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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Pediatric renal stone disease

Amira Peco-Antić
Bel Medic Hospital, Belgrade, Serbia

SUMMARY
Pediatric renal stone disease is manifested as nephro/urolithiasis (UL) and/or nephrocalcinosis (NC). Compared to adults, UL in childhood is less common, and it is believed to be around 5% in industrialized countries, while the incidence of NC is even lower except for critically ill premature infants, in whom it may reach 64%. The formation of UL and NC is caused by increased concentrations of relevant solutes, and their aggregations and adherence to renal tubule cells is facilitated by factors such as urine pH, inability of natural crystallization inhibitors, stasis of urine, as well as renal tubule damage. UL is associated with significant morbidity because of pain, susceptibility to urinary tract obstruction and infections, and the necessity of surgical procedures. NC is usually asymptomatic but is frequently progressive, and leads to chronic renal failure more often than UL. Although other imaging modalities can be used in the diagnosis of renal stone disease, ultrasound has the least risk and is most cost-effective. The majority of cases of UL and NC in children is of metabolic origin; thus, they are prone to recurrence and may cause chronic renal damage. Therefore, they deserve, even after their initial presentation, a detailed metabolic evaluation. Genetic source of renal stone disease is suspected in the following conditions: early onset, familial prevalence, familial consanguinity, multiple or recurrent stones, and NC. For all UL/NC etiologies, early identification and personalized treatment of the basic disorder is of the utmost importance.
Keywords: nephrolithiasis; nephrocalcinosis; metabolic disorders; children; chronic renal failure

INTRODUCTION

Pediatric renal stone disease is manifested as nephro/urolithiasis (UL) and/or nephrocalcinosis (NC). UL is characterized by stones that may be found anywhere in the urinary tract, including kidney and/or ureter or bladder, while NC is defined as calcium salt deposition in the renal parenchyma including the tubular epithelium and interstitial renal tissue [1]. Both UL and NC may be discovered in children of all ages. Although other imaging modalities can be used in the diagnosis of UL/NC, ultrasound has the least risk and is the most cost-effective.

UL/NC is associated with significant morbidity because of pain, susceptibility to urinary tract infections, the necessity of surgical procedures, and/or progression to chronic kidney failure. The most cases of UL and NC in children are of metabolic origin and are thus prone to recurrence and may cause chronic renal damage. Therefore, they deserve, even after their initial presentation, a detailed metabolic evaluation.

There are important differences of UL and NC in children compared to those in adults. In this review article, the epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment of the pediatric renal stone disease are discussed. The most attention is paid to the hypercalciuric renal stone diseases, as these are more likely to present in childhood.

EPIDEMIOLOGY

Compared to adults, UL in childhood is less common, and it is believed to be approximately 10% of that in adults, which is around 5% in industrialized countries [2–6]. The infants constitute up to one third of all pediatric UL patients [3, 4]. Overall, reported incidence of pediatric UL varies from 5.6 to 36 per 100,000 children and adolescents younger than 18 years [5, 6]. The differences in incidence rates reported in children with UL reflect differences in genetic, geographic, and socioeconomic background, but also depend on the design and the time of the study [7]. Endemic UL is found in Southeast Asia, the Middle East, India, and Pakistan, while it is uncommon in children of African descent. It is very likely that the high consanguinity rate contributes to the higher incidence of UL/NC among ethnic groups that live in the Middle East and Asia. Additionally, the endemic calculi observed in these parts of the world are composed predominantly of ammonium and uric acid, and seem to correlate with dietary habits, malnutrition, urinary tract infections, and hot climate. Epidemiology of UL in the European population of the 19th century is similar to that of the 20th century population in Asia [8]. Changes that have occurred in the socio-economic sphere, as well as their consequences, primarily in dietary habits (food rich in proteins and calories), have influenced the incidence, the site (decreased rate of bladder stones) and chemical composition of calculi (raising rate of calcium oxalate and

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Correspondence to:
Amira PECO-ANTIĆ
5 Dr Nike Miljanića
Belgrade 11000
Serbia
amirapecoantic@yahoo.com

calcium phosphate stones) [7]. As in adults, an increased trend of UL incidence, the so-called "stone wave," has also been observed in children [9–15]. VanDervoort et al. [10] demonstrated that pediatric UL increased almost five-fold over the last decade in the United States. An increasing incidence of UL may be explained at least partially by the increasing rate of routine ultrasound examination in children with nonspecific symptoms, as well as with specific ones. As in adults, UL is more common in males than in females, although there are some opposite findings [12, 16]. Pediatric UL morbidity is responsible for 1/685 pediatric hospitalizations in the United States and for 2.5/1,000 pediatric hospitalizations in Croatia [11, 17].

The incidence of NC in children is even less known than that of UL due to its typically asymptomatic course. Thus, NC diagnosis is usually made accidentally by ultrasound examination for other reasons. Due to the increasing application of ultrasound in recent times, NC is more frequent than previously revealed. NC epidemiology in neonates is much better known than in older children, especially in premature babies. It is all the greater if the gestational age and birth body weight of the newborn is less and its condition is more critical [18]. Jacinto et al. [19] reported NC incidence of 64% in premature infants at a mean age of 39.3 ± 26.7 days of life. Infants with NC had shorter gestations (28.2 ± 1.8 vs. 31 ± 1.4 weeks) and lighter birth weights (924 ± 195 vs. 1,338 ± 100 g) than those infants without renal calcifications [19]. In another study, 26.6% of 79 infants born at less than 32 weeks' gestation developed NC [20]. Affected infants were significantly smaller (mean birth weight 940 g) and significantly less mature (mean gestation 26.9 weeks). Multivariate analysis showed that the strongest clinical indicator of NC was the duration of oxygen treatment. Infants who still required oxygen treatment at 28 days of life had a 62% chance of developing renal calcification [20]. Other predisposing factors for NC in newborns are the use of diuretics (furosemide), corticosteroids, parenteral nutrition, and hypocitraturia.

PATHOPHYSIOLOGY

A primary event in the formation of UL and NC is the increased concentration of relevant solutes (calcium phosphate, calcium oxalate, sodium urate, cystine, or other substances) in urine above their saturation threshold due to their increased rate of urinary excretion and/or a low urine volume. The formation of crystals of the relevant salts, their aggregations and adherence to the renal tubule cells are also influenced by other factors such as urine pH, inability of natural crystallization inhibitors (citrate, pyrophosphate, sulfate, and magnesium), stasis of urine, as well as renal tubule damage (due to urinary tract infections or some drugs). Crystal binding to the surface of tubular cells is facilitated by a number of luminal membrane molecules, including acidic fragment of nucleolin-related protein, annexin-II, osteopontin, and hyaluronan, which are exclusively expressed at the luminal surface of regenerating/(re)differentiating renal tubular cells [21].

Calcium oxalate is the predominant constituent of at least 75% renal calcifications in pediatrics as well as in adults from industrialized countries [21]. However, the initial role in their formation belongs to calcium phosphate crystals, which start forming apatite plaque (Randall plaques) at the basement membrane of the thin loops of Henle, location predisposed to urothelial erosion due to the urine flux [22]. Aggregations of calcium oxalate crystals at apatite plaques provide further stone formation attached to the papillary tip of the kidney. It is considered that calcium phosphate stones are developed from crystal aggregates deposited at the tip of the Bellini ducts [21].

The kidney itself has a great role in renal stone diseases in association with calcitropic hormones such as vitamin D_3 and parathyroid hormone. The intrinsic renal calcium-sensing receptor (*CaSR*) feedback system, the regulation of paracellular calcium transport involving claudins, and new paracrine regulators such as klotho, give kidney a crucial position not only in modulation of calciuria but also of calcium homeostasis [23]. Genetic disorders in any of these systems may cause calcium nephropathy.

ETIOLOGY

As compared with the adult population, a higher proportion of pediatric patients have a well-defined etiology of renal stones. The etiology may be classified as metabolic, infection-related, structural urinary anomalies causing obstruction, or idiopathic. Metabolic abnormalities account for 25–96% of UL/NC, while urinary tract infection and anatomical obstructive abnormalities account for 25% and 30%, respectively [24, 25]. Metabolic alterations include hypercalciuria, hypocitraturia, hyperuricosuria, phosphaturia with hypophosphatemia, distal renal tubular acidosis, idiopathic infantile hypercalcemia, Bartter and Dent diseases, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, cystinuria, hyperoxaluria, and renal hypouricemia [26–31]. Heritability has been one of the strongest risks for UL/NC; 35–65% of affected patients will have relatives with UL/NC, compared with 5–20% of those without renal stone who have relatives with UL/NC [6, 27]. At least 30 genes have been shown to cause monogenic UL/NC by autosomal-dominant, autosomal-recessive, or X-linked transmission [28]. Polygenic disorders have also a significant role in UL, such as idiopathic hypercalciuria, but they are less cleared.

The study by Halbritter et al. [32], which included an international cohort of 272 patients with UL/NC, has shown that the percentage of monogenic cases was 11.4% in adult and 20.8% in pediatric patient cohorts. Recessive monogenic diseases typically manifest earlier in life than dominant monogenic diseases [33]. In more than 40% of the cases in the aforementioned study, the genetic diagnoses contributed a new aspect to the previously established clinical diagnosis, suggesting practical implications, such as avoiding vitamin D (*CYP24A1*), initiating audiometry (*ATP6V1B1*), excluding the risk of recurrence in renal transplants (*CLCN5* or *CLDN16*), or pyridoxine sensitivity

in the presence of *AGXT* allele (Gly170Arg [32]. Based on the study results, Braun et al. [33] give recommendation for clinicians to be aware of the genetic source of UL/NC in the following conditions: early onset, familial prevalence, familial consanguinity, multiple or recurrent stones, and NC.

Hypercalciuria is the commonest metabolic abnormality causing UL in children. It may be associated with increased, decreased, or normal serum calcium levels (Tables 1–3). Idiopathic hypercalciuria (IH) is defined by hypercalciuria, normocalcemia, and the absence of diseases known to cause increased urine calcium excretion. In children, hypercalciuria is diagnosed if the urine calcium excretion is ≥ 0.1 mmol (≥ 4 mg)/kg/day in at least two separate collections of urine during 24 hours (24h). Adequate collection is estimated via measuring 24h-urine creatinine of 0.1–0.2 mmol/kg/24h. In situations where 24h-urine collection is not possible, random urine measurements are implemented, using spot urine ratio of the calcium and creatinine and comparing it with its age-related reference values (Table 4) [34]. Pathogenesis of IH is very complex and many potential factors can be involved, such as polymorphisms of the gene coding for proteins regulating tubular phosphate and calcium reabsorption [vitamin D receptor (*VDR*), *SLC34A1*, *SLC34A4, CLDN14,* and *CaSR*] and those responsible for proteins preventing calcium salt precipitation (*CaSR*, *MGP*, *OPN, PLAU,* and *UMOD)* or gene coding for a water channel in the proximal tubule *(AQP1)* [35]. Furthermore, in families with an autosomal dominant mode of IH, inheritance connection between IH and loci on chromosome 1q23.3-q24, which contains the human soluble adenylyl cyclase gene, chromosome 12q12-q14, which contains the *VDR* gene and chromosome 9q33.2-q34.2, were established [27]. Environmental factors may also significantly affect renal stone formation. Nutrient intake may change urine composition, but may also influence gene expression by epigenetic mechanisms [35].

Table 1. Hereditary diseases associated with hypercalcemia and hypercalciuria (modified [27])

Disorder	Clinical feature	Mode of inheritance	Gene product	Chromosomal location of the gene	Comment
FIHP	Familial isolated parathyroid tumors	A-r/A-d	menin parafibromin CaSR	11q13 1q31.2 3q21.1	PTH increased
MEN1	Parathyroid hyperplasia and/or tumors associated with pituitary and pancreaticoduodenal neuro-endocrine tumors	A-d	menin	11q13	PTH increased
MEN2a	Parathyroid tumors with medullary thyroid cancer and pheochromocytoma	A-d	ret	10q11.2	PTH increased
HPT-JT	Parathyroid tumors with ossifying fibromas of the jaw	A-d	parafibromin	1q31.2	PTH increased
IHH	Idiopathic hypercalcemia with hypercalciuria	A-r	CYP24A1		PTH decreased
Hypophosphatemic nephrolithiasis/ osteoporosis	Renal phosphate leak, hypophosphatemia, hypercalciuria urolithiasis, osteoporosis	A-d/A-r	NPT2a/SLC34A1 solute carrier family 34 (sodium phosphate), member 1	5q35	$1,25(OH)_2D_3$ increased

A-d – autosomal dominant; A-r – autosomal recessive; FIHP – familial isolated hyperparathyroidism; MEN – multiple endocrine neoplasia; HPT-JT – hyperparathyroidism – jaw tumor syndrome; IHH – idiopathic hypercalcemia with hypercalciuria; CaSR – calcium-sensing receptor; NPT2c/a – sodium–phosphate co-transporter type 2c/a; PTH – parathyroid hormone

Table 2. Hereditary diseases associated with hypocalcemia and hypercalciuria

Disorder	Clinical feature	Mode of inheritance	Gene product	Chromosomal location of the gene	Comment
ADHH	Hypocalcemia, hyperphosphatemia, hypomagnesemia	A-d	CaSR	3q21.1	PTH low – normal range
FHHNC	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	A-r	PCLN1/CLDN16	3q28	PTH raised
FHHNC	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular abnormalities	A-r	CLDN19	1p34.2	PTH raised
FIH	Hypoparathyroidism, familial isolated	A-d	GCM2	6p24.2	PTH low
APECED	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	A-r	AIRE		PTH low
FIH, recessive	Hypoparathyroidism, autosomal recessive	A-r	11p153	PTH	PTH low
FIH, x-linked	Hypoparathyroidism, familial isolated –x linked	X-r	GCM2	Xq26-q27	PTH low
FIH, dominant	Hypoparathyroidism, autosomal dominant	A-d	PTH	11p153	PTH low

A-d – autosomal dominant; A-r – autosomal recessive; X-r – X-linked recessive; ADHH – autosomal dominant hypocalcemia with hypercalciuria; FHHNC – familial hypomagnesemia with hypercalciuria and nephrocalcinosis; FIH – familial isolated hypoparathyroidism; APECED – autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; AIRE – autoimmune regulator; CaSR – calcium-sensing receptor; PCLN1 – paracellin; CLDN16/19 – claudin 16/19; PTH – parathyroid hormone

Table 3. Hereditary diseases associated with normocalcemia and hypercalciuria (modified [27])

Disorder	Clinical feature	Mode of inheritance	Gene product	Chromosomal location of the gene	Comment
IH	Idiopathic hypercalciuria	AD	SACR VDR ?	1q23.3-q24 12q12-q14 9q33.2-q34.2	Hypercalciuria, normocalcemia
Bartter syndrome characterized by hypokalemic alkalosis, renal salt wasting that may lead to hypotension, hyperreninemic hyperaldosteronism, increased urinary prostaglandin excretion					
Type I	+ Hypercalciuria with nephrocalcinosis	A-r	SLC12A1/NKCC2	15q15-q21.1	Neonatal
Type II	+ Hypercalciuria with nephrocalcinosis	A-r	KCNJ1/ROMK	11q24	Neonatal
Type IV	+ Hypercalciuria with nephrocalcinosis + sensoneural deafness + CRF	A-r	BSND/CLCNKB	1p31, 1p36	
Type V	+ Hypercalciuria with nephrocalcinosis +hypocalcemia	A-d	CASR	3q21.1	
Type VI	+ Dent	X-r	CLCN5	Xp11.22	
Dent's disease	Hypercalciuria, Phosphaturia, Hypophosphatemia, low molecular weight proteinuria, CRF	X-r	ClCN5	Xp11.22	
Lowe's syndrome	Psychomotor retardation, Fancony syndrome, Hypercalciuria, Phosphaturia, Megalin deficiency, Congenital cataract	X-r	OCRL1	Xq25	
HHRH	Hypophosphatemic rickets with hypercalciuria	A-r	NPT2c/SLC34A3 solute carrier family 34 (sodium phosphate)	9q34	
dRTA A-d	Hypercalciuria, Hypocitraturia, Hypokalemia, rickets	A-d	SLC4A1/kAE1	17q21.31	
dRTA with sensorineural deafness	Hypercalciuria, Hypocitraturia, Hypokalemia, rickets Hearing loss	A-r	ATP6B1/ATP6V1B1	2p13	
dRTA with preserved hearing	Hypercalciuria, Hypocitraturia, Hypokalemia, rickets	A-r	ATP6N1B/ATP6V0A4	7q34	

A-d – autosomal dominant; A-r – autosomal recessive; X-r – X-linked recessive; HHRH – hereditary hypophosphatemic rickets with hypercalciuria; dRTA – distal renal tubular acidosis; SAC – human soluble adenylyl cyclase; VDR – vitamin D receptor; CaSR – calcium-sensing receptor; SLC12A1 – solute carrier family 12, member 1; NKCC2 – sodium–potassium–chloride co-transporter 2; KCNJ1 – potassium channel, inwardly rectifying, subfamily J, member 1; ROMK – renal outer medullary potassium channel; CLCNKB – chloride channel Kb; BSND – barttin; CLCN5 – chloride channel 5; OCRL1 – oculo-cerebro-renal syndrome of Lowe 1; NPT2c/a – sodium–phosphate co-transporter type 2c/a; SLC34A1/3 – solute carrier family 34, member 1/3; SLC4A1 – solute carrier family 4, member 1; kAE1 – kidney anion exchanger 1; ATP6B1 – ATPase, H+ transporting (vacuolar proton pump), V1 subunit B1; ATP6N1B – ATPase, H+ transporting, lysosomal V0 subunit a4

CLINICAL MANIFESTATION

Unlike adults and adolescents, only 10–14% of children with UL have classic renal colic [17, 34, 36]. Exceptionally, UL in children may be manifested by signs and symptoms of post renal acute kidney injury due to urethral or ureteral obstruction of both or single functioning kidney [37]. Instead, microscopic or macroscopic hematuria, flank or abdominal pain, as well as recurrent urinary tract infection, are predominant clinical presentations of UL in children [16]. Hematuria may precede noticeable UL for some time. Recurrent urinary tract infection or unexplained sterile pyuria in young children should arouse suspicion of UL. The recurrence rate of UL may be as high as 50% at five years [27]. In addition, signs and symptoms of lower urinary tract dysfunction, such as nocturnal enuresis and/or diurnal incontinence, suprapubic or urethral pain may be found in about 10% of children with UL [7]. Finally, 10–25% of young children have no symptoms of UL, which then may be discovered as an incidental finding during abdominal ultrasound imaging for any other reason [7, 34, 38].

Nephrocalcinosis is usually asymptomatic or occult symptomatic and is diagnosed incidentally during the search for causes of hematuria, abdominal pains, or sterile leukocyturia. NC is often progressive, and more often than UL leads to chronic renal failure [28, 31, 34, 38].

DIAGNOSTIC EXAMINATION

Given the complexity of children's UL/NC and especially its predominant metabolic hereditary etiology, it is advised, as the best solution, to perform the systemic diagnostic evaluation and personalized treatment in the Center for Pediatric Renal Stone Disease, as it is practiced in some Western countries [36]. System diagnostic evaluation includes a detailed medical history, careful and complete physical examination, followed by imaging studies and specific blood and urine analyses. In medical history, special attention should be given to information on family renal stones, hematuria, renal failure, but also on diet habits, fluid intake, medications, vitamin and mineral supplements,

Table 4. Normal values of solute for 24 hour urine collection, or for spot urine samples: creatinine ratios (solute/creatinine) (modified [34])

The age-specific parameter values	Ratio of solute to creatinine		Comments
	mmol/mmol	mg/mg	
Calcium			< 0.1 mmol (< 4 mg)/kg/24h After meals with milk, excretion increases up to 40%.
< 12 months	< 2	0.81	
1–3 years	< 1.5	0.53	
3–5 years	< 1.1	0.39	
5–7 years	< 0.8	0.28	
> 7 years	< 0.6	0.21	
Oxalates			< 0.5 mmol (< 45 mg)/1.73 m^2 For primary hyperoxaluria types I and II also examine urinary glycolate, L-glycerol and oxalate in plasma
0–6 months	< 325–360	288–260	
7–24 months	< 132–174	110–139	
2–5 years	< 98–101	80	
5–14 years	< 70–82	60–65	
> 16 years	< 40	32	
Citrate		g/g	> 1.9 mmol (365 mg)/1.73 m^2 (M); > 1.6 mmol (310 mg)/1.73 m^2 (F) > 180 mg (94 µmol/g (8.84 mmol) creatinine Decreased: RTA, premature infants, hypokalemia, renal transplantation
0–5 years	> 0.25	0.42	
> 5 years	> 0.15	0.25	
Magnesium	0.63	> 0.13	> 0.04 mmol (0.8 mg)/kg; > 88 mg (44 mmol)/1.73 m^2/24h There is no data for children < 2 years old
Phosphates	TmP/GFR		
< 3 months	< 3.3 mmol/l		
< 6 months	< 2.6 mmol/l		
2–15 years	< 2.44 mmol/l		
Sodium	< 3 mmol/kg/24h		
Potassium	> 3 mmol/kg/24h		
Acidum uricum	Age > 2 years < 0.56 mg/dl (33 µmol/l) / GFR (ratio × serum creatinine)		< 815 mg (4.9 mmol)/1.73 m^2/24h or < 35 mg (0.21 mmol)/kg/24h Higher in children than in adults; there is no data for children < 2 years old
Xanthine	30–90 µg (20–60 µmol)/24h		
Cystine	< 60 mg (0.5 mmol)/1.73 m^2/24h		< 10 years < 55 µmol (13 mg)/1.73 m^2; > 10 years < 200 (48 mg)/1.73 m^2

GFR – glomerular filtration rate; TmP/GFR – tubular maximum reabsorption rate of phosphate to glomerular filtration rate

immobilization, chronic bowel diseases, and, of course, on urological anomalies and urinary tract infections [34].

Diagnostic imaging should start with an ultrasound examination, which is widely available, non-invasive, without ionizing radiation, and very useful for detecting kidney stones, obstructive anomalies, and other aspects of the urinary tract anatomy [34]. Usually, renal ultrasound is the only method required, but for detection of small stones or stones in the ureter, computed tomography (CT) is more sensitive than ultrasound. Conventional radiography, with or without contrast (plain X-ray) may replace CT in infants and young children as it does not require sedation and gives off less ionizing radiation. However, radiolucent uric acid stones cannot be visualized by conventional radiography while struvite (magnesium ammonium phosphate), cystine stones, and stones composed of some drugs (ceftriaxone) can be difficult to detect from the surrounding tissue. For diagnosing NC in children, high-resolution renal ultrasound is the optimal method due to its high sensitivity (96%), and very good specificity (85%) [39].

A complete analysis of the first morning urine is essential in diagnosing UL/NC. By microscopic urine examination it is possible to differentiate glomerular from non-glomerular hematuria, to diagnose crystals (e.g. hexagonal cystine crystals, orange-brown 2,8-dihydroxyadenine), to notice leucocytes and bacteria. Urine pH (done by a glass electrode or by pH paper), urine-specific gravity or osmolality, urine protein and glucose are part of the routine examination of urine. It is important to note that the results of urinalysis are credible only in the absence of urinary tract infection. Therefore, urine culture is checked prior to the chemical urine analysis, which includes measurements of creatinine, calcium, uric acid, oxalic acid, phosphate, magnesium, and citrate. Cystine is examined by nitroprusside test or by amino acid chromatography. Preferably, it should be done for 24 hours, but when this is unavailable, it can be replaced by the spot urine ratio of the test substance and creatinine (Table 4). All patients should also be examined for serum calcium, phosphorus, magnesium, uric acid, alkaline phosphatase, pH, bicarbonate, and creatinine. In patients with hypercalciuria, it is advised to do blood analyses for the parathyroid hormone, vitamin D metabolites, and vitamin A. For the diagnosis of primary hyperoxaluria, it is required to measure plasma

and urine oxalate, and glycolate and L-glycerate in urine. Determining intestinal oxalate absorption and stool *Oxalobacter formigenes* colonization is preferable for secondary hyperoxaluria. Finally, genetic tests are required to confirm the clinical diagnosis and are very useful for personalized treatment and preventive strategy [27–33].

THERAPY

In cases of acute renal colic, pain is usually very intense due to the irritation of receptors during dilatation of the urinary system and release of pain mediators through to local irritation and swelling of the wall of the renal pelvis or ureter. The use of nonsteroidal antiinflammatory drugs may be indicated as the first choice. Renal stone expulsive treatment may be managed with open surgery, extracorporeal shock wave lithotripsy, laparoscopic or robot-assisted uretero-pyelolithotomy, percutaneous nephrolithotomy, rigid and/or flexible ureteroscopy and medical expulsive treatment (MET) [40]. Choice of treatment for a specific patient is determined based on the renal stone location, its size and composition, urinary system anatomy, as well as available technology, cost of the treatment, experience of the physician, and preferences of both the physician and the patient's parents [40]. Alpha-blockers and calcium channel blockers have been found to be more effective and successful for MET than other drugs (antimuscarinic drugs, phosphodiesterase type-5 inhibitors and steroids) [40]. Both of these eliminate or alleviate uncoordinated contractions induced by the stone and do not affect the normal peristalsis of the ureter. MET may be useful for small stones (5–10 mm) within the distal part of ureter, and are usually applied after the extracorporeal shock wave lithotripsy treatment.

Non-pharmacological measures are still the initial and basic treatment and preventive measures [38]. These include an increase in urine output and crystallization inhibitors, and the setting of optimal urine pH. Increasing the intake of fluids (≈ 3 l/m^2 of body surface area) provides urine output > 1 ml/kg/h [38]. Reduced intake of table salt (NaCl) and increased potassium intake should maintain the Na/K ratio in urine to < 2.5 [38]. It should not reduce calcium intake below the age-recommended dose (800 mg/day for pre-school and 1,300 mg/day for school age) because of the increased risk for osteopenia and hyperoxaluria. It is also advised to reduce the intake of animal protein. The intake of phytate and magnesium should increase, while the intake of sucrose, fructose, and high doses of vitamin C should be reduced [38].

Pharmacological measures are specific regarding the etiology of UL/NC. For hypercalciuria and/or hypocitraturia, it is advised to give K citrate (0.5–1.5 mEq or 0.1–0.15 g / kg of body weight per day divided into two or three doses each), which is metabolized to bicarbonate in the liver, thus reducing intratubular citrate reabsorption and therefore increasing urinary citrate excretion. Citrate forms a complex with calcium, reducing precipitation of calcium with other substances such as oxalate. Thiazides (hydrochlorothiazide 1–2 mg/kg/day divided into one to two doses) with or without amiloride also decrease calcium urine excretion [38]. In patients with dominant hypocalcemia, hyperphosphatemia, and hypercalciuria due to a gain-of-function *CaSR* mutation, vitamin D is not indicated as it worsens hypercalcemia and hypercalciuria. For hypercalciuria + phosphaturia, phosphates are given. Treatment options for the *CYP24A1* mutation disorders include avoidance of vitamin D supplementation, sunlight exposure, and tanning beds, along with high water intake, but treatment with the cytochrome inhibitor ketoconazole may be beneficial in severely affected patients [41, 42].

For primary hyperoxaluria type I, in addition to large water intake (> 3 l/m^2/day), citrate or orthophosphate, vitamin B_6 (5–20 mg/kg/day) is given, which in about 30% of patients (those with a distinct allele – Gly170Arg) may enhance the reduced activity of alanine/glyoxylate aminotransferase (AGT), thus reducing hyperoxaluria. In others, hepatic AGT activity should be restored by liver transplantation. Sequential liver–kidney or liver combined with kidney transplantation is performed in patients with advanced stages of chronic kidney failure. In secondary (absorptive) hyperoxaluria, it is necessary to treat the primary gastrointestinal disease, to reduce the intake of oxalate in the food, increase the intake of calcium (to bind fatty acids, thereby preventing the intestinal absorption of oxalate), with potassium citrate and probiotics.

Hyperuricosuria is treated with alkalinization of urine (by potassium citrate), dietary purine restriction, and, if needed, allopurinol can be added.

In patients with cystinuria, urine pH should be kept between 7.0 and 7.5 by potassium citrate and bicarbonate, in addition to abundant rehydration. Specific drugs for cystinuria are tiopronin, D-penicillamine and captopril, which cleave cystine into two cysteine-disulfide moieties that are 50-times more soluble than cystine. However, care must be taken of their side effects.

In distal renal acidosis, treatment of acidosis by potassium citrate and bicarbonate is the cornerstone of therapy.

CONCLUSION

UL/NC in children is a very important problem due to its complications and possibility to cause chronic renal failure. Every child with renal stone should undergo the diagnostic evaluation. For all UL/NC etiologies, early identification and personalized treatment of the basic disorder is of the utmost importance.

REFERENCES

1. Popović-Rolović M, Peco-Antić A, Marsenić O. Nefrolitijaza i nefrokalcinoza. U: Dončev M (ured). Lekarski priručnik iz dečje nefrologije. Bor: Grafomed; 2001. p. 213–20.
2. Croppi E, Ferraro PM, Taddei L, Gambaro G. Prevalence of renal stones in an Italian urban population: a general practice-based study. Urol Res. 2012; 40:517–22.
3. Güven A, Koyun M, Baysal YE, Akman S, Alimoflu E, Akbas H, et al. Urolithiasis in the first year of life. Pediatr Nephrol 2010; 25:129–34.
4. Serdaroğlu E, Aydoğan M, Özdemir K, Bak M. Incidence and causes of urolithiasis in children between 0–2 years. Minerva Urol Nefrol. 2017; 69:181–8.
5. Edvardsson V, Elidottir H, Indridason OS, Palsson R. High incidence of kidney stones in Icelandic children. Pediatr Nephrol. 2005; 20:940–4
6. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. J Urol. 2012; 188:247–52.
7. López M, Hoppe B. History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol. 2010; 25(1):49–59.
8. Asper R. Epidemiology and socioeconomic aspects of urolithiasis. Urol Res. 1984; 12:1–5.
9. Turney BW, Reynard JM, Noble JG, Keoghane SR. Trends in urological stone disease. BJU Int. 2012; 109:1082–7.
10. VanDervoort K, Wiesen J, Frank R, Vento S, Crosby V, Chandra M, et al. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. J Urol. 2007; 177:2300–5.
11. Bush NC, Xu L, Brown BJ, Holzer MS, Gingrich A, Schuler B, et al. Hospitalizations for pediatric stone disease in United States, 2002-2007. J Urol. 2010; 183:1151–6.
12. Sas DJ, Hulsey TC, Shatat IF, Orak JK. Increasing incidence of kidney stones in children evaluated in the emergency department. J Pediatr. 2010; 157:132–7.
13. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. J Urol. 2010; 184:1100–4.
14. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. J Urol. 2012; 188:247–52.
15. Penido MG, Srivastava T, Alon US. Pediatric primary urolithiasis: 12-year experience at a Midwestern Children's Hospital. J Urol. 2013; 189:1493–7.
16. Yasui T, Iguchi M, Suzuki S, Kohri K. Prevalence and epidemiological characteristics of urolithiasis in Japan: national trends between 1965 and 2005. Urology. 2008; 71:209–13.
17. Milošević D, Batinić D, Turudić D, Batinić D, Topalović-Grković M, Gradiški IP. Demographic characteristics and metabolic risk factors in Croatian children with urolithiasis. Eur J Pediatr. 2014; 173:353–9.
18. Schell-Feith EA, Kist-van Holthe JE, van der Heijden AJ. Nephrocalcinosis in preterm neonates. Pediatr Nephrol. 2010; 25:221–30.
19. Jacinto JS, Modanlou HD, Crade M, Strauss AA, Bosu SK. Renal calcification incidence in very low birth weight infants. Pediatrics. 1988; 81:31–5.
20. Short A, Cooke RW. The incidence of renal calcification in preterm infants. Arch Dis Child. 1991; 66(4 Spec No):412–7.
21. Verkoelen CF, Verhulst A. Proposed mechanisms in renal tubular crystal retention Kidney Int. 2007; 72:13–8.
22. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006; 367:333–44.
23. Moor MB, Bonny O. Ways of calcium reabsorption in the kidney. Am J Physiol Renal Physiol. 2016; 310:F1337–50.
24. van't Hoff WG. Aetiological factors in paediatric urolithiasis. Nephron Clin Pract. 2004; 98(2):c45–8.
25. Cameron MA, Sakkhae K, Moe OW. Nephrolithiasis in children. Pediatr Nephrol. 2005; 20:1587–92.
26. Hunter DJ, Lange M, Snieder H, MacGregor AJ, Swaminathan R, Thakker RV, et al. Genetic contribution to renal function and electrolyte balance: a twin study. Clin Sci (Lond). 2002; 103:259–65.
27. Stechman MJ, Loh NY, Thakker RV. Genetic causes of hypercalciuric nephrolithiasis. Pediatr Nephrol. 2009; 24:2321–32.
28. Peco-Antić A, Smoljanić Z, Dimitrijević N, Kostić M, Marsenić O, Djordjević M. Lesch–Nyhan–ov sindrom. Srp Arh Celok Lek. 2001; 129(9–10):260–3.
29. Peco-Antić A, Dunjić R, Marsenić O, Živić G. Bartter-ov sindrom, nova podela, stara terapija. Srp Arh Celok Lek. 2001; 129(5–6):139–42.
30. Peco-Antić A, Konrad M, Milošević-Lomić G, Dimitrijević N. Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis: the first four patients in Serbia. Srp Arh Celok Lek. 2010: 138:351–5.
31. Konard M, Weber S, Dötsch J, Kari JA, Seeman T, Misselwitz J, et al. CLDN16 Genotype Predicts the Progression of Renal Failure in Familial Hypomagnesiemia with Hypercalciuria and Nephrocalcinosis. JASN. 2008; 19(1):171–81.
32. Halbritter J, Baum M, Hynes AM, Rice SJ, Thwaites DT, Gucev ZS, et al. Fourteen monogenic genes account for 15% of nephrolithiasis/nephrocalcinosis. JASN. 2015; 26:543–51.
33. Braun DA, Lawson JA, Gee HY, Halbritter J, Shril S, Tan W, Stein D, et al. Prevalence of Monogenic Causes in Pediatric Patients with Nephrolithiasis or nephrocalcinosis. Clin J Am Soc Nephrol. 2016; 11(4):664–72.
34. Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol. 2010; 25:403–13.
35. Arcidiacono A, Mingione A, Macrina L, Pivari F, Soldati L, Vezzoli G. Idiopathic Calcium Nephrolithiasis: A Review of Pathogenic Mechanisms in the Light of Genetic Studies. Am J Nephrol. 2014; 40:499–506.
36. Coward RJ, Peters CJ, Duffy PG, Corry D, Kellett MJ, Choong S, van't Hoff WG. Epidemiology of paediatric renal stone disease in the UK. Arch Dis Child. 2003; 88:962–5.
37. Patodia M, Sharma K, Sankhwar S, Goel A. Bladder calculus leading to acute renal failure in a girl child: a rare cause. BMJ Case Rep. 2017; 9:2017.
38. Alon US. Medical treatment of pediatric urolithiasis. Pediatr Nephrol. 2009; 24:2129–35.
39. Cramer B, Husa L, Pushpanathan C. Nephrocalcinosis in rabbits—correlation of ultrasound, computed tomography, pathology and renal function. Pediatr Radiol. 1998; 28(1):9–13.
40. Atan A, Balcı M. Medical expulsive treatment in pediatric urolithiasis. Turk J Urol. 2015; 41:39–42.
41. Peco-Antić A, Ivelja B, Miloševski-Lomić G, Paripović D, Konrad M. Hypercalciuria caused by CYP24A1 mutation – fourteen years of the patient's follow-up. Srp Arh Celok Lek. 2017; OnLine-First: March 31, 2017; (00):95–95. [DOI: https://doi.org/10.2298/SARH170116095P]
42. Sayers J, Hynes AM, Srivastava S, Dowen F, Quinton R, Datta HK, et al. Successful treatment of hypercalcaemia associated with a CYP24A1 mutation with fluconazole. Clin Kidney J. 2015; 8:453–5.

Обољења са бубрежним камењем код деце

Амира Пецо-Антић

Болница „*Bel Medic*“, Београд, Србија

САЖЕТАК

Бубрежно камење код деце се испољава као постојање каменчићи у бубрезима и уринарним путевима – уролитијаза (УЛ), или као калцификација бубрежног паренхима – нефрокалциноза (НК). УЛ код деце је ређа у односу на одрасле и износи око 5% у индустријским земљама, а НК је још ређа, осим код критично болесних прематуруса, код којих може достићи чак 64%. Формирање УЛ и НК су условљени повећаном концентрацијом соли у урину, а њихова агрегација и адхеренција за бубрежне тубулске ћелије је олакшана факторима као што су *pH* урина, слабост природних инхибитора кристализације, стаза урина и оштећења тубула. УЛ прати значајан морбидитет због болова, подложности опструкцији и инфекцији уринарног тракта и честих потреба за хируршким интервенцијама. НК је обично асимптоматска, али је често прогресивна и много чешће од УЛ изазива хроничну бубрежну слабост. УЛ и НК се дијагностикују применом различитих испитивања која дају слику уринарног тракта, а ултразвучно испитивање је најмање ризично и најисплатљивије. У већини случајева УЛ и НК су метаболичког порекла те су склони поновном јављању и хроничном оштећењу бубрега. Због тога они заслужују, чак и при првој појави, да се детаљно испита узрок њиховог настанка. На генетички узрок калкулозе и НК треба помислити у следећим околностима: рана појава, фамилијарно оптерећење бубрежним болестима, консангвинитет, више калкулуса или њихово понављање и присуство НК. За све типове бубрежног камења веома је важна рана дијагноза и персонална терапија основне болести.

Кључне речи: нефролитијаза; нефрокалциноза; метаболичке болести; деца; хронична бубрежна инсуфицијенција