deterioration of renal function.

The risk of renal damage and chronic renal failure due to urinary lithiasis is low; however, some types of stones have a higher risk, such as those of hereditary origin (cystinuria, primary hyperoxaluria, Dent's disease), infection-related urolithiasis, anatomical or functional anomalies of the urinary tract or spinal cord (1).

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