Current medical treatment in pediatric urolithiasis

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ABSTRACT

Although the prevalence of urolithiasis is nearly 2-3% in childhood, the risk of recurrence may range from 6.5-54%. There has been an increase in urinary stone disease among pediatric age groups, and stone disease has a multifactorial etiology. After the diagnosis, detailed metabolic evaluation is required. High recurrence rates, therapeutic irregularities and deficiency in diagnosis may lead to comorbidities such as loss of kidney function. Following diagnosis, the requirement for surgery, such as stone extraction and correction of anatomical anomalies, is determined. Medical and supportive treatments are also needed to prevent recurrence and urinary tract infections and to preserve renal function. Supportive care includes increased fluid intake and dietary modifications. Medical treatment is dependent on the cause of the urinary stone disease. The morbidities associated with pediatric urolithiasis can be prevented by early diagnosis, detailed metabolic analysis, regular follow-up and medical treatment protocols.

Key words: Children; hypercalciuria; hypocitraturia; oxaluria; urolithiasis.

Introduction

In the pediatric age group urinary stone disease is considered as a rarely seen disease, however in recent years the prevalence, and incidence of especially renal, and ureteral stones have increased.^[1] Even though its prevalence ranges between 2, and 3%, pediatric stone diseases have a recurrence risk ranging between 6.5, and 54 percent.^[2] Besides, because of its higher morbidity, and risk of end-stage renal failure, it is an important health problem.^[3] It has a multifactorial etiology including ethnicity, inherited characteristics, climate, and nutritional habits.^[4] In developing countries endemic pediatric stone diseases are confined to bladder. This condition is related to decrease in phosphate intake, and frequently it leads to the formation of ammonium, urate, and uric acid stones. Chou et al.^[5] have demonstrated that in parallel with improved standards of life in developing countries, and thus higher consumption of proteins of animal origin, incidence of stone disease increases.

Though in all pediatric age groups urinary stone disease is encountered, mean age at diagnosis ranges between 4.2, and 9.4 years.^[1]

In children with established diagnosis before this age bracket should remind us hereditary etiologies.^[6]

The goals for the treatment of pediatric urinary stone disease include removal of the stone, prevention of recurrences, and urinary system infections, preservation of renal functions, and correction of anatomical, and underlying metabolic problems.

Medical treatment used in the management of urinary system stone disease is specific to the type of the stone, and it is effective only in minority of the cases. In uric acid stones alkalization is effective. When used in combination with thiols, it can be also effective in cystine stones. In infection stones acidification of urine is another medical treatment modality. The objectives of the medical treatment are prevention of formation of stones or growth of already existing stones, and decreasing the need for surgery, with resultant decrease in morbidity. In the light of all these information, medical treatment can be said to be a preventive therapy. Initiation of medical treatment requires definitive establishment of the diagnosis. Therefore, metabolic investigations encompassing stone, urine, and serum analyses gain importance.

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In this review article we have browsed general recommendations on pediatric urinary stone diseases, and special medical treatment alternatives specific to types of stones, and metabolic disorders.

General recommendations

In all urinary stone diseases, the first general recommendation is abundant amounts of fluid intake. With abundant fluid load, urine output increases, and concentration of insoluble substances in urine, and their supersaturation can be decreased. Miller et al.^[7], detected that pediatric stone disease patients had ingested lesser amounts of fluids when compared with the control group. Lande et al.^[8] reported that in patients with daily urine output of more than 1 ml/kg bwt, supersaturation of calcium oxalate, calcium phosphate, and uric acid, and also formation of renal stones were prevented. Fluid intake is a critical component of stone prophylaxis. Stone prophylaxis is achieved by effectively decreasing concentration of lithogenic factors including calcium, oxalate, uric acid, and cystine. In addition to all of these factors, the only treatment modality for patients with primary xanthinuria is excess fluid intake. Curhan et al.^[9] performed a study in adult women with stone disease, and reported that beverages like coffee, and tea decreased, while grapefruit juice increased stone formation. Higher oxalate content of grapefruit may increase predisposition to the formation of oxalate stones. As far as we know, any literature study on this subject has not been performed with pediatric stone disease patients. Excess consumption of water, and fruit juices excluding milk, and grape fruit within normal dietary limits can be recommended.^[10] No doubt, alkaline drinks like lemonade predispose to the risk of stone formation rather than acidic beverages.^[11]

The association between higher urinary calcium, and sodium concentrations, and increased intake of dietary sodium in urinary stone disease has been demonstrated.^[12] Frassetto et al.^[13] emphasized that chloride content of excess dietary intake of sodium chloride could lead to low grade metabolic acidosis. Thus, bone mineralization may be impaired, and contribute to stone formation. Abundant amounts of dietary salt intake increase stone formation which has been associated with salt intake in excess of daily requirements in developed countries. Another pathogenetic mechanism appears to be related to excess dietary potassium intake.^[14] Potassium salts generally come from from alkaline salts like potassium citrate. Potassium citrate decreases urinary excretion of calcium.^[15] Potassium salts are retrieved from fruits, and vegetables in the diet. Sodium, and potassium have opposite effects on urinary calcium, and also blood pressure. Excess intake of dietary sodium increases blood pressure, and decreases concentration of potassium.

In stone diseases associated with hypercalciuria, decreased urinary calcium output has been recommended. This can be

achieved by decreasing dietary intake of protein load of animal origin, ie. acid load.^[16] Acids formed following metabolization of dietary proteins of animal origin induce release of bicarbonates from bones which leads to bone resorptions as a cause of osteopenia, and hypercalciuria.^[17] Nouvenne et al.^[18], reported that in patients with recurrent calcium oxalate stones, and hypercalciuria, restricted intake of protein of animal origin, and salt increased incidence of recurrent stone diseases when compared with normal levels of calcium consumption. In addition to all of these factors, intake of lower levels of dietary calcium leads to decrease in the amount of oxalate conjugated with intestinal calcium, and increase in urinary excretion of oxalate.^[19] Besides, higher levels of dietary vitamin C, sucrose, and fructose can induce development of stone disease. However increased intake of magnesium decrease the risk of stone formation.^[20]

In the treatment of pediatric urinary stone disease, recommendations about the diet to be followed should be explained to the families. More importantly, it should be kept in mind that dietary habits can not be changed within one night time.

Medical Treatment

Hypercalciuria

In children majority of urinary system stones consists of calcium oxalate, and calcium phosphate stones. In nearly 30-50% of the children with urinary stones, hypercalciuria is detected.^[21] Hypercalciuria is the most prevalent cause of pediatric urolithiasis. In children older than 2 years it is defined as daily urinary excretion of calcium over 4 mg/kg or urinary calcium/creatinine ratio above 0.21. In many children collection of urine samples for 24 hours is not practical. Therefore calcium/creatinine ratio is used to estimate daily excretion of calcium. It should not be forgotten that calcium excretion increases with age. For optimal evaluation, urinary calcium oxalate, and phosphate levels should be also measured.^[22]

Hypercalciuria generally occurs as a result of functional impairments in three or more than three bodily systems including increased gastrointestinal absorption of calcium, disorders in bone formation, and resorption, and enhanced renal loss.^[22] Hypercalciuric calcium stones are divided into two categories as normocalcemic, and hypercalcemic stones.

Hypercalciuria is not the only factor, but it is associated with many etiologies. In children, and adults idiopathic hypercalciuria is the most frequently encountered etiological factor. Idiopathic hypercalciuria is defined as hypercalciuria without any apparent cause or hypercalcemia. Gene(s) responsible for familial idiopathic hypercalciuria has/have not been identified yet. However the disease has an autosomal dominant inheritance. In nearly 4% of asymptomatic healthy children, evidence of idiopathic hypercalciuria is observed.^[23] In 40-50%

of these children, a positive familial history for urolithiasis is found.^[24]

If hypercalciuria is observed, then some pathological conditions should be ruled out so as to establish the diagnosis of idiopathic hypercalciuria. As a prerequisite for diagnosis blood calcium level of the patient should be within normal limits. In patients with hypercalcemic hypercalciuria, hyperparathyroidism, and D hypervitaminosis should be investigated. Long-lasting immobilization, sarcoidosis, malignancy, juvenile idiopathic arthritis, corticosteroid excess, adrenal failure or William's syndrome should be contemplated in the differential diagnosis. Children with hypocalcemic hypercalciuria should be evaluated as for hypoparathyroidism, and autosomal dominant hypocalcemic hypercalciuria (mutation affecting the functions of calcium receptor). Children with normocalcemic hypercalciuria are mostly diagnosed as idiopathic hypercalciuria. However prematurity, excess diuretic intake (furosemide, and acetazolamide), anticonvulsant use (topiramate, and zonisamide), ketogenic diet, Dent's disease, Bartter syndrome, familial hypomagnesemia, and nephrocalcinosis with hypercalciuria, distal renal tubular acidosis (dRTA), hereditary hypophosphatemic rickets with hypercalciuria, and probable medullary sponge kidney should be ruled out, and differential diagnoses should be kept in mind during the initial evaluation.

Genetic conditions associated with normocalcemic hypercalciemic hypercalciuria

Dent's disease is a X-linked hereditary condition, and develops as a result of mutation in the CLCN5 gene. This condition is characterized by low-molecular weight proteinuria, nephrocalcinosis, hypercalciuria, nephrolithiasis, and chronic renal disease. It leads a clinically occult course, and its pediatric form is asymptomatic. Besides, signs, and symptoms of nephrocalcinosis, and hypercalciuria are not frequently seen in affected children. Proximal tubular functions are impaired, and they manifest rarely as glucosuria, aminoaciduria, metabolic acidosis, and hypophosphatemia related to Fanconi syndrome. In a scarce number of patients, mutation in the OCRL gene (Dent 2) leads to the manifestation of Dent phenotype. This condition is also associated with Lowe's oculocerebrorenal syndrome.

Bartter's syndrome is an autosomal recessive condition characterized by salt-losing renal pathology, hypokalemia, metabolic alkalosis, hypercalciuria, and normal serum magnesium levels. In children less than six years of age, it typically manifests itself as salt deficiency, polyuria, dehydration, emesis, constipation, and growth retardation. Serious polyhydroamniosis, prematurity, and rarely sensorineural hearing loss are discriminative features of the disease. Mutations in SLC12A, KCNJ1, and BSND genes (Bartter's syndrome types I, II, and IV, respectively) typically end up in serious dysfunction of the thick ascending

limb of loop of Henle during the neonatal period. Mutations in C1CKB gene (type III Bartter's syndrome), generally lead to moderate dysfunction in the thick ascending limb of loop of Henle. They are usually seen in phases of life other than neonatal period (classical Bartter's syndrome).

Familial hypomagnesemia, and nephrocalcinosis are usually seen during the childhood, and characterized by seizures or tetany associated with hypomagnesemia. Other clinical findings include frequent urinary tract infections (UTIs), polyuria, polydipsia, growth retardation, nephrolithiasis, and progressive renal insufficiency.^[25] Familial hypomagnesemia, hypercalciuria, and nephrocalcinosis syndrome (FHHNS) is an autosomal recessive condition. Its onset is related to mutations in both CLDN-16, and CLDN-19 genes. Homozygous CLDN-16 or CLDN-19 mutations are associated with impairments involving the integrity of tight junction located on the ascending limb of loop of Henle, urinary loss of magnesium, and calcium with resultant hypomagnesemia. In patients, usually a classical triad of hypomagnesemia, hypercalciuria, and nephrocalcinosis develops. In association with CLDN-19 mutations, severe hearing impairment characterized by serious myopia, and horizontal nystagmus can be seen.^[26]

Primary dRTA is a hereditary disease, and it is characterized by systemic acidosis as a result of the the loss of proper acidification function of distal tubuli. Growth retardation, polyuria, polydipsia, hypercalciuria, hypocitraturia, nephrocalcinosis, renal stones, and hypokalemia are usually seen during infancy. Primary dRTA can be autosomal dominant (SLC4A1 gene) or recessive (ATP6V1B1 or ATP6V0A4 genes).

Because of a dysfunctional vacuolar H1-ATPase (ATP6V1B1 or ATP6V0A4 genes) or a defective Cl⁻/HCO₃⁻ anion exchange -1 (SLC4A1 gene) gene, H1 ions are not released from α -intercalate cells of distal tubuli. In patients with ATP6V1B1 mutations sensorineural hearing loss can be seen.

Hereditary hypophosphatemic rickets is a rarely seen autosomal recessive disease which manifests itself with a mutation in the SLC34A3 gene. This condition results in the formation of dysfunctional type IIc sodium phosphate transporters. Decreased renal phosphate reabsorption results in severe hypophosphatemia, normokalemia, rickets, and bone pain. In addition, frequently hypercalciuria, and nephrolithiasis are detected. It may develop as an outcome of the synthesis of 1,25-dihydroxyvitamin D triggered by hypophosphatemia. Increased synthesis of 1,25-dihydroxy-vitamin D, together with enhanced gastrointestinal reabsorption, and normal serum calcium levels leads to excess urinary calcium excretion.^[27]

In the presence of hypercalciuria, increased sodium consumption, ketogenic diet, and different environmental factors which

lead to higher rates of urinary calcium excretion should be also considered. In its treatment, body weight, and age adjusted dietary sodium restriction, abundant amounts of fluid intake, diet rich in potassium, but poor in oxalate should be recommended. Thiazide diuretics prevent excretion of calcium from distal renal tubuli. After establishment of differential diagnosis, for patients diagnosed as renal leak hypercalciuria thiazide diuretics are recommended as the first-line treatment alternative.^[28] Amiloride is another diuretic alternative. These diuretics can correct calciuria, but they can result in lassitude, nausea, orthostatic hypotension, hypercholesterolemia, and electrolyte abnormalities. In hypercalciuria associated with dRTA, potassium citrate can be used in that it can correct metabolic acidemia, and hypokalemia, and normalize increased urinary excretion of calcium, and citrate.^[29] In addition combinations of thiazide diuretics, and potassium citrate can be used.^[30]

Patients with idiopathic hypercalciuria can be treated with potassium citrate.^[31] This treatment modality decreases urinary excretion of calcium, but increases urinary output of citrate. At the same time bone mineral density increases. Urine pH of the patients should be monitored. Very high urine pH may predispose to formation of calcium phosphate stones.^[32] Penido et al.^[33] reported decreased bone mineral density in one-third of the hypercalcemic children. In parallel with this study, Freundlich et al.^[34] indicated potential beneficial effects of alendronate on bone tissue, and calcium excretion in patients with osteopenia, and urinary stone disease.

Hyperoxaluria

Oxalate is the end product of metabolic pathway of glyoxylate, and ascorbic acid. It is primarily secreted from kidneys. Majority (80-85%) of urinary oxalate comes from normal metabolic homeostasis, and the rest (10-15%) is derived from dietary oxalate. Daily urinary oxalate output is usually less than 50 mg/d/1.73 m². In small children, because of difficulties in collection of urine for 24 hours, urinary oxalate/creatinine ratio is used to estimate daily oxalate excretion. Increased urinary oxalate excretion can be related to a hereditary metabolic disease (primary hyperoxaluria [PH]), more frequently increased oxalate reabsorption or enhanced intake of oxalate precursors.

Primary hyperoxaluria

Type I, and II PH are rarely seen autosomal recessive diseases where production of endogenous oxalate increases. Excess production of oxalate by liver together with increased oxalate excretion leads to nephrocalcinosis, and nephrolithiasis. Calcium oxalate deposits result in increasingly severe renal damage. Its clinical picture can vary from incidental stone disease in adults to end-stage renal failure in the neonatal period. Because of clinical variability, diagnosis is usually overlooked or even it can be recognized after loss of transplant kidney.^[35]

Type I PH develops as a result of mutations in the AGTX gene which induces formation of defective hepatic peroxymal enzyme alanine-glycolate aminotransferase (AGT) This enzymatic deficiency leads to accumulation of glyoxalate, glycolate, and oxalate in urine Pyridoxine is the basic cofactor for the proper AGT activity, and long-lasting B6 vitamin deficiency can mimic type I PH. Type II PH results from mutation in GRHPR gene which leads to defective enzymatic activities of glyoxalate reductase-hydroxypyruvate reductase Increased oxalate, and L-glyceric acid are excreted in urine.^[36] Type II PH is a mild form of the disease relative to Type I PH, but it is not benign. Recently in 8 families who had hyperoxaluria, and a mutation in DHAPSL gene, a Type III PH has been defined.^[37] Exact pathogenetic mechanism of hyperoxaluria in Type III has not been fully elucidated yet.

Secondary hyperoxaluria

In secondary hyperoxaluria, increased dietary intake of oxalate (or oxalate precursors), and increased reabsorption of dietary oxalic acid from intestinal system are detected. Gastrointestinal absorption changes inversely with dietary intake of calcium, and diet deficiency in calcium can accelerate absorption of oxalate, and hyperoxaluria.^[38] Oxalate is the side product of ascorbic acid metabolism, and higher doses of vitamin C are associated with hyperoxaluria. Increased absorption of dietary oxalate is usually characterized by malabsorption of fats or chronic diarrhea. Among secondary etiologies of hyperoxaluria, inflammatory bowel disease related to gastrointestinal disorders, celiac disease, exocrine pancreatic insufficiency (cystic fibrosis), bile duct diseases, intestinal resection or short bowel syndrome can be enumerated. In these conditions, pathogenetic mechanism is related to the presence of free fatty acids which bind to calcium within the intestinal lumen. This phenomenon leads to the formation of free, absorbable, and unconjugated oxalate.

Oxalobacter formigenes not only reduces intestinal calcium, it also changes endogenously secreted oxalate. Thus, it decreases blood, and urine levels of oxalate, and it can be applied in the treatment of PH.^[39] Besides, pyridoxine is used to decrease the rate of oxalate excretion in PH.^[38] Pyridoxine is an important cofactor of AGT. Nearly 10-30% of the children with Type I PH is responsive to pyridoxine (>30% decrease in urinary excretion of oxalate). Especially in patients homozygous for Gly170Arg or Phe152Ile mutations, pyridoxine can protect renal functions with an appropriate treatment period. In suspect PH Type I patients, treatment should be initiated with daily pyridoxine doses of 2-5 mg/kg, and it should be titrated up to 8-10 mg/kg/d till definitive diagnosis is made, and response to treatment is obtained. Higher doses of pyridoxine are known to trigger sensory neuropathy. Apart from actual pyridoxine deficiency, strong evidence supporting beneficial effects of pyridoxine treatment in other forms of hyperoxaluria is lacking.

Liver, and kidney transplantation in patients with primary hyperoxaluria who developed chronic renal failure is the optimal mode of treatment. In the treatment of secondary hyperoxaluria, it is essential to prevent excess dietary intake of oxalate, increase oral calcium consumption, and cure gastrointestinal disorders. Besides, in the treatment of secondary hyperoxaluria, cause-specific treatment alternatives include cholestyramine, magnesium, and potassium citrate.^[38]

Hypocitraturia

Citrate is an important stone inhibitor which prevents adherence of oxalate, and phosphate to calcium to form calcium oxalate, and phosphate crystals. Its absorption, and metabolism is regulated in proximal tubuli. Hypocitraturia is the most frequently seen metabolic disorder in our country.^[40,41] Hypocitraturia is considered to be present when the amount of citrate in 24-hour urine sample is lower than 180 mg/24 hr in men, and 300 mg/24 hr in women.^[42] Intracellular acidosis in proximal tubuli is the result of either metabolic acidosis or increased citrate absorption in the proximal tubuli. Consequently, ketogenic diet, some medications (topiramate, zonisamide, and acetazolamide), dRTA, and chronic diarrhea are frequently associated with hypocitraturia. Besides thiazide diuretics can also lead to hypocitraturia. Incomplete dRTA can appear in the absence of manifest systemic acidosis or hypokalemia. If provocative acid loading test is not performed dRTA can be overlooked in the presence of hypocitraturia.^[42] In the treatment of hypocitraturia potassium citrate is an ideal medical agent. Excluding its minor gastrointestinal adverse effects, it is a safe therapeutic agent.

Hipomagnesuria

It can emerge in deficient intake of dietary magnesium. Dietary magnesium can make a complex with magnesium oxalate, decrease urinary supersaturation of calcium oxalate, and inhibit intestinal reabsorption of oxalate. In the treatment, increased dietary intake of magnesium is mandatory.

Hyperuricosuria

In children, greater amount of uric acid is excreted when compared with adults. The highest fractional excretion (Fe) is detected in newborns (Fe 30-50%). In adolescents, it reaches to values encountered in adults (Fe 8-12%).^[43] Hyperuricosuria is defined as uric acid excretion in excess of 815 mg/d/1.73m². Uric acid excretion adjusted to glomerular filtration rate (GFR) is relatively constant after age of two. In children older than 2 years of age who didn't receive toilet training, if GFR is above 0.56 mg/dL, hyperuricosuria can be detected in spot urine samples. It can be calculated based on the formula: urinary uric acid (mg/dL) x Plasma creatinine (mg/dL)/Urinary creatinine (mg/dL).

Hyperuricosuria is the greatest risk especially for the stone formation in lower urine pH. Hereditary disorders of purine

metabolism are associated with lymphoproliferative diseases, polycythemia, and manifest hyperuricemic hyperuricosuria. Rarely, a condition known as hereditary hyperuricemia characterized by lower serum uric acid level, hyperuricosuria, nephrolithiasis, and renal failure triggered by activity is detected. Mutations in both SLC22A12 and SLC2A9 genes which encode urate transport in proximal tubuli are recognized pathogenetic factors.^[44] Other causes of hyperuricosuria, include excess purine intake (proteins of animal origin), hemolysis, uricosuric drugs (probenecide, salicylates, and losartane), cyanotic heart disease, melamine toxicity, and idiopathic (familial) factors. Besides, a primary condition known as hyperuricosuric calcium oxalate stones is detected in adults. In this case hyperuricosuria forms the basis of calcium oxalate stones with minimal (if any) uric acid content (epitaxis).

Hereditary diseases of purine metabolism

Phosphoribosyl pyrophosphate synthetase superactivity (PRPSS) is an X-linked disorder which develops as a result of a mutation in the PRPS1 gene. PRPS hyperactivity is related to increases production of purine. Subsequent purine degeneration results in hyperuricemia, gout, hyperuricosuria, and uric acid nephrolithiasis. In some affected individuals, neural developmental abnormalities, and neural type deafness are detected.^[45] Hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency is an X-linked neonatal purine metabolism abnormality associated with excess uric acid production related to mutations in HPRT1 gene. Total lack of HPRT activity is associated with Lesh-Nyhan syndrome characterized by mental retardation, spastic cerebral paralysis, choreoathetosis, uric acid stones, and self-inflicting behaviours. In children with partial HPRT deficiency can have similar phenotypic characteristics as seen in children with complete HPRT deficiency or moderate neurological symptoms. First manifestations of the disease can be renal stones, uric acid nephropathy, renal obstruction or gout.

First-line treatment is alkalinization of urine, and usually potassium citrate is used to that end. Restriction of excess intake of dietary protein of animal origin results in increased purine, and uric acid production, and can contribute to both uricosuria, and acidic urine. Allopurinol (4-10 mg/kg/d; adult max. 300 mg/d) is required for the treatment of both deficient PRPSS or HPTR, in other words in hyperuricemia, and hyperuricosuria. Inhibition of xanthine dehydrogenase with allopurinol may lead to accumulation of xanthine, and increased excretion of xanthine. Rarely, secondary xanthinuria together with xanthine stones can be detected in children under long-term therapy. In case of concomitant hypercalciuria, hyperoxaluria, and hypocitraturia, allopurinol can be a treatment alternative in the management of hyperuricemic calcium oxalate.^[46]

Cystinuria

Cystinuria is an autosomal recessive disease caused by mutations in both SLC3A1, and SLC7A9 genes which end up with deranged amino acid transport in proximal tubuli. Cystinuria is characterized by urinary hypersecretion of cystine, and dibasic amino acids including lysine, ornithine, and arginine. Normal individuals secrete cystine at a rate of 50-60 mg/d/1.73 m² (<30 mg/24 hr). In homozygotes, urinary cystine excretion is in excess of 400 mg/d/1.73 m² (400-3000 mg/24 hr).^[47] Typically patients suffer from renal colic, and urolithiasis in their second or third decade of their lives. However during the neonatal period staghorn stones can be found. Weak solubility of cystine in urine leads to its precipitation in collecting systems. If not treated, it generally results in frequently recurring renal stones, and renal failure in the long run. Frequently it is associated with UTIs. Combined cystine-struvite stones can be detected.^[48]

In cystinuria, irregular cystine transport occurs priorly because of dysfunctional impairment (rBAT/b0,1AT) in heavy (rBAT), and light (b0, 1AT) subunits of heteromeric amino acid transporter. Cystinuria is divided in two groups as Type I, and non-type I cystinuria. This categorization depends on obligatory heterozygous urine cystine concentration pattern, and estimated mode of inheritance. In Type I, classical autosomal recessive inheritance, and normal urinary excretion of cystine are detected in obligate heterozygotes. On the contrary, in non-type I heterozygotes (Type II, and III), moderate, and higher amounts of cystine are excreted. Type II, and III demonstrate intragroup variations. In Type III homozygotes, after oral intake of cystine plasma cystine levels increase up to nearly normal levels.^[49] Homozygous mutations which encode rBAT in SLC3A1 gene are associated with Type I cystinuria, while homozygous mutations encoding b0,1AT in the SLC7A9 gene are related to Type II, and III in most of the cases. A new classification system has been developed. In this system, homozygotes for SLC3A1, SLC7A9, and both SLC3A1, and SLC7A9 mutations are determined as Type A, B, and AB cystinuria patients, respectively.^[50]

In patients with cystinuria, scarce evidence exists in dietary restriction of proteins with higher cystine content, however consumption of proteins of animal origin may aid in increasing urine pH. Children with stone disease are recommended against intake of increased amounts of protein, but proper protein consumption adjusted for their nutrition, and physiologic growth percentile should be encouraged. The aim of the treatment is to ensure urine concentration, and output in which cystine crystals can dissolve. This is achieved with abundant amounts of fluid intake, and medical treatment. Most frequently, D-penicillamine, and α -mercaptopyrionylglycine (thiopronin) are used. Cystine is a dimer of cysteine, and these

therapeutic agents function by decreasing disulfide bonds linking two cystine molecules. Thiol group combines with cysteine, and forms a more soluble, and excretable cysteine-drug combination. D-penicillamine has a wide spectrum of adverse effects including febrile reactions, gastrointestinal discomfort, hepatic dysfunctions, altered taste perception, bone marrow depression, mental deficiencies, membranous glomerulonephritis, myasthenia gravis, and skin eruptions (elastosis perforans serpiginosa).^[6] Alpha-mercaptopyrionylglycine also has a similar, but probably less severe adverse effects. On a routine basis, hepatic enzymes should be evaluated, whole blood counts, urinalysis, measurement of copper, and zinc levels should be performed. Special examination techniques (solid phase or high-performance liquid chromatography) can be helpful in discriminating urinary cystine from cysteine-drug complexes, and also in the long-term drug therapy. Captopril which contains a disulfidril group can be used in the treatment, but its hypotensive effects should be taken into consideration.

Infection stones

In 2-24% of the children with renal stones, infection stones can be seen.^[6] They consist 75% of the stones detected in European children. They are generally seen before the age of six. Males constitute 80% of the patient population. Infection stones are more frequently seen in patients with anatomic, and functional disorders leading to stasis in the urinary system. Infection stones are formed in infections triggered by microorganisms hydrolyzing urea via urease enzyme with resultant production of ammonium, and bicarbonate.^[22] *Proteus*, *Providencia*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia*, *Enterobacter*, *Stafilococci* are urease producing microorganisms. However *Escherichia coli* do not produce urease, but aids in stone formation by facilitating precipitation of stone components as magnesium, and phosphate in higher urine pH.^[29]

Infection stones contain ammonium phosphate, carbonate apatite, and monoammonium urate. Ammonium phosphate is the basic component of most of the infection stones. Ammonia impairs glycosaminoglycan layer of uroepithelium which constitutes defense mechanism against bacteria. These stones, inherent to their composition, may require intervention after a long-lasting antibiotherapy. Thanks to advances in the diagnosis, and treatment of infections, incidence rate of this stone is gradually decreasing.^[50]

Treatment encompasses stone extraction, and correction of the underlying anatomical and/or functional obstruction. During long-lasting treatment, and follow-up, antibiotherapy based on antibacterial susceptibility tests has an important role. Acidification of urine, and balanced fibrous diet low in phosphate content contribute favourably to therapy.

Figure 1. A practical algorithm for the diagnosis, and differential diagnosis of pediatric urolithiasis

Orotic acid stones

Hereditary orotic aciduria is a rarely seen genetic disease. Deficiency of orotidinephosphoribosyltransferase, and orotidine-5-phosphate-decarboxylase enzymes which function in the conversion of orotic acid into uridine-5-phosphate result in this abnormality. As a result, urinary output of orotic acid increases, and crystallized to form orotic acid stones. Uridine is used for its treatment.^[29]

2,8-Dihydroxyl adenyluria

It is an autosomal recessive disease caused by defective adenine phosphorybosyl transferase with resultant excessive accumulation of 2,8 dihydroxyadenine. They closely resemble uric acid stones, and discrimination between them can be only possible using metabolic, and stone analyses. They can be treated with allopurinol, and dietary modification.^[10]

Figure 2. First-line treatment alternatives targeted at etiological agent in pediatric stone disease

Xanthinuria

Xanthinuria is a rarely seen disease with autosomal recessive inheritance. It is observed as an outcome of deficient xanthine oxidase which involves in the formation of uric acid which is the end product of purine metabolism. Urinary excretion of hypoxanthine, and xanthine increases. Xanthine is less soluble in urine. Allopurinol can be used in the treatment of the disease. Amount of dietary xanthine should be reduced, and abundant amounts of fluid should be ingested.

Cases of pediatric urolithiasis encountered during daily pediatric urology practice should be examined in detail. Priorly, a detailed anamnesis, and physical examination should be performed. Family history of stone disease, additional diseases, and medications used which may cause stone disease should be recorded. The most prevalent non-metabolic disorders in the pediatric age group may include vesicoureteral reflux disease, ureteropelvic junction obstructions, neurogenic bladder, and other voiding dysfunctions.^[51] Then simple clinical evaluations can be made. Priorly simple urinalysis, and ultrasonographic examinations can be performed. Following initial diagnosis made based on analyses on spot urine samples, and other clinical information, for definitive diagnosis observance of the following algorithm may be helpful (Figure 1).

Following simple clinical examinations, pH, calcium, phosphorus, magnesium, oxalate, sodium, potassium, uric acid, citrate, cystine, and creatinine levels, and amount of urine output in 24-hour urine samples collected for metabolic analysis should be measured. Besides, urine culture is recommended.^[51] Serum levels of sodium, potassium chloride, calcium, phosphorus, magnesium, creatinine, urea nitrogen, alkaline phosphatase, uric acid, free parathyroid hormone should be measured, and whole blood cell counts should be made. Calcium/citrate ratio above 0.326 in 24-hour urine sample increases probability of stone formation.^[52] Pediatric urolithiasis which is frequently encountered in daily clinical practice, after completion of diagnostic steps, cause-driven first, second, and third-line treatment alternatives have been revived. For most frequently encountered pathologies, and their practical treatments, compliance with the following algorithms has been recommended. (Figure 2-4). As stated above, at every step of the treatment, obedience to general treatment recommendations which include abundant fluid intake, and dietary modifications, has a critical importance. If the patient passes stone fragments spontaneously or stones are retrieved following ESWL and/or surgical procedures, stone analysis should be performed. After establishment of definitive treatment

Figure 3. Second-line treatment alternatives targeted at etiological agent in pediatric stone disease

Figure 4. Third-line treatment alternatives targeted at etiological agent in pediatric stone disease

based on stone analysis, and metabolic analysis, metaphylaxis should be applied as described above (Figure 5).

In conclusion, urolithiasis frequently seen in the pediatric age group requires detailed investigation. Delays in diagnosis, and treatment can induce serious outcomes which may lead to renal failure. Metabolic abnormalities are frequently seen in pediatric urolithiasis, and they are responsible for recurrent stone diseases. Early diagnosis, and detailed metabolic investigation, together with proper monitorization, and treatment protocols can preclude stone recurrences, and renal damage. The above-cited algorithms which summarize the whole review, may be useful for the diagnosis, treatment, and

Figure 5. Treatment recommendations based on the results of the stone analysis and metabolic evaluations

follow-up of stone disease patients referred to daily pediatric urology polyclinics.

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