ROBOTICS, LAPAROSCOPY & ENDOSURGERY

WHAT IS NEW FOR METABOLIC MANAGEMENT OF CHILDHOOD STONE DISEASES?

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ABSTRACT

Today, it is very well-known truth that the prevalence of urolithiasis is nearly 2-3% in childhood and risk of recurrence may range between 6.5-54%. The stone disease has multi factorial etiologies in these patient populations. Detailed metabolic evaluation is needed after the diagnosis. The major problems are following as high recurrence rates, therapeutic irregularities, and deficiency in diagnosis. These may lead to co-morbidities such as loss of kidney functions. After the diagnosis, surgical requirements such as the stone extraction and correction of the anatomical anomalies come into question. Besides these, medical and supportive treatments are needed for preventing of recurrences, urinary infections and, preserving renal functions. Supportive care includes more fluid intake and dietary modifications. Medical treatment depends on the cause of urinary stone disease. Morbidities of pediatric urolithiasis can be prevented by early diagnosis, detailed metabolic analysis, follow-up regularly, and medical treatment protocols. In this review the classical and especially new approaches have been presented for nephrolith management in children.

Key Words: Children, Hypercalciuria, Hypocitraturia, Oxaluria, Urolithiasis

INTRODUCTION

Urinary stone diseases are considered to be occurring rarely in the pediatric age group; however, studies in recent years have shown increases especially in the prevalence and incidence of ureter stones (1). Although they have a prevalence of about 2-3%, pediatric stone diseases have a recurrence risk that may vary between 6.5 - 54% (2). Besides, it is an important health problem due to high morbidity and risk of end-stage renal failure (3). It has a multi factorial etiology such as race, gender, genetics, climate, dietary habits (4). In developing countries, endemic pediatric Stone diseases are often limited to the bladder. This is associated with decreased phosphate intake and may often manifest as ammonium acid, urate or uric acid stones. Again, studies in recent years have shown that incidence of stone disease has increased with increased animal protein consumption in parallel with the rising standards of living in developed countries (5).

Although, urinary stone diseases are common in all pediatric age groups, the average age at diagnosis is between 4.2 - 9.4% (1).

Hereditary factors should be considered in case of children who are diagnosed earlier than these age groups (6).

In pediatric group, the objective in the treatment of urinary Stone disease covers removing the stone, preventing recurrences, maintaining renal functions, preventing urinary system infections, and correcting the anatomical and underlying metabolic problems. The majority of children with urinary tract stone disease exhibited ≥1 metabolic risk factors. Metabolic risk factors should be evaluated in all children with urinary stone

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disease to provide appropriate treatment (7). Mohammadjafari et al. concluded the similar and noted that Patients should be carefully evaluated considering this point of view (8).

Unfortunately, incidence of urolithiasis in pediatric age groups have been increasing in developed countries mainly due to changes in daily routine diet. Additionally, urolithiasis must be suspected in the face of abdominal pain even central or diffuse pain in younger children when there is a positive family history even though specific urinary symptoms such haematuria and dysuria may be lacking (9).

The medical treatment are used in the urinary system stone diseases and these are specific to the type of stone and is effective only in a small group of stones. Alkalization in uric acid stones may also be effective for cystine Stones when used in combination with thiols; besides urine acidification is another method used in infection stones. Objectives of medical treatment cover preventing the formation of new Stones, preventing of the growth of existing stones and thus reducing the surgical need and hence, morbidity. In light of all of these, medical treatment may be considered as a preventive treatment. In order to start medical treatment, exact diagnosis should be made. Therefore, metabolic investigations covering stone analysis, urine and serum analysis gain importance.

In this compilation, general recommendations in pediatric urinary Stone diseases and treatment options specific to the type of Stone or metabolic disorder are reviewed.

General Recommendations

The first general recommendation in all urinary stone diseases is abundant fluid intake. Urine production increases with abundant fluid intake and insoluble concentration in urine and super saturation may be reduced. In studies conducted, children with Stone diseases have been detected as taking less fluid than the ones in the control group (10). Lande et al. have reported that calcium oxalate, calcium phosphate and uric acid super saturation do not occur when urine amount is more than 1ml/kg (11). Fluid intake is a critical component of prevention of stones. This is done by effectively reducing the lithogenic factors including calcium, oxalate, uric acid and cystine; besides, the only treatment for patients with primary xanthinuria is large fluid intake. Curhan et al. reported that drinks such as coffee and tea reduced stone formation while grapefruit juice increased stone formation in a study conducted in adult females with stone (12). The reason for this may be that it increases the tendency to oxalate stones due to its high oxalate content. To the best of our knowledge, there are no such studies conducted in pediatric stone patients in the literature. Milk, other fruit juices and water are fluid sources that may be recommended to the pediatric stone patients to be consumed in excess. Surely, alkaline drinks such as lemonade are more advantageous than acid ones in terms of the risk of stone formation (13).

In studies conducted, increased calcium and sodium in urine have been shown to be associated with the increased dietary sodium intake (14). Frasetto et al. emphasized that the chloride in the excess dietary sodium chloride intake may lead to low degree metabolic acidosis (15). By this means, bone mineralization may deteriorate and may also contribute to stone formation. The fact that excess dietary salt intake increases the risk for stone formation has been associated with excess salt intake in developed countries. The reverse mechanism is seen in the case of excess dietary potassium intake (16). Potassium salts generally come from alkali salts such as potassium citrate. Potassium citrate reduces urinary calcium excretion (17). Potassium salts are taken from fruits and vegetables in diet. Sodium and potassium have opposite effects on blood pressure similar to their opposite effects on urinary calcium. Excess dietary sodium increases blood pressure whereas excess dietary potassium decreases blood pressure.

In stone diseases accompanied by hypercalciuria, reduction of urinary calcium excretion is recommended. This may be ensured by reducing the dietary animal protein load, that is by reducing the acid load (18). Acids that form when these dietary animal proteins are metabolized lead to bicarbonate secretion from the bones. Therefore, bone resorption that cause osteopenia and hypercalciuria occur (19). Nouvenne et al. reported that limiting animal protein and salt intake increased recurrences compared to calcium intake at a normal level in patients with recurrent calcium oxalate stone and hypercalciuria (20). Apart from these, low dietary calcium intake leads to decreased oxalate that binds with calcium in the intestines and increased urinary oxalate excretion (21). Moreover, high amount of dietary vitamin C, sucrose and fructose intake may lead to Stone formation. On the other hand, high levels of magnesium intake decrease the risk of stone (22).

Furthermore, Shavit et al reported importance of body mass index on urinary stone disease (23). They revealed that weight loss may reduce stone recurrence but these needs more studies for exact results (23).

Dietary recommendations should be explained to families in the treatment of pediatric urinary stone diseases and most importantly, it should be noted that dietary habits do not change overnight.

MEDICAL TREATMENT

Hypercalciuria

Calcium oxalate and calcium phosphate stones constitute the majority of urinary system stones in children. About 30%-50% of children who develop stones have hypercalciuria (24). Metabolic calculi accounted for 48% of the patients with idiopathic hypercalciuria as the main cause (25).

Alemzadeh-Ansari et al. noted similar findings and reported that high rate of metabolic abnormalities in infants with urolithiasis (26).

Hypercalciuria is the most common cause of pediatric urolithiasis. It means that urinary calcium excretion is above 4mg/kg/day or that urinary calcium/creatinine ratio is above 0.21 in older children. In many children 24 hour urine collection is not practical and calcium-creatinine ratio in the urine is used to estimate daily calcium excretion. It should be noted that urinary calcium excretion increases with age. Urinary calcium oxalate and phosphate should also be measured for an optimal evaluation (27).

Hypercalciuria usually occurs as a result of disturbances in one or more of the 3 systems such as increased gastrointestinal calcium absorption, disturbances in bone formation and resorption and renal loss (27). Hypercalciuric calcium stones are categorized as normo-calcemic and hypercalcemic.

Hypercalciuria is not the only factor, but it is associated with many factors. The most common cause in children and adults is idiopathic hypercalciuria. Idiopathic hypercalciuria is defined as hypercalciuria despite the absence of hypercalcemia and occurs in patients without any apparent cause. The gene(s) responsible for familial idiopathic hypercalciuria have not been defined yet, but it is observed as having autosomal dominant character. 4% of asymptomatic healthy children have evidence of idiopathic hypercalciuria (28), and 40%-50% of these children have positive family history for urolithiasis (29).

When hypercalciuria is observed, some issues must be ruled out for the diagnosis of idiopathic hypercalciuria. In definition, blood calcium level of the patient should be normal. In patients with hypercalcemic hypercalciuria, hyperparathyroidism and D hypervitaminosis should be investigated and when clinically detected, prolonged immobilization, sarcoidosis, malignity, juvenile idiopathic arthritis, excess corticosteroids, adrenal failure or Williams syndrome should be considered. Children with hypercalcemic hypercalciuria should be evaluated in terms of hypoparathyroidism and autosomal dominant hypocalcemic hypercalciuria (mutation in calcium receptor function). Although patients with normocalcemic hypercalciuria are often diagnosed with idiopathic hypercalciuria; prematurity, history of diuretic use (furosemide and acetezolamide), anticonvulsant use (topiramate and zonisamide), ketogenic diet, Dent disease, Bartter syndrome, familial hypomagnesemia and nephrocalcinosis (AHHNK) with hypercalciuria, distal renal tubular acidosis (dRTA), hereditary hypophosphatemic rachitism with hypercalciuria (HHRH) and potential medullar sponge kidney must be ruled out and kept in mind in the first assessment.

Genetic Conditions Associated with Normo-Calcemic Hypercalciuria

Dent disease is a condition based on X and occurs as a result of the mutation in CLCN5 gene. This condition is characterized by molecule weighted proteinuria, nephrocalcinosis, hypercalciuria, nephrolithiasis and chronic kidney disease. Clinical picture is usually insidious and asymptomatic throughout the childhood period; signs and symptoms of nephrocalcinosis and hypercalciuria are not common in children. The damage occurs in proximal tubular function and rarely it may manifest as a part of glycosuria, aminoaciduria, metabolic acidosis and Fanconi syndrome associated with hypophosphatemia. In a limited number of patients, Dent phenotype occurs with the mutation in the OCRL gene (Dent 2). This condition is also associated with the oculocerebrorenal syndrome of Lowe.

Bartter syndrome is an autosomal recessive condition characterized by loss of salt in kidneys, hypokalemia, metabolic alkalosis, hypercalciuria and normal serum magnesium levels. The disease typically manifests itself as salt deficiency, polyuria, dehydration, emesis, and constipation and growth retardation in children below six years of age. Severe polyhydramnios, prematurity and rarely sensorineural hearing loss are distinctive characteristics of the disease. Mutations in SLC12A, KCNJ1 ve BSND genes (type 1, type 2 and type 4 Bartter syndrome, respectively) typically result in serious dysfunction in the thick ascending limb of the loop of Henle in the neonatal period (neonatal Bartter syndrome). Mutations in the C1CKB gene (type 3 Bartter syndrome) usually lead to medium level dysfunction in the thick ascending limb of the loop of Henle. It is usually seen out of the neonatal period (classic Bartter syndrome).

AHHNK is usually seen in childhood together with seizures or tetany accompanying hypomagnesemia. Other clinical findings are recurrent urinary tract infections (UTI), polyuria, polydipsia, growth retardation, nephrolithiasis and progressive kidney failure (30). AHHNK is an autosomal recessive condition. It occurs with the mutations of both CLDN-16 and CLDN-19 genes. Homozygous CLDN-16 or CLDN-19 mutations are associated with disturbances in the integrity of the tight junctions in the ascending limb of Henle, magnesium, calcium loss in the urine and the resulting hypomagnesemia. Patients usually develop a classical triad composed of hypomagnesemia, hypercalciuria

and nephrocalcinosis. In case of the combination of CLDN-19 mutations, deep visual disturbances characterized by macular coloboma, considerable myopia and horizontal nystagmus may be seen (31).

Primary dRTA is a hereditary disease and is characterized by systemic acidosis that occurs as a result of the loss of the ability of the distal tubule to properly acidize the urine. Growth retardation, polyuria, polydipsia, hypercalciuria, hypocitraturia, nephrocalcinosis, kidney stones and hypokalemia are common findings in infancy. Primary dRTA may be autosomal dominant (SLC4A1 gene) or recessive (ATP6V1B1 or ATP6V0A4 genes).

Failure to release H1 ions from α-intercalated cells is caused by vacuols H1-ATPaz (ATP6V1B1 or ATP6V0A4 genes) or a damaged Cl_/HCO3_ anion exchanger-1(SLC4A1 gene). Patients with ATP6V1B1 mutations may have hearing loss or neural type hearing loss.

HHRH is rare autosomal recessive disease that is caused by a mutation in the SLC34A3 gene. This condition results in loss of function in the type IIc sodium phosphate carriers of the proximal tubule. Decreased renal phosphate reabsorption results in deep hypophosphatemia, normokalemia, rickets and bone ache. In addition, hypercalciuria and nephrolithiasis are detected. It may occur as a result of the stimulation of 1,25-dihydroxyvitamin D synthesis triggered by hypophosphatemia. Increased synthesis causes excess urine calcium losses in the face of increased gastrointestinal reabsorption of calcium and normal calcium levels (32).

When there is hypercalciuria, environmental factors that increase calcium excretion such as high sodium consumption and ketogenic diet should be considered. In treatment, sodium restriction, large fluid intake, and a diet rich in proteins and poor in oxalate should be recommended according to weight and age. Tiazid diuretics prevent calcium excretion through proximal and distal renal tubules. Another diuretic is amiloride. These diuretics may improve calciuria; however, they may also cause abnormalities such as weakness, nausea, orthostatic hypotension, hypercholesterolemia and electrolyte abnormalities. Potassium citrate may be used in hypercalciuria associated with dRTA since it improves metabolic acidemia and hypokalemia and it brings urinary calcium and citrate excretion to normal levels (33). In addition to all of these, a combination of tiazid diuretics and potassium citrate may also be used (34).

Patients with idiopathic hypercalciuria may also be treated with potassium citrate (35). This treatment reduces urinary calcium excretion while increasing urinary citrate excretion. Moreover, mineral density of the bone also increases. Urinary pH of the patients should be monitored. At very high pH levels, formation of calcium phosphate stones may become easier (36). Penido et al. reported decreased bone mineral density in one third of hypercalcemic children (37). Parallel to this study, Freundlich et al. reported that alendronate may have beneficial effects on bone tissue and calcium excretion in children with osteopenia and urinary stone disease (38).

Hyperoxaluria

Oxalate is the last product of the metabolic path of glyoxylate and ascorbic acid. It is secreted primarily by kidneys. A majority of the daily oxalate excretion (80-85%) is derived from normal metabolic homeostasis and diet constitutes the rest (10-15%). Daily urinary oxalate excretion is usually less than 50 mg/d/1.73m^2. Due to the challenge of 24-hour urine collection in little children, urinary oxalate/creatinine ratio is used to estimate the oxalate excretion. Increased urinary oxalate excretion may occur due to a hereditary metabolic condition, (primary hyperoxaluria (PH)), more often due to oxalate reabsorption or increased oxalate precursors.

Primary Hyperoxaluria

Type 1 and type 2 PH are rare; they are autosomal recessive diseases in which endogenous oxalate production is increased. Excess oxalate production by the liver leads to nephrocalsinosis and nephrolithiasis which result in increased oxalate excretion. Calcium oxalate deposits cause progressive kidney damage. Its clinical Picture may vary from end stage renal failure in newborns to possible random stone disease in adulthood. The diagnosis is often eludes observation and there may even be cases where it is realized after the loss of the transplanted kidney (39).

Type 1 PH occurs due to the mutations in the AGXT gene which causes functional damage in hepatic peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). Deficiency leads to the accumulation of glyoxylate, glycolate and oxalate in urine. Prydoxin is the basic cofactor for proper AGT activity and rarely, prolonged vitamin B6 deficiency may mimic type 1 PH. Type 2 PH occurs due to the mutation in the GRHPR gene which leads to dysfunction in glyoxylate reductase-hydroxypyruvate reductase enzyme activity. Increased oxalate and L-glyceric acid are excreted through the kidney (40). Type 2 PH is a lighter form than type 1 PH, but it is not benign. Recently, a third form type III PH has been defined in 8 families who have hyperoxaluria and mutations in the DHDPSL gene (41). The exact mechanism of the hyperoxaluria that occurs in Type 3 PH has not been cleared yet.

Secondary Hyperoxaluria

In secondary hyperoxaluria, there are both high amounts of dietary oxalate (or oxalate precursors) intake and the dysfunction that causes increased absorption of the dietary oxalic acid

into the intestinal system. Gastrointestinal absorption varies in opposite directions with dietary calcium intake and calcium-dependent diet increases oxalate absorption and hypercalciuria (42). Oxalate is a side product of ascorbic acid metabolism and high dose of vitamin C is also associated with hyperoxaluria. Increased diet absorption is usually characterized by disturbance in fat absorption or chronic diarrhea. Among secondary causes of hypercalciuria is inflammatory bowel disease associated with gastrointestinal disease, celiac disease, exocrine pancreatic insufficiency (cystic fibrosis), biliary tract disease and small intestine resection or short bowel syndrome. Pathogenesis in these cases is caused by the presence of free fatty acids that bind to the calcium in the intestinal lumen. This results in free, absorbable, unbound oxalate formation.

Oxalobacter formigenes not only reduces oxalate, it also changes the oxalate released endogenously in the intestines. Thus it reduces the oxalate in blood and in urine and it may be applied orally in PH treatment (43). Moreover pyridoxine is used to decrease oxalate excretion in PH. Pyridoxine is an important cofactor of AGT. About 10%-30% of children with PH type 1 are sensitive to pyridoxine (>30% decrease in urinary oxalate excretion). Particularly, they may ensure protection of renal functions in patients who are homozygous for Gly170Arg and Phe152Ile mutations within the appropriate treatment period. Treatment should be started in patients with suspicious PH type 1 (2-5 mg/kg/g) and it should be titrated until a diagnosis is made and a response is received (8-10 mg/kg/g). High doses of prydoxine are known to trigger sensory nephropathy. There is no apparent evidence showing that pyridoxine additions are beneficial unless there is a real pyridoxine deficiency.

In PH, liver and kidney transplant are the best treatment methods in patients who developed chronic renal failure. It is essential to prevent excess dietary intake, increase oral calcium intake and to improve gastrointestinal disorders in the treatment of hypercalciuria.

Hypocitraturia

Citrate is an important stone inhibitor that prevents the growth of calcium oxalate and calcium phosphate crystals by binding to calcium in urine. Additionally, it can prevent new stone formation. It is adjusted in the proximal tubule both by absorption and by metabolism. Hypocitraturia is defined as a citrate/creatinine ratio of below 180 mg/g in men, and below 300 mg/g in women. Intra-cell acidosis of the proximal tubule occurs due to the hypocitraturia associated both with metabolic acidosis and increased citrate absorption in the proximal tubule. Consequently, ketogenic diet, medications (topiramate, zonisamide and acetazolamide), dRTA and chronic diarrhea are often associated with hypocitraturia. Incomplete dRTA may occur in the absence of apparent systemic acidosis or in hypokalemia. This may usually be neglected in the face of hypocitraturia in case no provocative acid loading test is conducted. Nevertheless, hypocitraturia is idiopathic although many cases are rich animal protein and little amounts of fibre vegetables, potassium that lead to low dietary citrate excretion (44). Elmaci et al. reported the most frequent metabolic abnormalities in preschool-age children with urolithiasis were hyperuricosuria and hypocitraturia (45). A comprehensive investigation of stone disease in children presenting with hematuria and urinary tract infection is important to prevent the development of renal parenchyma scarring (45).

Potassium citrate is an ideal medical option in treatment. The treatment is safe except for its minor gastrointestinal effects.

Hypomagnesuria

It may occur in dietary magnesium deficiency. Magnesium may form a complex with oxalate and it reduces calcium oxalate super-saturation in urine and it may also prevent oxalate reuptake. It is essential to increase dietary intake in treatment. It is also very important to evaluate magnesium level in urine that hypomagnesiuria is also an important risk factor in adults and children.

Hyperuricosuria

Uric acid excretion is greater in children than in adults. The highest fractional excretion (Fe) is in newborns (Fe 30%-50%). It reaches adult values (Fe 8%-12%) in adolescence (46). Hyperuricosuria is defined as uric acid excretion greater than 815 mg/d/1.73m^2. When the glomerular filtration rate (GFR) is adjusted, uric acid excretion is relatively stable after 2 years of age. When GFR is greater than 0.56 mg/dL in children older than two years who do not have toilet training, hyperuricosuria may be detected in spot urine. This value may be calculated by using the formula, "Urinary uric acid (mg/dL) x Plasma creatinine (mg/dL) / Urinary creatinine (mg/dL)".

Hyperuricosuria is the greatest risk for stone formation especially at low urine pH. Hereditary purine metabolism disorders are lymphoproliferative diseases and diseases associated with polystemia and apparent hyperuricemia hyperuricosuria. Rarely a condition known as hereditary hyperuricemia characterized by hyperuricosuria, nephrolithiasis and activity induced renal failure is also detected. Mutations in both SLC22A12 gene and SLC2A9 gene that code the urate transport in the proximal tubule are known casues for its formation (47). Other causes of hyperuricosuria include excess purine intake (animal protein), hemolysis, uricosuric medications (probenesid, salycylates and losartan), cyanotic congenital heart disease, melamine toxicity and idiopathic (familial) causes. Moreover, a phenomenon primarily detected in adults is referred to as hyperuricosuric

calcium oxalate stones. In this case, hyperuricosuria forms the fundamental basis for the formation of oxalate stones without or minimal uric acid content (epitaxy).

Hereditary Diseases of the Purine Metabolism

Phosphoribosyl pyrophosphate synthethase superactivity (PRPSS) is hereditary based on X and is formed by the mutation in the PRPS1 gene. Increased PRPSS activity is associated with excess purine production. The following purine degeneration results in hyperuricemia, gout, hyperuricosuria and uric acid nephrolithiasis. Nerve development abnormalities, neural type hearing loss are seen in some affected individuals (48). Hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency is a purine metabolism disorder in the neonatal period which occurs due to the mutations in the HPRT1 gene associated with excess uric acid production. Complete deficiency of HPRT activity is associated with Lesh-Nyhan syndrome characterized by mental retardation, spastic cerebral palsy, choreoathetosis, uric acid Stones, and self-destructive behaviors. Children with partial HPRT deficiency may be phenotypically similar to the patients who have complete phenotypical deficiency or moderate neurological symptoms. Kidney stones, uric acid nephropathy, kidney obstruction or gout may be the first signs of the disease.

First line treatment is urine alkalization and usually potassium citrate is used. Restricting excess dietary animal protein intake in patients may result in increased purine intake and increased uric acid production, and it may contribute both to uricosuria and acidic urine. Allopurinol (4–10 mg/kg/g, adults maximum 300 mg/g) is necessary in both hyperuricemia and hyperuricosuria such as PRPSS or HPRT deficiency. Xanthine dehydrogenase inhibition with allopurinol may lead to xanthine accumulation and its excess excretion in the urine. Rarely, secondary xanthuria with xanthine Stones may be detected in children in long term treatments. If there are co-morbid findings of hypercalciuria, hyperoxaluria or hypocitraturia, allopurinol may also be a treatment option for the treatment of hyperuricemic calcium oxalate stones (49).

Cystinuria

Cystinuria is an autosomal recessive disease caused by mutations in both SLC3A1 and SLC7A9 genes which results in irregular amino acid transport in the proximal tubule.Cystinuria is characterized by urinary hypersecretion of cystine and lysin, ornitin and arginin, which are among dibasic amino acids. Normal individuals release cystine at a rate of 50-60 mg/g/1.73 m^2 (less than 30 mg daily). Patients who are homozygous for cystinuria have a cystinuria excretion of more than 400 mg/g/1.73m^2 (varies between 400 mg and 3000 mg) (50). Patients typically have renal colic and urolithiasis in the second and third decades of their lives. However, they may also have staghorn stones in the neonatal period. Weak solubility of cystine in urine causes precipitation in collecting duct systems. If this is not treated, it usually results in frequently recurring kidney stones and renal failure in the long run. Related UTI is frequent; combined cystine and struvite stones may be detected (51).

Irregular cystine transport in cystinuria primarily results from the dysfunction in heavy (rBAT) and light (b0, 1AT) subunits (rBAT/b0,1AT) in the heteromeric amino acid transporter. Cystinuria is originally categorized into two classes: type 1 and non-type 1 (type 2 and type 3). The distinction is based on urine cystine concentration pattern compulsory heterozygote and estimated mode of inheritance. There is classical autosomal recessive inheritance in type 1 and normal cystine excretion is seen. On the contrary, non-type 1 heterozygotes (type 2 and type 3) show moderate and high urinary cystine excretion. Types 2 and 3 vary among themselves. There is a quasi-normal increase in plasma levels of cystine after oral cystine administration in type 3 homozygotes (52).

Homozygous mutations in the SLC3A1 gene which code rBAT are associated with type 1 cystinuria and homozygous mutations in the SLC7A9 gene which code b0,1AT are associated with type 2 and 3 cystinuria. A new classification system has been developed. In this system, patients who are homozygous for SLC3A1 mutations are determined as cystinuria type A, patients who are homozygous for SLC7A9 mutations are determined as cystinuria type B, and mutations in both SLC3A1 and SLC7A9 genes are considered as type AB (53).

There is little evidence concerning restriction of proteins which have high cystine content; however, animal protein intake may help increase urinary pH in patients with cystinuria. Children who have stones are recommended not to take increased amounts of protein; but proper protein intake for growth and nutrition according to age should be recommended. The objective in treatment is to ensure the concentration and amount of urine in which cystine may dissolve. This is ensured by large fluid intake and medical treatment. The 2 most frequently used agents are D-penicillamine and α-mercaptopropionylglycine (tiopronin). Cystine is formed as a dimer of cysteine and these agents work by reducing the disulphide bonds that bind the 2 molecules of cystine. Thiol group combines with cysteine and forms a more soluble product which is a combination of excreted cystein and the product. D-penicillamine has a wide range of adverse events including febrile reactions, gastrointestinal complaints, liver dysfunctions, taste disturbances, bone marrow suppression, metal deficiencies, membranous glomerulopathy, myasthenia gravis and skin eruptions (elastosis perforans serpiginosa) (6). A-mercaptopropionylglycine has a similar incidence of adverse events, but it may be slightly lower. Evaluation of liver enzymes,

complete blood count, urine analysis, copper and zinc levels should be regularly studied. Special studies (solid-phase trial and high performance liquid chromatography) may assist in distinguishing between urinary cystine and cysteine-drug complexes and in long-term treatment.

Although captopril containing disulfidryl is a drug that may be used in treatment, its hypotensive effects should be taken into account.

Infection Stones

Infection stones are seen in 2-24% of children who have been diagnosed with kidney stones (6). They constitute 75% of the stones diagnosed in European children. They are usually seen in children below 6 years of age. 80% of the patients are male. Infection stones in the urinary system are seen more commonly in patients with anatomic and functional disorders that cause stasis. Infection stones occur due to infections induced by organisms that ensure hydrolysis of urea with the urease enzyme and which form ammonium and bicarbonate as a result (27). Proteus, Providencia, Klebsiella pneumoniae, Pseudomonas aeruginosa, Serratia, Enterobacter, Staphylococcus are bacteria that produce urease. The compound at high pH which does not produce urease but is rich in ammonium is magnesium and the bacterium which help Stone formation by facilitating precipitation of phosphate is Escherichia coli (33).

Infection stones contain ammonium phosphate, carbonate apatite and monoammonium urate. Ammonium phosphate is the main constituent of many infection stones. Ammoniac damages the urothelial glycosaminoglycan layer which is the defense mechanism against bacteria. These stones may require intervention following long-term antibiotherapy as of their structure. The incidence of this stone is gradually decreasing thanks to the developments in infection diagnosis and treatment (53).

The treatment is composed of extracting the stones and correcting the underlying anatomical and/or functional obstruction. In the long-term treatment and follow-up, antibiotherapy according to urine culture antibiogram is important. Urinary acidification and a balanced fiber diet that is poor in phosphate helps in the treatment.

Orotic Acid Stones

Hereditary orotic aciduria is a rare genetic disease. It occurs due to orotate-phosphoribosyl-transferase and orotidine-5-phosphate-decarboxylase enzyme deficiency responsible for transformation of orotic acid into uridine-5-phosphate. Consequently, orotic acid excreted in urine increases and it crystallizes forming orotic acid stones. Uridine is used in the treatment (33).

2,8-Dihydroxyadenineuria

It is an autosomal recessive disease and there is adenine – phosphoribosyl transferase defect. As a result, there is excess accumulation of 2,8 dihydroxyadenine. It is very similar to uric acid stones; however it may be distinguished by metabolic and stone analysis. It may be treated by allopurinol therapy and regulation of diet (54).

Xanthuria

Xanthuria is a rare disease and its inheritance is autosomal recessive. Xanthin, which takes part in the formation of uric acid, the final product of purine metabolism, is seen as a result of oxidase enzyme deficiency. Urinary excretion of hypoxanthin and xanthin increases. Urinary solubility of xanthin is minor. Allopurinol may be used in the treatment of this disease. Dietary purine intake should be reduced and a lot of fluids should be taken.

Finally, hypomagnesiuria, hypocitraturia, and hypercalciuria are the most important risk factors for stone formation in adults and pediatric patients (55). Dietary changes, more fluid intake, decreased salt usage, increased potassium intake are useful for preventing stone diseases in children. According to these, balanced consumption of fruit and vegetables and a low consumption of chocolate and cola according to general nutritional guidelines, although no studies have assessed in pediatric stone formers the effect of fruit and vegetables supplementation on urinary citrate and the effects of chocolate and cola restriction on urinary oxalate in pediatric stone formers. Despite the low level of scientific evidence, a low-protein (< 20 g/day) low-salt (<2 g/day) diet with high hydration (>3 liters/day) is strongly advised in children with cystinuria (56). Nevertheless, infantile patients should be separated from all pediatric groups and coexistence of systemic disorders, anatomic anomalies at high frequencies may indicate a role of distinct pathologic mechanisms (57). Besides urinary infections should be detected more details in infants.

In the daily pediatric urology practice, detailed examination is necessary in cases where urolithiasis is seen. Detailed medical history should be recorded first and physical examination should be conducted. Familial history of stones, additional diseases and medications used should be recorded. Metabolic and non-metabolic problems which may be the reason for stone diseases should be kept in mind. In urolithiasis seen in the pediatric age group, the most common non-metabolic disorders may include vesicoureteral reflux disease, uroteropelvic junction obstructions, neurogenic bladder and other micturition disorders (58). Then simple clinical assessment may be made. In the simple assessment, first simple urine analysis and ultrasound are among the tests that may be requested. It may be useful to

consider the following algorithm to reach an exact diagnosis after reaching pre-diagnosis with examinations to be made in the urine and other clinical information.

Following simple clinical examinations; pH, calcium, phosphorus, magnesium, oxalate, sodium, potassium, uric acid, citrate, cystine, creatine should be investigated in urine collected over 24 hours and the urine amount should be recorded. Moreover, urine culture is recommended (58). On the other hand, sodium, potassium chloride, calcium, phosphorus, magnesium, creatine, blood urea nitrogen, alkaline phosphatase, uric acid, intact parathyroid hormone should be investigated in the serum and complete blood count should be made. The probability of stone formation is high if the calcium/citrate ratio in the 24-hour urine is above 0.326 (59). In pediatric urolithiasis that is commonly seen in daily clinical practices, when it is time to decide on the treatment after diagnostic stages; first, second and third line treatment options are considered according to the cause. It is recommended that the following algorithms are followed for the most commonly seen pathologies and their practical treatments. As mentioned above, it is crucial to apply general therapy recommendations in pediatric urolithiasis including large fluid intake and dietary modifications in each stage of these lines of treatment.

If the patient had spontaneously passes a stone or a stone was acquired as a result of ESWL and/or surgical procedures, a stone analysis should definitely be made. After an exact diagnosis is made according to the results of the stone analysis and metabolic analysis, a metaphylaxis should be given as mentioned above (60).

In conclusion; urolithiasis, which is common also in our community in the pediatric and adult age groups, requires detailed examinations. Delays in diagnosis and treatment may lead to serious consequences that may develop into renal failure. Today, dietary modifications should be offered to families who have children with urolithiasis. Stone analyses are mandatory and metabolic analyses with urine evaluations are required. Metabolic abnormalities are common in pediatric urolithiasis and they are also responsible for stone recurrences. Recurrence of stones and renal damages may be prevented with the help of early diagnosis, detailed metabolic examination as well as appropriate follow-up and treatment protocols. In view of all these, pediatric urolithiasis needs more interest relevance.

REFERENCES

1. Ece A, Ozdemir E, Gurkan F, Dokucu AI, Akdeniz O. Charecteristics of pediatric urolithiasis in South-east Anatolia. Int J Urol 2000; 7: 330-4.
2. Spivacow FR, Negri AL, del Valle EE, Forrester M, Rosende G, Pinduli I. Role of overweight and obesity on the urinary excretion of promoters and inhibitors of stone formation in stone formers. Urol Res 2008; 36: 303-7.
3. Kit LC, Filler G, Pike J, Leonard MP. Pediatric urolithiasis: experience at a tertiary care pediatric hospital. Can Urol Assoc J 2008; 2: 381-6.
4. Dursun I, Poyrazoglu HM, Dusunsel R, et al. Pediatric urolithiasis: an 8-year experience of single centre. Int Urol Nephrol. 2008; 40: 3-9.
5. Chou YH, Li CC, Wu WJ, et al. Urinary stone analysis of 1,000 patients in southern Taiwan. Kaohsiung J Med Sci 2007; 23: 63-6.
6. Sarica K. Pediatric urolithiasis:etiology, specific pathogenesis and medical treatment. Urol Res 2006; 34: 96-101.
7. Celiksoy MH, Yilmaz A, Aydogan G, Kiyak A, Topal E, Sander S. Metabolic disorders in Turkish children with urolithiasis. Urology 2015; 85: 909-13.
8. Mohammadjafari H, Barzin M, Salehifar E, Khademi Kord M, Aalaee A, Mohammadjafari R. Etiologic and epidemiologic pattern of urolithiasis in north iran;review of 10-year findings. Iran J Pediatr 2014; 24: 69-74.
9. La Manna A, Apicella A, Cangiano G, Polito C. Urolithiasis in children: diagnostic difficulties. G Ital Nefrol 2013; 30.
10. Miller LA, Stapleton FB. Urinary volüme in children with urolithiasis. J Urol 1989; 141: 918-20.
14. Lande MB, Varade W, Erkan E, Niederbracht Y, Schwartz GJ. Role of urinary supersaturation in the evaluation of children with urolithiasis. Pediatr Nephrol 2005; 20: 491-4.
12. Curhan GC, Willet WC, Rimm EB, Spiegelman D, Stampfer MJ. Prospective study of beverage use and the risk of kidney stones. Am J Epidemiol 1996; 143: 240-7.
13. Seltzer MA, Low RK, McDonald M, Shami GS, Stoller ML. Dietary manipulation with lemonade to treat hypocitraturic calcium nephrolithiasis. J Urol 1996; 156: 907-9.
14. Srivastava T, Alon US. Pathophysiology of hypercalciuria in children. Pediatr Nephrol 2007; 22: 1659-73.
15. Frassetto LA, Morris RC Jr, Sebastian A. Dietary sodium chloride intake independently predicts the degree of hyperchloremic metabolic acidosis in healthy humans consuming a net acid-producing diet. Am J Physiol Renal Physiol 2007; 293: F521–5.
16. Osorio AV, Alon US. The relationship between urinary calcium, sodium and potassium excretion and the role of potassium in treating idiopathic hypercalciuria. Pediatrics 1997; 100: 675–81.
17. Frassetto LA, Nash E, Morris RC Jr, Sebastian A. Comparative effects of potassium chloride and bicarbonate on thiazide-induced reduction in urinary calcium excretion. Kidney Int 2000; 58: 748–52.
18. Ince BA, Anderson EJ, Neer RM. Lowering dietary protein to US recommended dietary allowance levels reduces urinary calcium excretion and bone resorption in young women. J Clin Endocrinol Metab 2004; 89: 3801–7.

19. Breslau NA, Brinkley L, Hill KD, Pak CY. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. J Clin Endocrinol Metab 1988; 66: 140–6.
20. Nouvenne A, Meschi T, Prati B, et al. Effects of a low-salt diet on idiopathic hypercalciuria in calcium-oxalate stone formers: a 3-mo randomized controlled trial. Am J Clin Nutr 2010; 91: 565-70.
21. Asplin JR, Bauer KA, Kinder J, et al. Bone mineral density and urine calcium excretion among subjects with and without nephrolithiasis. Kidney Int 2003; 63: 662–9.
22. Curhan GC. Epidemiology of stone disease. Urol Clin North Am 2007; 34: 287–93.
23. Shavit L, Ferraro PM, Johri N, Robertson W, Walsh SB, Moochhala S, Unwin R. Effect of being overweight on urinary metabolic risk factors for kidney stone formation. Nephrol Dial Transplant 2015; 30: 607-13.
24. Milliner DS, Murphy ME. Urolithiasis in pediatric patients. Mayo Clin Proc 1993; 68: 241–8.
25. Giraudon A, Richard E, Godron A, Bouty A, Dobremez E, Barat P, Blouin JM, Llanas B, Harambat J. Clinical and biochemical characterization of childhood urolithiasis. Arch Pediatr 2014; 21: 1322-9.
26. Alemzadeh-Ansari MH, Valavi E, Ahmadzadeh A. Predisposing factors for infantile urinary calculus in south-west of Iran. Iran J Kidney Dis 2014; 8: 53-7.
27. Mandeville JA, Nelson CP. Pediatric urolithiasis. Curr Opin Urol 2009; 19: 419-23.
28. Kruse K, Kracht U, Kruse U. Reference values for urinary calcium excretion and screening for hypercalciuria in children and adolescents. Eur J Pediatr 1984; 143: 25–31.
29. Coe FL, Parks JH, Moore ES. Familial idiopathic hypercalciuria. N Engl J Med 1979; 300: 337–40.
30. Hou J, Goodenough DA. Claudin-16 and claudin-19 function in the thick ascending limb. Curr Opin Nephrol Hypertens 2010; 19: 483–8.
31. Konrad M, Schaller A, Seelow D, et al. Mutations in the tight-junction gene claudin 19 (CLDN19) are associated with renal magnesium wasting, renal failure, and severe ocular involvement. Am J Hum Genet 2006; 79: 949–57.
32. Lorenz-Depiereux B, Benet-Pages A, Eckstein G, et al. Hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in the sodium-phosphate cotransporter gene SLC34A3. Am J Hum Genet 2006; 78: 193–201.
33. Bak M, Ural R, Ağın H. Pediyatrik ürolitiaziste metabolik nedenler. T Klin Pediatri 2004; 13: 104-13.
34. Alon U, Costanzo LS, Chan JC. Miner Additive hypocalciuric effects of amiloride and hydrochlorothiazide in patients treated with calcitriol. Electrolyte Metab 1984; 10: 379-86.
35. Jehle S, Zanetti A, Muser J, Hulter HN, Krapf R. Partial neutralization of the acidogenic Western diet with potassium citrate increases bone mass in postmenopausal women with osteopenia. J Am Soc Nephrol 2006; 17: 3213-22.
36. Parks JH, Worcester EM, Coe FL, Evan AP, Lingeman JE. Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. Kidney Int 2004; 66: 777-85.
37. Penido MG, Lima EM, Marino VS, Tupinambá AL, França A, Souto MF. Bone alterations in children with idiopathic hypercalciuria at the time of diagnosis. Pediatr Nephrol 2003; 18: 133-9.
38. Freundlich M, Alon US. Bisphosphonates in children with hypercalciuria and reduced bone mineral density. Pediatr Nephrol 2008; 23: 2215-20.
39. Spasovski G, Beck BB, Blau N, Hoppe B, Tasic V. Late diagnosis of primary hyperoxaluria after failed kidney transplantation. Int Urol Nephrol 2010; 42: 825–9.
40. Hoppe B, Beck BB, Milliner DS. The primary hyperoxalurias. Kidney Int 2009; 75: 1264–71.
41. Belostotsky R, Seboun E, Idelson GH, et al. Mutations in DHDPSL are responsible for primary hyperoxaluria type III. Am J Hum Genet 2010; 87: 392–9.
42. Polinsky MS, Kaiser BA, Baluarte JB. Urolithiasis in childhood. Pediatr Clin North Am 1987; 34: 683–710.
43. Hoppe B, Dittlich K, Fehrenbach H, Plum G, Beck BB. Reduction of plasma oxalate levels by oral application of Oxalobacter formigenes in 2 patients with infantile oxalosis. Am J Kidney Dis 2011 ;58: 453-5.
44. Hess B, Michel R, Takkinen R, Ackermann D, Jaeger P. Risk factors for low urinary citrate in calcium nephrolithiasis: low vegetable fiber and low urine volume to be added to the list. Nephrol Dial Transplant 1994; 9: 642–9.
45. Elmacı AM, Ece A, Akın F. Clinical characteristics and metabolic abnormalities in preschool-age children withurolithiasis in southeast Anatolia. J Pediatr Urol 2014; 10: 495-9.
46. Cameron JS, Moro F, Simmonds HA. Gout, uric acid and purine metabolism in paediatric nephrology. Pediatr Nephrol 1993; 7: 105–18.
47. Copelovitch L. Urolithiasis in children: medical approach. Pediatr Clin North Am. 2012; 59: 881-96.
48. Becker MA, Puig JG, Mateos FA, Jimenez ML, Kim M, Simmonds HA. Inherited superactivity of phosphoribosylpyrophosphate synthetase: association of uric acid production and sensorineural deafness. Am J Med 1988; 85: 383–90.
49. van Woerden CS, Groothoff JW, Wijburg FA, Annink C, Wanders RJ, Waterham HR. Clinical implications of mutational analysis in primary hyperoxaluria type I. Kidney Int 2004; 66: 746–52.
50. Coward RJ, Peters CJ, Duffy PG, et al. Epidemiology of paediatric renal stone disease in the UK. Arch Dis Child 2003; 88: 962–5.
51. Evans WP, Resnick MI, Boyce WH. Homozygous cystinuria–evaluation of 35 patients. J Urol 1982; 127: 707.
52. Dello Strologo L, Pras E, Pontesilli C, et al. Comparison between SLC3A1 and SLC7A9 cystinuria patients and carriers: a need for a new classification. J Am Soc Nephrol 2002; 13: 2547–53.
53. Delvecchio FC, Preminger GM. Medical management of stone disease. Curr Opin Urol 2003; 13: 229-33.

54. Alon US. Medical treatment of pediatric urolithiasis. Pediatr Nephrol 2009; 24: 2129-35.

55. Oğuz U, Resorlu B, Unsal A. Metabolic evaluation of patients with urinary system stone disease: a research of pediatric and adult patients. Int Urol Nephrol 2014; 46: 329-34.

56. Prezioso D, Strazzullo P, Lotti T, Bianchi G, Borghi L, Caione P, Carini M, Caudarella R, Gambaro G, Gelosa M, Guttilla A, Illiano E,Martino M, Meschi T, Messa P, Miano R, Napodano G, Nouvenne A, Rendina D, Rocco F, Rosa M, Sanseverino R, Salerno A,Spatafora S, Tasca A, Ticinesi A, Travaglini F, Trinchieri A, Vespasiani G, Zattoni F; CLU Working Group. Dietary treatment of urinary risk factors for renal stone formation. A review of CLU Working Group. Arch Ital Urol Androl 2015; 87: 105-20.

57. Alpay H, Gokce I, Özen A, Bıyıklı N. Urinary stone disease in the first year of life: is it dangerous? Pediatr Surg Int 2013; 29: 311-6.)

58. Straub M, Strohmaier WL, Berg W, et al. Diagnosis and metaphylaxis of stone disease. Consensus concept of National Working Committee on Stone Disease fort he upcoming German Urolithiasis Guideline. World J Urol 2005; 23: 309-23.

59. Srivastava T,Winston MJ, Auron A, Alon US. Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res 2009; 66: 85-90.

60. Akin Y, Yucel S, Danisman A, Erdogru T, Baykara M. The impact of metabolic risk management on recurrence of urinary stones. Kuwait Medical Journal 2012;44(3):215-218.