Specificities of Urolithiasis in Pediatrics

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Renal lithiasis is less frequent in children than in adults; in pediatrics, lithiasis may be caused by genetic abnormalities, infections, and complex uropathies, but the association of urological and metabolic abnormalities is not uncommon.

nephrolithiasis pediatrics hydration

1. Stone Compositions

Concerning stone composition, the main components of stones were calcium oxalate and calcium phosphate [1][2][3][4]. One study reported an increase in the proportion of calcium oxalate stones and a decrease in the proportion of infectious stones in a cohort of 111 children with at least one stone analyzed by Fourier transformed infrared spectroscopy between 2013 and 2017 [5]. These changes in the epidemiology of stone components may be attributable to metabolic and environmental factors [3][5][6], keeping in mind that a significant part of pediatric urolithiasis is nevertheless due to genetic and metabolic causes. In contrast to adults in which urolithiasis is most often “idiopathic” or “diet-induced” [7], a cause is found in almost 50% of pediatric patients, metabolic disorders such as hypercalciuria, hypocitraturia, and hyperoxaluria being the more common [8].

The composition of stones depends on age: the proportion of calcium oxalate stones increase while carbapatite stones decrease with age. This can be partly explained by the evolution of etiologies by age group: indeed, metabolic and genetic disorders are more often found in infants before 1 year, infection in children between 1 and 5 years, and “idiopathic” causes after 6 years [5][6][8][9].

Data are more controversial for gender specificities [2], even though it is well accepted that gender distribution differs according to age. During the first decade, stone disease is more prevalent amongst boys, mainly due to a higher prevalence of urinary tract infections in boys during this life period. In contrast, during the second decade of life, girls are affected more often than boys [10]. Bergsland et al. reported that age and sex have a profound influence on urinary calcium and oxalate. Puberty is a time of rapid growth and hormonal changes, which could plausibly also affect stone pathogenesis [11].

2. From the Diagnostic Approach to Genetics

An etiology is reported in 30 to 80% of pediatric cases (average 50%) and is related to genetic abnormalities in 10–20% [5][8][12]. A complete metabolic assessment should be systematically performed after the first stone in a child,

especially in the youngest ones [2]. Patients with stones present a two-fold increased risk of developing chronic kidney disease (CKD) in the long term compared to general populations [13]. It is crucial to provide an adequate diagnosis for these patients, since the prognosis of an orphan and severe inherited form of urolithiasis and nephrocalcinosis, namely primary hyperoxaluria type 1, has been recently dramatically modified by the onset of RNA-interfering therapies [14][15].

The first step is based on the search for factors pointing to a genetic origin: familial history of kidney stones and consanguinity, as well as active, bilateral, and early lithiasis. The second step is to identify favoring factors, notably urological abnormalities, chronic digestive diseases inducing malabsorption, drug intake, and/or history of infections. **Table 1** summarizes the biological evaluation that should be performed when evaluating a child with a first episode of lithiasis [2][16]. In **Table 2** there are pediatric references about plasmatic and urinary electrolytes [17]

Table 1. Biological evaluation concerning every first episode of lithiasis in a childhood.

	Blood Biology	Urinary Biology	Others
First line	Ionogram: sodium, potassium, chloremia, creatinine, calcium, phosphate, bicarbonate, uric acid, magnesium, PTH, 25OHVitD	Density, osmolarity, calcium, phosphate, oxalate, cystine, citrate, magnesium, uric acid, creatinine, sodium, urea	Spectroscopy analysis: a carbonation rate (detected by infrared spectrometry) of less than 10% suggests lithiasis of metabolic origin (phosphate), whereas a carbonation rate of 15% or more points to infectious stones. Crystalluria (if available)
Additional explorations	When?	What?	Why?
	If hypercalciuria, or weddellite or brushite stones	Calcium load test	To show resorption or absorption hypercalciuria, or abnormalities of PTH regulation or Vitamin D metabolism
	If normal bicarbonate, hypocitraturia, normal or increased urinary pH, and carbapatite or weddellite stones	Acid load test	To demonstrate incomplete tubular acidosis

PTH: parathyroid hormone, 25OHVitD: 25-OH vitamin D.

Table 2. Plasmatic and urinary electrolyte references in pediatrics.

	Age	Ratio Solute/Creatinine (95 ^{e} per) mmol/mmol mg/mg		Urinary 24 h (d)
Calcium	0–6 months	<2	<0.8	<0.1 mmol/kg/d (<4 mg/kg/d)
	7–12 months	<1.5	<0.6	
	1–3 years	<1.5	<0.53	
	3–5 years	<1.1	<0.39	

	Age	Ratio Solute/Creatinine (95 [e] per) mmol/mmol	mg/mg	Urinary 24 h (d)
	5–7 years	<0.8	<0.28	
	>7 years	<0.6	<0.21	
Oxalate	0–6 months	<0.36	<0.26	<0.5 mmol/1.73 m^2/d (<45 mg/1.73 m^2/d)
	7–24 months	<0.17	<0.14	
	2–5 years	<0.10	<0.08	
	5–14 years	<0.08	<0.06	
	>16 years	<0.04	<0.03	
Citrate	0–5 years	>0.25	>0.42	M: > 1.9 mmol/1.73 m^2/d (>365 mg/1.73 m^2/d)
	>5 years	>0.15	>0.25	F: > 1.6 mmol/1.73 m^2/d (> 310 mg/1.73 m^2/d)
Uric acid	<1 years	<1.5	<2.2	<70 µmol/kg/d (<1.3 mg/kg/d)
	1–3 years	<1.3	<1.9	<65 µmol/kg/d (<1.1 mg/kg/d)
	3–5 years	<1.0	<1.5	<65 µmol/kg/d (<1.1 mg/kg/d)
	5–10 years	<0.6	<0.9	<55 µmol/kg/d (<0.9 mg/kg/d)
	>10 years	<0.4	<0.6	<55 µmol/kg/d (<0.9 mg/kg/d)
Magnesium	>2 years	>0.63	>0.13	>0.04 mmol/kg/d (>0.8 mg/kg/d)
Cystine	<10 years	<12		<55 µmol/1.73 m^2/d (<13 mg/1.73 m^2/d)
	>10 years	<12	<0.07	<200 µmol/1.73 m^2/d (<48 mg/1.73 m^2/d)
	Adult	<12		<250 µmol/1.73 m^2/d (<60 mg/1.73 m^2/d)
Creatinine	3–5 years			12–20 mg/d
	6–8 years			15–25 mg/d
	14–18 years			M: 18–27 mg/d F: 17–24 mg/d
Phosphore		mmol/L		TmP/GFR (mmol/L) urinary
	1–3 years	1.38–2.19		1.53 (1.13–1.92)
	3–5 years	1.38–2.19		1.47 (1.19–1.74)
	5–7 years	1.33–1.92		1.42 (1.13–1.70)
	7–9 years	1.33–1.92		1.40 (1.11–1.69)
	9–11 years	1.33–1.92		1.41 (1.14–1.67)
	11–13 years	1.33–1.92		1.41 (1.14–1.67)
	13–16 years	F: 1.02–1.79		F: 1.24 (0.87–1.60)
	16–19 years	M: 1.14–1.99		M: 1.34 (0.98–1.69)
		0.95–1.62		F: 1.12 (0.77–1.46) M: 1.16 (0.71–1.61)

When this complete metabolic evaluation is performed, **Table 3** proposes a classification that may help diagnosis and further genetic analysis and management of pediatric lithiasis.

Table 3. Proposed classification of hereditary renal lithiasis in children.

	Biology	Etiology	Lithiasis	Genetic
Hypercalciuria	Normal Ca Normal PTH Normal Ca/creat (U) After calcium loading,	Anomaly VitD metabolism	Weddellite (IIa)/carbapatite (IVa1)/Brushite (Ivd)	Inhibitory mutations of 24 hydroxylase

	Biology	Etiology	Lithiasis	Genetic
	adapted PTH braking and Delta Ca/creat (U) >0.05 mmol/mmol			(*CYP24A1* gene)
		Familial hyperparathyroidism		*MEN1*
				HRPT2
				Ca Sr genes
	Normal or high Ca High PTH High Ca/creat(U) After calcium loading, high PTH and delta Ca(U)/creat(U) < 0.05 mmol/L	Anomaly tubular reabsorption Ph		Gene *Npt2a, Npt2c*
				Gene *NHERF1*
Hyperoxaluria	Oxalate/creat U increased	Type 1	Whewellite (Ia/Ic)	*AGXT*
		Type 2		*GRHPR*
		Type 3		*HOGA1*
Tubular acidosis, Uric acid lithiasis	Acide pH U Urinary uric acide/creatinuria > 1.5 mmol/mmol (<2 years), >0.4mmol/mmol (>10 years)	Hyperuciemia	Type III	*HRPT* (Lesh Nyhan syndrom) X-linked recessive
		PRPPS		X-linked recessive
		APRT		Autosomal recessive
Cystinuria	Alkaline pH Cystinuria increased	Defects in the reabsorption of dibasic amino acids	Type V	*SLC3A1* (type A), *SLC7A9* (type B)

Ca: calcemia, PTH parathyroid hormone, creat: creatininemia, VitD: vitamin D.

3. Other Factors

Typically, in adults, hypercalciuria and hyperuricuria can be induced by a bad lifestyle. Indeed, high intake of sodium, animal proteins, calcium, and fructose increase calcium excretion and subsequently the incidence of calcium oxalate stones. Obesity is associated with risk factors contributing to the formation of lithiasis, such as lower urinary pH (due to insulin resistance) and increased excretion of calcium oxalate, uric acid, sodium, and phosphate [2]. The metabolic syndrome also leads to a defect of ammoniogenesis whilst an acidic urinary pH favors the precipitation of uric acid crystals [18]. While pediatricians observe an increased prevalence of overweight and obesity in children as well as metabolic syndrome in adolescents, there is also an increase of “nutritional” lithiasis at the pediatric age [5][7][19].

Complex uropathies malformations can favor lithiasis of infectious origin by stasis and hyperoxaluria (Ia) [20]. Infectious lithiasis such as struvite or carbapatite can be induced by an alkaline pHU. Indeed, struvite lithiasis

(ammonium magnesium phosphate [AMP], IVc) is secondary to an infection with urea bacteria, in order of frequency: *Proteus mirabilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus* or epidermidis, and *Pseudomonas* spp. A carbapatite lithiasis (IVa) with a carbonation rate higher than 15% also points to an infectious stone with urea bacteria; in such a case, an underlying metabolic factor is often associated.

Gut microbiota also seems to have an impact on the formation of nephrolithiasis. Gut microbiomes of children and adolescents with calcium oxalate kidney stone disease is less diverse [21]. In fact, the loss of bacteria producing butyrate and degrade oxalate is associated with perturbations of the microbiome and early-onset calcium oxalate kidney stone disease [22]. Denburg et al. have shown in a case-control study of 88 individuals aged 4–18 years a significantly less diverse gut microbiome in participants with lithiasis [21]. Many recent papers propose a model of lithogenesis prevention by using antibiotics, probiotics, and nutrition in children, but this remains to be further confirmed [23][24].

Last, secondary hyperoxaluria can be due to intestinal causes, malabsorption, low calcium intake, cystic fibrosis, shortened blood vessels, drugs, or toxins [25][26].

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