Approach and Medical Management of Urinary Tract Stone in Children

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Abstract:

Kidney stone disease has become more common in children, but it remains non diagnosed in a significant proportion of patients, due to a lack of notable signs and symptoms. All children with colicky abdominal pain or microscopic hematuria should be examined thoroughly for urolithiasis. Patients' histories in terms of family, medical, and drug and a thorough physical examination are required to be considered during diagnostic evaluation. Thereafter, diagnostic imaging methods should be aimed to detect the size, shape and location of calculi and also urinary tract anomalies. Ultrasound should be used as the initial imaging method to evaluate children with suspected nephrolithiasis. The noncontrast computerized tomography reserved for those in whom ultrasound is unable to diagnose stone. Increased water and fluid intake and a reduction of salt consumption are the common recommendation to those children with a history of kidney stones, though the rate of stone recurrence in children is unknown. Since metabolic disorders are the most frequent causes of stone in children, diagnostic evaluation should also target the detection of metabolic disorders including hypercalciuria, hyperoxaluria, hyperuricosuria and so on that may cause recurrent nephrolithiasis. Kidney stone is not a disease itself, but it is only a symptom. Therefore, its early diagnosis is mandatory for every child with the first stone event. In this article, we have summarized literature and emphasize that a few studies with acceptable quality are available on children with urolithiasis in Iran and the world that warrant future studies on this topic.

Keywords: Urolithiasis, Hypercalciuria, Children, Treatment

Introduction:

Nephrolithiasis occurs following an interaction between environment and heredity traits [1]. The incidence rate of this disease in children has increased [2, 3]. The worldwide prevalence of the disease has been reported 1-15% [3, 4, 5, 6, 7]. Iran is in the "belt stone" with a prevalence rate of about 2-3% [4, 8, 9]. Urolithiasis as an important health issue is being recognized more commonly in the pediatric age group [10, 11, 12]. However, the exact incidence rate of kidney stone disease in children is unknown [13, 14]. In some areas of the world, the prevalence rates are significantly higher [15, 16]. Different incidence rates reported in children with urolithiasis reflect the differences in geographic, genetic and socioeconomic backgrounds. [17, 18, 19]. Urolithiasis appears in all pediatric age groups, but male predominance is observed [3]. The strong male predominance seen in the adult population is less clear in children [5, 7, 20]. Such an increase in the incidence of nephrolithiasis in children has some implications for health care [18]. The characteristics of this disease in children are different than adults [5, 6, 18]. Approximately, 75% to 85% of all kidney stones contain calcium salts composed of calcium oxalate and/or calcium

phosphate in the literature. The recurrence rate of nephrolithiasis in patients with kidney stones that are developed during childhood is poorly defined [4, 5, 21, 22]. Within ten years, this disease usually recurs in more than 50% of patients [3].

There are limited studies in pediatric patients. Also, a comprehensive review on the number of diseases that cause and affect kidney stones is restricted. Therefore, we reviewed the current literature on the diagnostic approach and dietary or pharmacological interventions aimed at decreasing the recurrence of kidney stones in children. Finally, we suggested carrying out metabolic workup in every child with nephrolithiasis, the need for sufficient attention to recurrence stones, and we highlighted areas in need of research in future.

Clinical findings:

The symptoms of urinary tract stones are often non-specific, particularly in infants and young children [4]. In addition, stones may remain asymptomatic during childhood and after that. The presentation of nephrolithiasis in children and adolescents differs from that in adults. The classic unilateral colicky flank pain occurs in only about 7% of patients [17].

The most common symptom of urolithiasis is flank or abdominal pain; however, colicky pain in older children is also reported. Some studies reported "non-specific" abdominal pain in infants that makes it difficult to be differentiated from acute abdomen. Sterile pyuria, or recurrent or urinary tract infections (UTIs) should raise the probability of the presence of urolithiasis. Gross hematuria may be present before other symptoms of urolithiasis [9, 11, 17]. Main clinical presentation of renal stone is hematuria [5]. However, its symptoms may be different based on the location of the stone [18]. Stones located in the lower urinary tract may presented by dysuria, complete urine retention, enuresis, frequent voiding, and gross hematuria [5, 17]. Also, the manipulation of genitals in younger children may be a first sign of urolithiasis in the urethra. A missed diagnosis may have serious consequences. Therefore, the underlying pathological condition is not often evident and may require patients' history and following diagnostic work-up.

UTI frequently is the presenting sign of urolithiasis in children [5, 11, 17]. Urinary tract infection is an important disease, which can highlight the presence of renal stone diseases. In this respect, clinicians should take a precise history regarding urinary tract infection and ask for urine analysis and urine culture for all pediatric patients with urolithiasis [2, 9]. Of the total of 100 patients with urolithiasis, 54% referred with UTI [5].

Underlying causes of renal stone:

Children with urolithiasis are high-risk patients due to recurrent stone formation. The metabolic disorders are frequently associated disorders with urolithiasis in pediatric patients. Thereafter, the investigations for the diagnosis and detection of the etiology of stone, especially metabolic disorders are recommended. All patients with urolithiaisis should be evaluated regarding the possibility of metabolic abnormalities based on stone analysis [1, 5, 17].

Through an awareness of serum and urine analyses, the stone composition is helpful for the diagnosis of metabolic disorders. Additional studies may be required notably in cases without available stone for analysis. Some authors believe that underlying metabolic disorders are not always indicated by stone analysis. Thus, the assessment of urine biochemistry has more useful results than stone analysis in children [17].

Obtaining a thorough medical history followed by a careful physical examination seems to be a lost art, though it is indispensable for an early and accurate diagnosis. It is important to obtain information regarding the family history, familial metabolic diseases, nutrition or specific diets, fluid intake, previous history of dehydration, medications, immobilization, gastrointestinal and neurologic diseases, and any mineral supplementation [17, 18, 21].

Anatomic abnormalities such as ureteropelvic junction (UPJ) obstruction or ureterovesical junction (UVJ) obstruction, vesicoureteral reflux, and neurogenic bladder are found during the workup of nephrolithiasis in 11-24% of children [6,17,20].

The anomalies of the urinary tract predisposing to urine stasis and urinary tract infection are special risk factors of stone formation. Approximately, 40% of children with urolithiasis have a positive family history of kidney stones [7, 18].

According to another study, family history of urolithiasis is reported in 23% of patients [5]. Depend on the geographical location of loving, hypercalciuria, hyperoxaluria, hypocitraturia or their combinations can be the most frequent metabolic disorders in children with nephrolithiasis [16, 17, 18]. According to our study, 68% hypocitraturia, 23% hypercalciuria, 11.4% hyperuricosuria, 8.4% hyperoxaluria, 8.9% cystinuria

and finally 1.2% proteinuria were observed in patients [5]. Hence, a systematic diagnostic examination of patients is necessary for every child who has experienced even a single kidney stone in order to prevent the recurrence of stone [1, 17].

Laboratory Studies:

Urinalysis should be performed in any child with nephrolithiasis. Microhematuria is the most common abnormality found in 60-95%. Pyuria is found in only 20% of patients. Urinary leukocyte esterase and nitrites may be detected if there is an associated UTI. Blood cell counts and urine cultures should be performed, if the child is referred with the signs of infection [4, 11, 32].

Risk Evaluation:

Predisposing factors can be identified in up to 87% of children with urolithiasis and periodic stone disease occurs in 67% of pediatric patients [17]. For these reasons, every child with the first stone event should have a complete evaluation of potential risk factors [5, 23, 33].

Metabolic Evaluation:

The metabolic evaluation for urolithiasis is to identify children at the increased risk of the recurrent stone disease and specific metabolic diseases. If stones have been surgically removed or excreted from urine during spontaneous passage, analysis is helpful to guide the workup and determine the underlying pathologic processes [3, 17].

Predisposing causes of urolithiasis can be recognized in more than 75% of children. Therefore, an early diagnostic examination is mandatory for every child with the first stone episode to prevent a delay in treatment that may lead to future complications [1,3]. However, the detection of predisposing metabolic factors requires further examination. Metabolic factors are determined by the assessment of urinary solutes and naturally occurring inhibitors of crystal and stone formation such as citrate. Infection, obstruction, or stasis will be identified by the diagnostic evaluation outlined above.

Serum Testing:

Serum studies are typically not as informative as urine studies, but may provide useful information for a detailed evaluation of urine analysis results. Serum creatinine can identify renal insufficiency and is used to determine the expected excretion of creatinine in a given urine sample. The abnormality of serum potassium and magnesium can be associated with stone formation. For all patients, analyses for serum calcium, phosphorus, magnesium, uric acid, alkaline phosphatase, Vit D, bicarbonate, and creatinine should be performed. In other cases, further blood analyses for parathyroid hormone (PTH), vitamin B6 levels and plasma oxalate and, of course, molecular genetic testing may later be necessary [4, 17 ,18].

Urinalysis:

A complete analysis of a urine random sample is needed diagnostic evaluation in every acute stone episode. Hematuria, white blood cell (WBC) count, pH, density, crystals and urinary protein excretion can easily be determined. Since the pH of the urine is a major factor in the formation of different types of stones, a low urine pH may be associated with Ca, uric acid stones and a high pH may be associated with the possibility of infection stones or renal tubular acidosis (RTA).

The elements of chemical urine analysis consist of creatinine, cystine, calcium, uric acid, oxalic acid, phosphate, magnesium and citrate. All crystals are seen in normal urine except cystine. The urine analysis is advisable for diagnostic evaluation and follow-up, and to assess the effect of the administration of alkali or to check the patient's compliance with treatment now and future. The presence or absence of infection can be addressed by a urine culture [17, 33, 34].

Since urinary components are influenced by dietary intake, 24h urine collections provide the best information about them and also about the daily intake of fluid. Urine should be collected for 24h to maintain the normal fluid intake and the normal dietary habits. The sampling should be avoided under parenteral infusions, during UTI, dehydration, diarrhea and fever. In children, or in situations where a 24h urine collection is difficult, a random urine measurement is accepted [32, 35, 36].

Analysis should be deferred until UTI has been treated completely and at least four weeks after lithotripsy or resolution of the obstruction. The normal values for the excretion rates of solutes are affected by regional and cultural variability. Many children and adolescents with stones have more than one predisposing factor. When an inherited metabolic

disorder is suspected, urine samples from family members can be help to diagnosis. In patients with multiple stones at the onset, or those in whom there is active stone formation and no anatomical abnormalities have been determined, additional examinations can be helpful [3, 4].

A spot urine sample is limited in its ability to evaluate metabolic risk, but it may provide useful information. A positive urine culture, urinary leukocytes, nitrites, and leukocyte esterase may suggest the presence of infection [4, 16, 17, 36]. (table 1) [37]

In addition to spot urine and serum tests, a formal 24-h urine collection is essential to determine the risk of stone formation. Because of variation in diet and fluid intake, results from 24h urine collections, ideally six weeks after that the patient achieves a stone-free status, should be used to guide treatment [17].

Table 1. Random urine solute-to-creatinine ratio by age

Urinary Solute	Age	Solute-to-creatinine ratio	
		mmol/ mmol	mg/ mg
Calcium	0-1 years	2.29	0.81
	1-2 years	1.58	0.56
	2-3 years	1.41	0.50
	3-5 years	1.16	0.41
	5-7 years	0.85	0.30
	7-10 years	0.71	0.25
	10-17 years	0.68	0.24
Oxalate	< 6 months	0.37	0.29
	6 months-2 years	0.26	0.20
	>2-5 years	0.14	0.11
	6-12 years	0.08	0.063
	> 18 years	0.04	0.031
Cystine	< 1 month	85	180
	1-6 months	53	112
	> 6 months	18	38
Uric acid	< 12 months	1.5	2.2
	1-3 years	1.3	1.9
	3-5 years	1.0	1.5
	5-10 years	0.6	0.9
	< 10 years	0.4	0.6
Citrate	0-5 years	0.25	0.42
	> 5 years	0.15	0.25
Magnesium	0-1 years	2.2	0.48
	1-2 years	1.7	0.37
	2-3 years	1.6	0.34
	3-5 years	1.3	0.29
	5-7 years	1.0	0.21
	7-10 years	0.9	0.18
	10-14 years	0.7	0.15
	14-17 years	0.6	0.13

Specific Metabolic Findings:

Hypercalciuria:

Hypercalciuria is the most common cause of metabolic risk factor of renal stones in children, (representing up to 50%) [1, 5].

In infants, it can be measured in random urine as calcium/creatinine ratio and in older children; it is measured in 24 hours urine collection. Defined as a urinary calcium excretion of more than 4 mg/kg/day, it is found in as many as up 10% of healthy children. In children, hypercalciuria can cause refractory haematuria, frequency-dysuria syndrome, UTI and abdominal and lumbar pain. In a majority of cases, the cause of hypercalciuria is idiopathic, both sporadic and familial. Alternatively, an increased number of vitamin D receptors may be responsible for hypercalciuria in certain patients. Other causes of hypercalciuria include distal RTA, medullary sponge kidney, UTI, and the use of medications such as adrenocorticotropic hormone (ACTH), theophylline, loop diuretics, and corticosteroids. Most children with hypercalciuria have normal serum calcium [38-41].

A calcium-to-creatinine ratio can be derived from a single specimen and is often used as an initial screening test for hypercalciuria. If hypercalciuria is suspected based on a random spot sample. This should be confirmed with a 24-h urine collection. The infants with age below 12 month may have calcium-to-creatinine ratio < 0.81 but infants with age 12- 24 month may have ratio < 0/56 in normal condition [24, 36, 42, 43].

Hyperoxaluria:

Oxalate is a metabolite excreted in urine. It is produced by metabolic pathways in body or comes from diet. It appears that 10-15% of urine oxalate is related to diet and restriction of diet oxalate affects this amount of urinary oxalate.

Hyperoxaluria and consequently renal stones can be due to increased oxalate intake, decreased Ca intake, increased intestinal absorption of oxalate or inborn errors of metabolism. Inborn errors of metabolisms are the most severe causes of excessive urinary oxalate excretion named primary hyperoxaluria. Hyperoxaluria, may be detected in up to 20% of children with nephrolithiasis and most commonly is caused by idiopathic hyperoxaluria and mild elevations of urinary oxalate levels. Foods with high in oxalate

are beet and turnip greens, rhubarb, strawberries, star fruit, sweet potatoes, wheat bran, tea, cocoa, pepper, chocolate, parsley, spinach, beets, dill, nuts and citrus juices.

The malabsorbed fatty acids displace luminal calcium from oxalate allowing increased absorption. In patients with hyperoxaluria, intestinal absorption of oxalate may be increased, due to either an increased intake of dietary oxalate or enteric reasons such as chronic inflammatory bowel diseases or a lack of colony count intestinal oxalate-degrading bacteria. Intestinal oxalate absorption is normal in patients with primary hyperoxaluria and would be significantly increased in those with dietary or enteric hyperoxaluria [1].

Also, a stool analysis for evaluation of Oxalobacter formigenes, will give further evidence of the existence of a secondary reason for hyperoxaluria [18].

Hyperuricosuria:

Hyperuricosuria is common in children especially during infancy. Hyperuricosuria has been found in 2-10% of children who are metabolically predisposed to kidney stone formation. Most patients with hyperuricosuria also have hypercalciuria; calcium oxalate urolithiasis may be coexistent. Hyperuricosuria may be familial or idiopathic and results in the overproduction of uric acid that occur secondary to inborn errors of metabolism, hemolysis, myeloproliferative disorders or a ketogenic diet [17].

Cystinuria:

Cystine stones consist approximately 2-8% of the stones in the pediatric population and result from elevated urinary excretion of cystine caused by an autosomal recessive disorder of tubular cell transport that are characteristically lifelong stone-formers. It is characterized by failure in the renal tubules to reabsorb four basic amino acids: cystine, ornithine, lysine and arginine. Cystine is poorly soluble at acidic pH, and at urine pH < 7.0 cystine it is precipitated and form stones [1, 18].

Stone analysis:

The analysis of the stone obtained after spontaneous stone passage or intervention is one of the most important diagnostic evaluation methods. Only one-third of all stones are composed of one single

substance, and hence all components should be determined. The best methods of evaluation are infrared spectroscopy or X-ray diffraction. Chemical stone analysis is inappropriate, as it is prone to errors and is obsolete [4, 18]. Recurrent stones should be analyzed, since the stone composition may change. With regard to treatment regimens, the stone components should be assessed [4].

Imaging modality to diagnose renal stones in children:

The imaging evaluation of nephrolithiasis in pediatric patients presents several unique issues.

Initial diagnostic examinations have to uncover obstruction or stasis, infection, and metabolic abnormalities and profoundly rely on imaging of the urinary tract. With the availability of noninvasive imaging modalities, such as ultrasound, stones are increasingly being detected incidentally during the evaluation of nonspecific symptoms or unrelated problems. Individual clinical characteristics, type of stone, and questions to be addressed should be considered in making decisions regarding the best imaging modality. The imaging of the urinary tract has to be sufficiently thorough to rule out, assertively, stasis or obstruction related to a stone in urinary tract [11, 23, 24]. The ultrasound is the best diagnostic imaging method in children with suspected nephrolithiasis. KUB (ureter bladder imaging), IVP (intravenous pyelography), and CT are other imaging modalities and reserving CT is for those with no symptomatic stones [4, 11].

Although ultrasound is less sensitive than CT, ultrasound is usually a good initial choice and the most suitable method for the detection of urolithiasis in children because of radiation absence, no requirement of anesthesia, providing detailed anatomic information, cost–benefit issues, wide availability, detection of hydronephrosis and other anatomical disorders of the urinary tract. [2, 5, 25]

Ultrasound provides information about size, shape and location of stone in urinary tract, the grade of hydronephrosis, presence of obstruction due to stone and associated anomalies. However, ultrasonography is not as sensitive as CT for the detection of small stones or stones in the ureter. The measurement of stone size is less reproducible by ultrasound than CT; therefore, it may reduce its utility for active monitoring of metabolic stone formation over time. Nevertheless, as stones is smaller than 2 mm in diameter, it can be

visualized using ultrasonography (US), but the success of this imaging method depends on the observer's skills [26,27].

Ultrasonography will be sufficient in most circumstances; however, sometimes ultrasound fails to diagnose urinary tract stone in up to 40% of children. Some pitfalls in the renal ultrasonography occur with small stones, thin papillary or calyceal stones, ureteral stones and in neonates especially preterm infants. Also, Tamm–Horsfall protein (THP) deposits within the renal calyces may look like nephrocalcinosis. THP deposition, however, disappears within 2 weeks, and follow-up will show completely normal kidneys. Furthermore, the echogenicity of the renal cortex in neonates is increased; therefore, the detection of cortical nephrocalcinosis can be difficult [4, 11, 28, 29].

Although KUB may detect stones, its sensitivity is low and lead to diagnosis in 30-60% cases [17, 25]. KUB in combination with ultrasound helps clinicians to diagnose and follow renal stones. Many stones will contain elements of compound calcium within them and therefore are easily seen on x-ray. Some pitfalls of the KUB are small stones, ureteral stones, radiation exposure and the need to preparation [17, 25].

Stones comprised of calcium oxalate or calcium phosphate are very radiodense and readily seen by both ultrasound and CT. Their appearance on imaging studies depends on the stone's composition. Those composed of calcium oxalate or calcium phosphate creates a very dense image on x-ray and CT scans. Struvite and cystine stones are of intermediate radiodensity. Uric acid, xanthine, 2, 8 dihydroxyadenine, and orotic acid stones are radiolucent by conventional radiography, but visible by ultrasonography or unenhanced CT [11, 18, 19, 30].

Non-contrast spiral computed tomography (CT) scan is the gold standard for the diagnosis of nephrolithiasis, because it has an excellent visualization of all stones whether they are opaque or nonopaque. Except for indinavir stones, size and location of stones, it is rapid and nearly 100% sensitive and specific. CT scan provides detailed anatomic information and is sensitivity for very small stones. It is recommended to perform CT scan in children with refractory urolithiasis symptoms but without clear evidence of stone in KUB and ultrasonography. Some disadvantages of CT scan in children with nephrolithiasis include cumulative risk of radiation exposure associated with an increased risk of cancer, cost–benefit issues, need to anesthesia, availability and requirement for preparation. It is reported that 5% of

stones in children cannot be diagnosed by CT scan. Nowadays, patients are less required to anesthesia and sedation and are less exposed to radiation with modern high speed CT scans. Long-term risks of radiation exposure in children are not completely understood. Although the risk of cancer from a single CT imaging performed for kidney stones is small, the cumulative risk is higher for those undergoing repeated studies. Additionally, the risk may be greater in children than in adults, because of a longer life expectancy and the sensitivity of developing tissues to the effects of radiation [5, 4, 11, 30, 31].

Recently, there has been interest in CT techniques with low-dose radiations for the diagnosis of renal stones. By the improvement of scanner settings, the ionizing radiation dose delivered can be reduced by 50-80% with minimal loss of diagnostic accuracy. While these modifications are appropriate for stone diagnosis, they may result in a reduced accuracy for other abdominal pathologies [1, 17, 26, 28, 31].

Most stones can be imaged without the use of contrast agents. However, when obstruction is a concern, when non-opaque or low-density stones require careful delineation, or when details of urinary tract anatomy are needed, contrast agents are recommended. The most common ureteral calcification is a stone that has moved low from the kidney. These stones typically become impacted at narrowed anatomic sites and are especially difficult to be detected when they create altitude with bony structures such as the sacrum. The detection of a ureteral stone via ultrasonography is difficult [17]. CT scan is better modality for its diagnosis [10, 17, 26, 28].

Next, the color Doppler twinkling artifact can be used in all sides that are negative for stones in B mode ultrasonography. IVP is rarely indicated in patients with renal stone, but it can be helpful in some cases for determining the anatomy of calyces and pelvis before surgery. Some disadvantages of IVP in children with nephrolithiasis are radiation exposure, availability and the need to preparation [17, 18].

Magnetic Resonance Impedance (MRI) and Magnetic Resonance urography (MRU) are unable to detect stones in urinary tract, but they can show an excellent view of urinary tract anatomy. The limitation of MRI and MRU is availability, cost–benefit issues and the need for preparation [31].

Treatment:

The spontaneous stone passage is more common in children compared with adults. There are some medical and non-medical treatments for urolithiasis in children.

Medical Treatment:

Data on medical therapy of urolithiasis in pediatric patients are limited. There are very low numbers of trials focusing on the conservative treatment in children with varied metabolic types of renal stones. The main aims of medical therapy are to prevent further growth of existing stones and prevent the formation of new stones [43, 44]. A high fluid intake is believed to be a key and universal treatment that is suggested for all types of stones. Other dietary considerations depend on the types of stones [44].

Hypercalciuria:

Hypercalciuria is one of the most common metabolic disorders in children with urolithiasis. In all children without available stone for analysis, the urine calcium concentration should be measured. The treatment aim is to reduce urinary calcium concentration as follows;

1. Diet:

The best initial management is increased fluid intake. However, the calcium intake restriction should not be recommended for a long time, because of increased risk of osteopenia, hyperoxaluria and then renal stone containing oxalate compounds. Adult's studies have shown that low sodium and protein diets are more effective than low calcium diets in reducing urinary calcium concentration. In this respect, the first treatment of hypercalciruia is dietary changes including low protein and sodium diet, high potassium diet, avoidance excess calcium and vitamin D supplements and high fluid intake [44].

2. Hydrochlorthiazide:

Thiazide diuretics can be the choice of prescription (1-2 mg/kg/day) in patients with hypercalciuria. Some observational studies have shown a reduction in urine calcium concentration in those children treated with hydrochlorthiazide. Some guideline believes that thiazides are not efficient in children with hypercalciuria to reduce renal stone recurrence [44].

There is some evidence that in patients with idiopathic hypercalciuria and recurrent stones, adding thiazides to a normal or modified diet reduces the number of stone recurrences and decreases the rate of stone formation. Thiazides and neutral potassium phosphate drugs could decrease hypercalciuria in symptomatic patients [41].

3. Citrate potassium:

Citrate potassium therapy is suggested in patients with chronic hypercalciuria. It is also useful in patients who have hypocitraturia and hypercalciuria concurrently. In this regard, the starting dose of citrate potassium is 1-2 meq/kg/day divided in two doses.

No study is available regarding the comparison between citrate and thiazide diuretics in hypercalciuric patients. Also, no prospective studies have been performed on medical therapy for stone prevention in children with hypercaciuria [44, 45]. Thiazides plus potassium salts significantly decrease calciuria and vitamin D levels [41].

Hyperoxaluria:

The goal of treatment of hyperoxaluria is to reduce oxalate production and increase its urinary solubility. The suggested treatments are high fluid intake, pyridoxine, low oxalate diet, regular calcium intake and medications such as calcium oxalate deposition inhibitors.

It is believed that the restriction of diet oxalate has a limited effect on such patients. Pyridoxine can reduce the urinary oxalate concentration and may be useful in 10-30% of patients with primary hyperoxaluria. The response to an initial pyridoxine dose (5-10 mg/kg/day) as test dose is defined as 30% reduction in urine oxalate after treatment [41, 45].

Citrate potassium and neutral phosphate compound can be used in these patients.

Cystinuria:

The aim of treatment in cystinuria is to decrease cystin saturation in urine and to increase its solubility. High fluid intake, low salt diet, urine alkalization and the use of chelators are suggested. The restriction of methionine intake is not suggested by most researchers in the field of pediatric.

Cystine chelators such as Mercaptopropionil glycine or tiopronine, D-penicillamine and/or captopril

are suggested when preliminary citrate and high fluid therapy fail to treat patients. It is believed that the maximal urinary cystine concentration is found during night, thus the night time treatment such as fluid intake and chelating therapy at bedtime is important. The aim is to reach urine PH to 7.5-8, and specific gravity less than 1010 [16, 41].

Hyperuricosuria:

Uric acid stone formation depends on not only hyperuricosuria, but also the level of acidic urine. Thus the most important treatment for these patients is alkalization of urine by citrate therapy.

Medical explosive therapy:

This therapy includes the drugs that expel ureteral stones by relaxing smooth muscle.

Calcium channel and alpha-1 receptors blockers are the main prescribed drugs. In some guidelines, this therapy is not recommended, because of little data in pediatric age group. Some clinicians administer alpha blocker medications in children with distal ureteral stone [1, 41].

Extracorporeal Shock Wave Lithotripsy (ESWL):

Currently, Extracorporeal Shock Wave Lithotripsy (ESWL) can be performed in children without long term kidney damage. The success of ESWL depends on some factors such as the type, size and location of stone. ESWL may be less efficient in cases of cystine stone, calcium monohydrate stones and the presence of anatomical abnormalities. It appears that the response to ESWL in children is higher than in adults even for large and staghorn stones. Although the available data about ESWL in children is insufficient, it appears that the percutaneous ESWL is safe and effective in this age group [22, 46, 47].

For all children, the indications of ESWL are identical to those in adults. In this regard, renal stones with a diameter up to 20 mm are ideal for ESWL. On the other hand, ESWL is more effective for upper ureteral calculi in comparison with ureteroscopy. The PCNL is suggested as the first choice modality to treat staghorn and large size stones in children and it seems that the combination of PCNL and ESWL may be useful.

After ESWL, the administration of citrate potassium is suggested to prevent stone regrowth and new stone formation in long run [22, 48, 49].

Uretereoscopic lithotripsy:

Both uretereoscopic lithotripsy and ESWL are effective modalities to treat ureteral stones. The selection of these modalities depends on the available equipment, expertise of surgeons, child's age, urinary tract anatomy and the location of stone. ESWL is recommended in small children. Ureteroscopy is useful for middle and distal ureter stones [16, 23, 46, 47].

Surgery Treatment:

PCNL is a less invasive treatment compared with open surgery. Therefore, this technique is a useful alternative to open surgery in children. The indications of PCNL are similar in children and adults. PCNL is indicated in renal stones with a diameter more than 20 mm.

Most pediatric urinary tract stones are removed by ESWL, ureteroscopy and PCNL and a low number of stones are removed by open surgery. The indication of open surgery is the presence of large stones especially in small children and very obese children and those with malformation [41, 50, 51].

Conclusions:

The incidence of nephrolithiasis in children is increasing, yet few studies have assessed whether approach, diagnosis and dietary or pharmacological interventions decrease the recurrence of kidney stones in children. The clinical manifestation and evaluation of nephrolithiasis in children is different from those in adults. Imaging must be undertaken with care to identify stones, while avoiding excess radiation exposure. Because of the prevalence of metabolic risk factors and the significant risk of recurrence in this population, all children require a metabolic workup [18].

Hence, thorough and early diagnostic examination is mandatory, for every patient with the first stone event. Following this advice, the recurrence of stone disease can be prevented. We reviewed the current literature on this topic, but further clinical trials are needed to determine the increasing prevalence, efficacy and effectiveness of different treatment modalities in children with nephrolithiasis. Additional areas in need of study are the optimal length of time for a trial of

stone passage in children, the cost-effectiveness of medical therapy, and the size and location of stones for which different therapies are most effective [5, 17, 18].

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