Inherited conditions resulting in nephrolithiasis

Bernd Hoppe[a] *and Cristina Martin-Higueras*[b]

Purpose of review
Prevalence of pediatric urolithiasis is increasing, which is definitively visible in increasing numbers of presentations in emergency or outpatient clinics. In pediatric patients, a genetic or metabolic disease has to be excluded, so that adequate treatment can be installed as early as possible. Only then either recurrent stone events and chronic or even end-stage kidney disease can be prevented.

Recent findings
The genetic background of mostly monogenic kidney stone diseases was unravelled recently. In hypercalcuria, for example, the commonly used definition of idiopathic hypercalciuria was adopted to the genetic background, here three autosomal recessive hereditary forms of CYP24A1, SLC34A1 and SLC34A3 associated nephrocalcinosis/urolithiasis with elevated 1.25-dihydroxy-vitamin D3 (1.25-(OH)2-VitD3) (calcitriol) levels. In addition either activating or inactivating mutations of the calcium-sensing receptor gene lead either to hypocalcemic hypercalciuria or hypercalcemic hypocalciuria. In primary hyperoxaluria, a third gene defect was unravelled explaining most of the so far unclassified patients. In addition, these findings lead to new treatment options, which are currently evaluated in phase III studies.

Summary
Kidney stones are not the disease itself, but only its first symptom. The underlying disease has to be diagnosed in every pediatric patient with the first stone event.

Keywords
genetics, hypercalciuria, hyperoxaluria, hypocitraturia, nephrolithiasis

INTRODUCTION

A significant increase in incidence and prevalence of nephrolithiasis in adults has been observed. According to the number of children admitted or presented as outpatients because of stone disease, prevalence in children seems also to rise [1,2]. In pediatric patients, genetic and anatomical causes are the main risk factors (~75%) for the development of kidney stones [3]. Stones are usually only the first symptom of the underlying disease and do not represent the diagnosis [1,4]. However, environmental factors, such as eating habits, for example, excessive consumption of animal protein, so-called metabolic syndrome, are also found in children.

Urolithiasis describes stones found in the kidneys and urinary tract, nephrolithiasis means stones localized in the kidneys, nephrocalcinosis means calcium salt deposits in the tubules, the tubule epithelium and/or the interstitium [5]. Nephrocalcinosis is also described by the anatomical region of the deposit: medullary increase in echogenicity, divided into three degrees of severity, is distinguished from cortical (e.g. in acute cortical necrosis) and diffuse, generalized nephrocalcinosis [6]. Pathologists describe calcium phosphate deposits as nephrcalcinosis and calcium oxalate (CaOx) deposits as oxalosis.

Stones and nephrocalcinosis can occur alone, together or in succession [7]. In case nephrocalcinosis is suspected, smaller stones of less than 2 mm diameter should be excluded by computer tomography [8▪▪]. Urolithiasis and/or nephrocalcinosis are found in children of all ages. A sex-specific difference is no longer observed, as more female patients are diagnosed (metabolic syndrome, obesity), [9]. Nephrocalcinosis usually begins in the first months of life, is more common in tubulopathies or congenital metabolic diseases and, like stones, can also occur unilaterally (Table 1, Fig. 1a). Younger children have a higher proportion of stones located in the kidneys, whereas older patients often become

[a]Pediatric Nephrology, University Children's Hospital and [b]Institute of Experimental Immunology, University Hospital Bonn, Germany

Correspondence to Bernd Hoppe, MD, PhD, German Hyperoxaluria Center, Adenauerallee 119, D-53113 Bonn, Germany.
Tel: +49 228 287 33223; fax: +49 228 287 33184;
e-mail: info@hyperoxaluria.center.com

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KEY POINTS

- The kidney stone is not the disease itself, but only its first symptom.
- Every first kidney stone in children has to be evaluated carefully to disclose the underlying disease.
- The genetic background of the disease gives profound evidence of possible treatment options.
- Monogenic kidney stone diseases frequently lead to severe clinical outcome and even to end-stage renal failure.

clinically symptomatic with obstructive ureteral stones [10,11].

RISK FACTORS

Genetic or metabolic stone diseases lead to changes in serum and/or urine electrolytes and/or the urinary excretion of prolithogenic substances, and are therefore, biochemically detectable (Tables 1–6); [3,12]. All children with a first stone or nephrocalcinosis should receive an appropriate diagnostic evaluation including stone analysis (by infrared spectroscopy/X-ray diffraction). The urine analysis plays a central role (hematuria, leucocyturia, pH, sediment, urine culture, crystalluria, excretion of prolithogenic/antilithogenic factors) [7,13].

Patients with chronic renal insufficiency, single kidneys, multiple stones, severe or progressive nephrocalcinosis, abnormal family history, organ involvement outside the urogenital tract, malabsorption syndromes or proven genetic stone disease belong to the high-risk group for further stone events and progression to renal failure [3,7,8▪▪,12,14].

A classification according to the main findings of the biochemical urine analysis has proved to be practicable. If possible, 24 h urines should be used for analysis. Shorter collection phases should not be extrapolated to 24 h and creatinine ratios (depending on muscle mass among others) from spontaneous urine samples often lead to an overestimation of excretion. Abnormal urine parameters should be taken into account before genetic clarification, as this allows targeted diagnostics. Panel diagnostics can be particularly helpful in very young patients or in patients with already significant kidney impairment, which may have led to a levelling of the urinary excretion of lithogenic risk factors.

HYPERCALCIURIA

Hypercalciuria is (one of) the main lithogenic risk factor(s) (Table 1), [15]. Normal calcium excretion is less than 0.1 mmol/kg or less than 4 mg/kg body weight per day, severe hypercalciuria is defined at least 0.2 mmol/kg per day. Primary idiopathic hypercalciuria is the most common cause of calcium-containing kidney stones (Table 1); [7,16]. Previously, a renal was distinguished from an absorptive subtype, however, this classification has proved to be unsuitable [10–13]. Primary idiopathic hypercalciuria is often a multifactorial disease in which complex interaction of environmental and individual genetic factors, processes of intestinal absorption, renal excretion and reabsorption as well as resorption from bone lead to hypercalcemia/hypercalciuria [16]. Up to 50% of all patients have a positive family history (Table 1).

From this group of formerly idiopathic hypercalciuria, the three autosomal recessive hereditary forms of CYP24A1, SLC34A1 and SLC34A3-associated nephrocalcinosis/stone diseases with elevated 1.25-dihydroxy-vitamin D3 (calcitriol) levels should be highlighted. The loss of function of 24-hydroxylase leads to reduced degradation of active vitamin D (1.25-dihydroxy-vitamin D3 and 25-hydroxy-vitamin D3) and hypercalcemia with consecutive hypercalciuria. In this case, intoxication symptoms with hypercalcemia induced kidney failure may already occur under a low vitamin supplementation [17▪▪,18▪▪,19,20]. Stressors (infections, operations, pregnancy, vitamin D administration, etc.) can also lead to manifestation later in adulthood. A loss of function of the sodium phosphate cotransporter SLC34A1 (NaPi 2a) and SLC34A3 (NaPi 2c) leads to increased production of 1.25-dihydroxy-vitamin D3 via hypophosphatemia (such as alimentary phosphate deficiency). In contrast to the CYP24A1-associated form, a phosphate substitute is required to break through the symptoms. Probably also heterozygous sequence changes in these genes (in combination) can lead to (milder) phenotypes associated with hypercalciuria, although the data is currently not sufficient for a final evaluation.

Special mention should also be made of mutations in the Calcium Sensing Receptor (CASR), which depending on whether they are activating or inactivating, can lead to the opposite phenotypes of hypocalcemic hypercalciuria or hypercalcemic hypocalciuria [21]. As the number of genetic studies continues to increase, new monogenic diseases are likely to emerge from the spectrum of idiopathic hypercalciuria.

Many different clinical pictures lead secondary to hypercalcemia and hypercalciuria. Primary hyperparathyroidism (pHPT), the most common form of hypercalcemic hypercalciuria in adults, is rarely found in childhood (e.g. neonatal HPT triggered by CASR mutations) [22]. Also for the isolated

Table 1. Hypercalciuria

Monogenic diseases	
Gene, gene location, OMIM phenotype #, inheritance	Short description
Dent disease (Dent 1) [Gene: *CLCN five* (Xp11.23); OMIM: 300009; inheritance: XLR]	Fanconi syndrome and hypercalcuria, LMW-proteinuria, glucosuria, aminoaciduria, phosphaturia, NC, rachitis, progress to ESRD
Lowe syndrome (Dent 2) (Gene: *OCRL* (Xq26.1); OMIM: 309000 or 300555; inheritance: XLR)	Additionally: cataracts, mental retardation, muscular hypotonia, failure to thrive, nephrotic proteinuria, metabolic acidosis, often ESRD
Autosomal-dominant hypocalcemia hypercalciuria (ADHH) [Gene: *CASR* (3q21.1); OMIM: 615361; inhertiance: AD]	Activating mutations in *CASR*-gene with (asymptomatic) hypocalciemia, hypercalciuria, hyperphosphatemia, hypomagnesemia, PTH low/normal although hypocalcemic, calcifications in kidneys and CNS. Nota bene: Vitamin-D substitution can aggravate hypercalciuria, therefore, symptom-free patients should not be treated. Patients with classic features of Bartter syndrome (see BS) were reported and sometimes falsely described as BS type five (OMIM 601198). Inactivating mutations in *CASR* gene lead to familial hypocalciuric hypercalcemia (FHH; OMIM 145918)
Familial hypomagnesemia and hypercalciuria syndrome (FFHNC) [Gene: *CLDN 16* (3q28); OMIM 248250 Or *CLDN 19* (1p34.2); OMIM 248190; Inheritance: AR]	Hypercalciuria, hypomagnesemia and hypercalcemia, medullary NC plus variable ocular symptoms.
Infantil idiopathic hypercalcemia (IHH) Gene: CYP24A1; OMIM: 277440; inheritance: AR)	Hypercalcemia, hypercalciuria, failure to thrive, chronic kidney disease, NC, reduced metabolism of Calcitriol → increased 1.25-(OH)2-D3-levels. Vitamin D sensitivity.
Bartter syndrome (BS) Type one (Gene: *SLC12A1* (15q21.1); OMIM: 601678; inheritance: AR Type two (Gene: *KCNJ1* (11q24.3); OMIM: 241200; inheritance: AR) Type three (Gene: *CLCNKB* (1p36.13); OMIM: 607364; inheritance: AR) Type 4a (Gene: *BSND* (1p32.3); OMIM: 602522; inheritance: AR) Type five (Gene: *MAGED2* (Xp11.21); OMIM: 300971; inheritance: XLR)	Hypercalciuria and NC are mostly found in BS type one and two as well as in type 5, rarely in BS Type three and 4. Classic and antenatal BS possible Classic BS: Hypokalemic metabolic alkalosis, renal salt wasting, hypercalciuria, increased renin, secondary hyperaldosteronism, NC, progress to CKD Antenatal BS: polyhydramnion, renal salt wasting, prematurity, hypecalciuria and NC Classic and antenatal BS possible. Hyperkalemia at birth. Manifestation frequently later as in types 1/2. Variable expression; antenatal BS with hypercalciuria and NC only in 20% of cases. BS with deafness, very minor hypercalciuria and NC Polyhydramnion and massive antenatal or transient BS with sometimes extreme hypercalciuria, NC
Infantile hypercalcemia 2 (HCINF2) (Gene: *SLC34A1* (5q35.3); OMIM: 616963; Inheritance: AR)	Hypercalemia, hypercalciuria with nephrocalcinosis and hypophosphatemia and lowish PTH levels and increased 1.25(OH)2D3 levels. Amelioration under phosphate substitution.
familial hypophosphatemic rickets with hypercalciuria (HHRH) (Gene: SLC34A3; OMIM: 241530; inheritance: AR)	Excessive urinary phosphate excretion, hypophosphatemia, hypercalciuria without hypercalcemia, massive rickets, uroliothiasis. Lowish to normal PTH Werte and increased 1.25(OH)2D3 levels.
Pseudohyperaldosteronism type two PHA2 PHA2B (Gene: *WNK4* (17q21.2; OMIM: 614491; inheritance: AD)	Hyperkaliemia, metabolic acidosis based on renal ammonium excretion, arterial hypertension Nephrolithiasis as complication of hypercalciuria. Treatment with low dose hydrochlorothiazide corrects blood pressure, hyperkalemia and hyperkalciuria.
Complex reasons	
Idiopathic hypercalciuria absorptive HC Renal HC Resorptive (bone) HC	Most frequent form of normocalcemic hypercalciuria PTH^{-} PTH big overlapping PTH
idiopathic infantile hypercalcemia (IIH)	Hypercalcemia and hypercalcuria, nephrocalcinosis, growth retardation, muskuläre hypotonia, lethargia. Manifestation in adults with less severe phenotype possible.

Table 1 (*Continued*)

Monogenic diseases	
Hypercalcemic hypercalcuria	Hyperparathyreoidism, tumor/bone metastasis, hypervitaminosis D/A, hypophosphatasia, immobilization, hyperthyreoidism, sarcoidosis, adrenal-insufficiency, corticosteroid exzess
Normocalcemic hypercalciuria	RTA (e.g. post chemotherapy), furosemide, hyperalimentation, juvenile rheumatoid arthritis, hypophosphatemia, familial hypomagnesemia, increased sodium intake
In systemic diseases, e.g. Tyrosinemia type 1 Wilson disease Glycogen storage disease type 1a Williams Beuren syndrome (WBS) 1,5–1,8 Mb Deletion auf 7q11.23 Trisomie 21	Variable disease courses Syndromal form of infantile hypercalcemia: neonatal hypercalcemia with NC, facial dysmorphism, inborn heart diseases, social interaction problems, hypertension
Granulomatous diseases (lymphoma, sarcoidosis)	

ESRD, end-stage renal disease; LMW, low-molecular-weight proteinuria; PTH, parathyroid hormone; NC, nephrocalcinosis; RTA, renal tubular acidosis.

pHPT genetic causes have been described (CDC73, GCM2 and CASR) [23,24], but for the majority of patients with isolated pHPT, no genetic cause has been currently found.

In addition to hypervitaminosis D, excessive vitamin A intake and chronic potassium deficiency lead to hypercalciuria. Other secondary reasons for hypercalciuria are treatment with loop diuretics, dexamethasone or adrenocorticotropin hormone (ACTH). Hypercalciuria is also found in various syndromes triggered by the pathogenesis of the underlying disease (Table 1). These include hyperthyroidism and hypothyroidism, Cushing's syndrome, adrenocortical insufficiency, malignancies and bone metastases, long-term ventilation, prolonged immobilization, persistent metabolic acidosis (and reduced bone density), and long-term parenteral nutrition. Other important entities with hypercalciuria are listed in Table 1 [7,10,13].

Preventive management is primarily based on the reduction of the concentration of lithogenic or increased excretion of antilithogenic parameters in urine. The highest possible fluid intake (>1.5–2 l/1.73 m^2 body surface distributed over the day) must be observed regardless of the underlying disease. Without such hydration, drug treatment makes no sense! Nutritional recommendations should be made carefully, dietary mistakes are quickly made. A reduced calcium intake leads to an even riskier increase in oxalate excretion, as less oxalate is bound in the intestinal tract, and thus absorption increases. A low oxalate diet should also only be recommended with caution; many patients exaggerate the dietary changes [25].

Crystallization inhibitors, mostly citrate or magnesium preparations, increase the solubility product of urine. Citrate is metabolized to bicarbonate in the liver leading to a higher urine pH, to reduced tubular citrate reabsorption, thus to an improved citrate excretion [8▪▪,26]. Citrate binds to calcium and less calcium is available for binding to oxalate or phosphate! In addition, the calcium excretion can be reduced by about 30%. The recommended daily dose is 0.1–0.2 g/kg body weight (0.3–0.6 mmol/kg) as sodium potassium, or best potassium citrate preparation [7]. In patients with distal renal tubular acidosis (dRTA), the dose is adjusted to the serum pH and applied as potassium citrate. The urine pH value should be measured regularly to avoid excessive pH values (>7), which increase the risk of calcium phosphate precipitation [27].

Thiazide preparations are used for strongly increased calcium excretion (>8 mg/kg/day). They reduce calcium excretion by increasing calcium uptake in the distal tubule and by stimulating

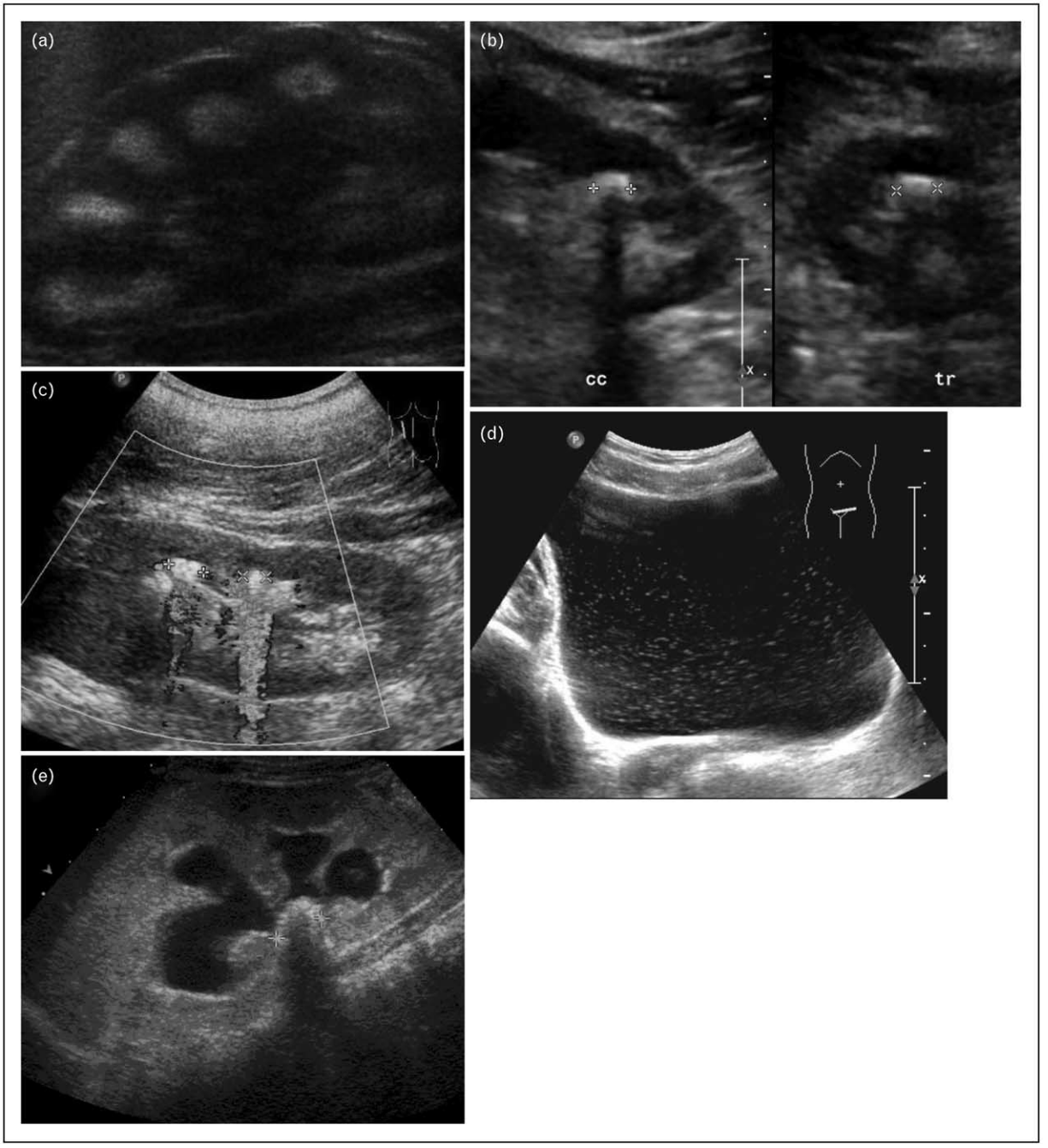

FIGURE 1. Kidney stones in a patient with primary hyperoxaluria type 1 (a), as well as type 3 (b) here with twinkling sign. Calcium-oxalate crystalluria as depicted in bladder ultrasound of a patient with primary hyperoxaluria type I (c). Medullary nephrocalcinosis in familial hypomagnesemia, hypercalciuria and nephrocalcinosis syndrome (FHHNC) (d) and obstructive kidney stone in a patient with cystinuria (e).

calcium reabsorption in the proximal tubule by volume control [28,29]. Especially in children with a negative calcium balance and reduced bone density, therapy (0.5–1 mg/kg; hydrochlorothiazide) is recommended. In order to avoid side effects, such as hypokalemia, hydrochlorothiazide is often combined with a potassium-saving diuretic, such as amiloride.

HYPEROXALURIA

In hyperoxaluria, primary and secondary causes are distinguished: all three currently known forms of primary hyperoxaluria are rare, autosomal recessive inherited diseases of the hepatic glyoxylate metabolism and lead (in normal renal function) to a significantly increased excretion of the metabolic

Table 2. Hyperoxaluria

Monogenic diseases	
Primary hyperoxaluria type 1 (Gene: *AGXT* (2q37.3); OMIM: 259900; inheritance: AR); >80% of all PH patients	Increased endogenous oxalate production in the liver. In urine: elevated oxalate + glycolate, in plasma: oxalate and glycolate (in CKD) In infantile type: diffuse NC ('white kidney') and rapid kidney failure Childhood: rec. urolithiasis, kidney failure variable between childhood and fifth to sixth decade of life Vitamin B6 therapy leads to reduction in endogenous oxalate production in specific mutation and thus to decrease of urinary oxalate excretion Combined liver/kidney or kidney after liver transplantation as only curative measure in CKD
Primary hyperoxaluria type 2 [gene: *GRHPR* (9p13.2); OMIM: 260000; inheritance: AR]; <10% of all PH patients	Increased endogenous oxalate production in the liver. In urine: elevated oxalate + L-Glycerate, in plasma: oxalate In contrary to PH I mostly moderate phenotype, however, CKD in approximately 50% of patients, in about 25% ESRD Isolated kidney transplantation in ESRD, in some cases, however, combined transplantation necessary
Primary hyperoxaluria type 3 [Gene: *HOGA1* (10q24.2); OMIM: 613616; inheritance: AR]; >10% of all PH patients	Increased endogenous oxalate production in the liver. In urine: elevated oxalate + hydroxy-oxo-glutarate (HOG) or -glutamate (DHG), (+ calcium + uric acid), in plasma: oxalate and HOG extreme rate of urolithisis already in infancy and early childhood, multiple stone removal procedures, amelioration of symptoms in adulthood, CKD possible, but up until now no true ESRD reported
Complex reasons	
Enteral/dietetic	Inflammatory bowel syndromes (Crohn disease), malabsorption, for example, in cystic fibrosis, post bowel resection/short bowel syndrome, fat-malabsorption, dietetic calcium restriction, lack of oxalate degrading intestinal bacteria (*Oxalobacter formigenes*)
Intoxication/drugs	Vitamin C overdosage, ethylene glycol-intoxication

CKD, chronic kidney disease; ESRD, end-stage renal disease.

end product oxalate (>1 mmol/1.73 m^2/day, norm value <0.5 mmol/1.73 m^2/day) (Table 2); [30,31]. The most common subtype, primary hyperoxaluria type I (PH I), is caused by a low, completely absent, or mitochondrial mislocalized activity of liver-specific peroxisomal alanine glyoxylate aminotransferase (AGT) [32]. The prevalence in Central Europe is about 1–3 patients per 10^6 population (Table 2) [33], genomic, population-based studies suggest a much higher prevalence (1 : 58000), and thus a significant number of undiagnosed patients [34]. Hyperoxaluria leads to the formation of kidney stones and/or medullary, often diffuse nephrocalcinosis (Fig. 1 b–d). With progressive renal insufficiency triggered by oxalate-induced chronic inflammation processes in the kidney, CaOx

Table 3. Hypocitraturia

Monogenic diseases	
Renal tubular acidosis Distal RTA, type 1 (Gene: *SLC4A1* (17q21.31; OMIM: 179800; inheritance: AD) Proximal RTA, type 2 (Gene: *SLC4A4* (4q13.3); OMIM: 604278; inheritance: AR) Mixed RTA, type 3 (Gene: *SLC4A4*; OMIM: 603345; inheritance: AR)	mit verminderter H+-Exkretionsfähigkeit und deutlicher Hypocitraturie und NC Bikarbonatverlust über Urin, weniger ausgeprägter Hypozitraturie sowie milderer NC/ nephrolithiasis Urin kann nicht angesäuert werden aufgrund renalen Bicarbonat-Verlustes, Osteoporose, Verkalkungen des Gehirns, Wachstumsarest, mentale Retardierung, Taubheit
Complex reasons	
Prematurity	In preterm infants <1500 g and <30 weeks gestation age, NC remains in 15–50% of cases, search for ongoing reasons
Patients with immunosuppressive medication (e.g. post transplantation)	Hypocitraturia, especially in calcineurin inhibitor treatment, tubulus damage posttransplantation
Dietary	Increased intake of animal protein

Table 4. Defects in purine metabolism

Monogenic diseases	
APRT deficiency [Gene: *APRT* (16q24.3); OMIM: 614723; inheritance: AR]	Accumulation of nonsoluble 2,8-dihydroxy-adenine, nephrolithiasis, CKD. Characteristic brownish crystals in urine sediment
Xanthinuria [Gene: *XDH* (2p23.1); OMIM: 278300; inheritance: AR]	Low uric acid in serum and urine, xanthinuria, nephrolithiasis, urine sediment with orange brown crystals
Urate-transporter one defect [Gene: *SLC22A12* (11q13.1); OMIM: 220150; inheritance: AR]	Hypouricemia, risk of acute kidney failure after sports
Lesch-Nyhan- syndrome [Gene: *HPRT1* (Xq26.2-q26.3); OMIM: 300322; inheritance: XLR]	Normal at birth, but then progressive mental retardation, gout, selfdestruction, hyperuricosuria with progressive NC
Partial HPRT deficiency [Gene: *HPRT1*; OMIM: 300323; inheritance: XLR]	Hyperuricosuria with a broad clinical spectrum
Glycogenosis type 1a [Gene: G6PC (17q21.31); OMIM: 232200; inheritance: AR]	Episodically hypoglycemia, hyperuricosuria and hypercalciemia, hypocitraturia, Fanconi syndrome, NC, progress to CKD
Complex reasons	
Tumor-lysis syndrome	Can lead to hyperuricosuria and consecutively to NC

CKD, chronic kidney disease; NC, nephrocalcinosis.

crystals are deposited systemically in many tissues (= systemic oxalosis) with possible lethal consequences [31,35]. The clinical spectrum of the disease is very heterogeneous and ranges from infantile oxalosis with failure to thrive and early end-stage renal insufficiency (ESRD) to asymptomatic/oligosymptomatic progressions, sometimes into high adulthood. The probability of developing ESRD in the course of life is very high, therefore, early diagnosis and initiation of therapy are mandatory [31,34,35]. Unfortunately, the diagnosis is often made very late only at complications of systemic oxalosis under dialysis treatment, or in case of rapid graft loss after isolated kidney transplantation [35].

Primary hyperoxaluria type II (PH II) accounts for approximately 10% of all primary hyperoxaluria diseases. PH II is characterized by a deficiency of glyoxylate reductase/hydroxypyruvate reductase (GRHPR), which leads to an increased urinary excretion of oxalate as well as L-glyceric acid [31,36]. The clinical symptoms are comparable with those of PH I, but said to be less problematic, nevertheless greater than 50% of patients experience CKD [35].

Table 5. Further diseases

Monogenic diseases	
Cystinuria [Gene: *SLC3A1* (2p21) OMIM220100 AR and *SLC7A9* (19q13.11); OMIM: 220100; inheritance: AR/AD]	Type I, type II, as well as mixed type High urinary cystine excretion, as well as increased excretion of ornithine, arginine and lysine, hexagonal cystine crystals in urine sediment, kidney stones Inheritance remains complex, as frequently typical aspects of autosomal–recessive inheritance are found, however, also heterozygous carriers can show elevated urinary cystine excretion
Complex reasons	
Urinary tract infections	Infectious stones, mostly because of *Proteus mirabilis* infections
Congenital anomalies of kidney and urinary tract	Obstruction, also in ADPKD (uric acid stones), as well as in megacalicosis
Medication	Substances, which frequently form nidus for stones or form stones itself: sulfonamide, ceftriaxon, amoxicillin, magnesium-silicate (antazida), allopurinol, indinavir, triamterene

Causes of nephrocalcinosis and nephrolithiasis in children. AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; BS, Bartter syndrome; CKD, chronic kidney disease; ESRD, end-stage renal disease; HC, hypercalciuria; LMW, low-molecular-weight proteinuria; NC, nephrocalcinosis; PH, primary hyperoxaluria; PTH, parathyroid hormone; RTA, renal tubular acidosis; UL, urolithiasis; XLR, x-linked recessive.

Table 6. Normal values for lithogenic or inhibitory substances in spontaneous urine, or 24 h collecting urine[a]

Plasma		
Oxalate	All age groups	<6.3 ± 1.1 μmol/l (free oxalate)
Glycolate	All age groups	<7.9 ± 2.4 μmol/l
Urinary excretion of soluble in 24-h urine samples:		
Oxalate	All age groups	<0.50 mmol/1.73 m^2 BSA/24 h <45 mg/1.73 m^2 BSA/24 h
Glycolate	All age groups	<0.50 mmol/1.73 m^2 BSA/24 h <45 mg/1.73 m^2/24 h
L-glycerate	All age groups	<5 μmol/l
Calcium	All age groups	<0.1 mmol/kg BW/24 h <4 mg/kg BW/24 h
Citrate	All age groups: Boys/men	>1.9 mmol/1.73 m^2 BSA/24 h >365 mg/1.73 m^2 BSA/24 h >0.61 mg/kg BW[a]/24 h
	Girls/women	>1.6 mmol/1.73 m^2 BSA/24 h >310 mg/1.73 m^2 BSA/24 h >0.47 mg/kg BW[a]/24 h
Cystine	<10 years	<55 μmol/1.73 m^2 BSA/24 h <13 mg/1.73 m^2 BSA/24 h
	>10 years	<200 μmol/1.73 m^2 BSA/24 h <48 mg/1.73 m^2 BSA/24 h
Uric acid	<1 years	<70 μmol/kg BW[a]/24 h <13 mg/kg BW[a]/24 h
	1–5 years	<65 μmol/kg BW[a]/24 h
	>5 years	<11 mg/kg BW[a]/24 h <55 μmol/kg BW[a]/24 h <9 mg/kg BW[a]/24 h
Soluble/creatinine ratio (spot urine samples)		
Calcium/creatinine	<12 months 1–3 years 3–5 years 5–7 years >7 years	<2.2 mol/mol, <0.8 g/g <1.5 mol/mol, <0.53 g/g <1.1 mol/mol, <0.4 g/g <0.8 mol/mol, <0.3 g/g <0.6 mol/mol, <0.21 g/g
Citrate/creatinine	0–5 years >5 years	>0.12–0.25 mol/mol, >0.2–0.42 g/g >0.08–0.15 mol/mol, >0.14–0.25 g/g
Oxalate/creatinine	0–6 months 7–24 months 2–5 years 5–14 years >14 years	<325–360 mmol/mol, <260–288 mg/g <132–174 mmol/mol, <110–139 mg/g <98–101 mmol/mol, <80–81 mg/g <70–82 mmol/mol, <60–65 mg/g <40 mmol/mol, <32 mg/g
Glycolate/creatinine	0–6 months 7–24 months 2–5 years 5–14 years >14 years	<363–425 mmol/mol <245–293 mmol/mol <191–229 mmol/mol <166–186 mmol/mol <99–125 mmol/mol
L-glycerate/creatinine	0–6 months 7–24 months 2–5 years 5–14 years >14 years	<14–205 mmol/mol <14–205 mmol/mol <14–205 mmol/mol <23–138 mmol/mol <138 mmol/mol
Cystine/creatinine	<1 months 1–6 months >6 months	<85 mmol/mol, <180 mg/g <53 mmol/mol, <112 mg/g <18 mmol/mol, <38 mg/g
Urate/creatinine	<12 months 1–3 years 3–5 years 5–10 years >10 years	<1.5 mol/mol, <2.2 g/g <1.3 mol/mol, <1.9 g/g <1.0 mol/mol, <1.5 g/g <0.6 mol/mol, <0.9 g/g <0.4 mol/mol, <0.6 g/g

Urine collection should be repeated after stone removal or surgery because stones may alter the excretion of lithogenic substances in situ. Before interpretation of the data, the correctness of the collection should be checked by determination of creatinine excretion (2 mg/kg ± 0.8 mg). BSA, body surface area; BW, body weight.

[a]Urine samples should be prepared either with thymol 5% in isopropanol, or 2 N HCl before collection for preservation.

Primary hyperoxaluria type III (PH III) is caused by a defect in mitochondrial 4-hydroxy-2-oxoglutarate aldolase one (HOGA1) [37,38]. Next to hyperoxaluria, hydroxy-oxo-glutarate (HOG) and glutamate excretions are elevated. It is probably the second most common subtype and next to hyperoxaluria, calcium and sometimes uric acid excretion are increased. The clinic usually manifests early in infancy with recurrent urolithiasis, and repeated stone removal procedures are performed. Although hyperoxaluria persists, patients show a silencing of symptoms (stones) [38,39], however, long-term follow-up is currently not available in registries [39]. Nevertheless, PH III patients with CKD were also reported, and both frequent stone removal procedures, as well as hyperoxaluria *per se*, like in PH I/II, were said to be the culprit [38,39].

Patients with PH I are treated with supraphysiological doses of pyridoxal-phosphate (5 - 20 mg/kg/day), the co-factor of the defective enzyme AGT [40]. The treatment helps one-third of patients, mostly those with mistargeting mutations, to reduce or even normalize urinary oxalate excretion. The most important side effect is polyneuropathy, which is why serum B6 levels must be measured regularly [40]. PH II and PH III are still only treated symptomatically like other patients with calcium oxalate stones. Patients with PH (I) and ESRD should be transplanted as soon as possible, as no form of renal replacement therapy allows adequate oxalate elimination [41]. Depending on the respective systemic oxalate deposition, either a combined liver/kidney transplantation (less systemic oxalosis) or a kidney after liver transplantation (severe oxalosis), is performed [42]. In PH II, the enzyme defect is not liver-specific, which is why isolated kidney transplantation is performed. However, PH II patients have also been described who required a combined transplant [43,44]. Only one patient with PH III has so far been reported with ESRD [45].

HYPOCITRATURIA

Citrate has antilithogenic effects by complexing free calcium in the urine and reducing the growth of CaOx crystals as well as their attachment to the epithelium. Hypocitraturia is a little-noticed risk parameter for the development of calcium-containing stones and nephrocalcinosis [46]. In certain regions of the world, for example in Turkey, and in risk populations, like premature babies, hypocitraturia is even the most frequent risk factor of nephrolithiasis [47]. It is characteristic of d-RTA, in mild or latent metabolic acidosis, after kidney transplantation, in hypokalemia and in patients with malabsorption syndromes, or secondary to low intestinal alkaline absorption (Table 3) [27].

CYSTINURIA

With an average prevalence of $\sim 1:7000$, autosomal recessive cystinuria is one of the most common genetic stone diseases and about 10% of all kidney stones in children are cystine stones (Table 5, Fig. 1e). Biallelic mutations in the *SLC3A1* and *SLC7A9* gene are found in approximately equal frequency. More rarely, heterozygous changes in the *SLC7A9* gene lead to a dominant form with incomplete penetrance and moderately increased urinary excretion of cystine, but an increased risk of nephrolithiasis compared with the general population [48]. Both genes are expressed in the proximal tubule of the kidney and code for subunits necessary for the transepithelial transport of the dibasic amino acids cystine, ornithine, lysine and arginine (COLA). A deficiency leads to the accumulation of these amino acids in urine with subsequent precipitation and formation of cystine crystals (typical hexagonal form) or stones, as the solubility of cystine is poor (from approximately 300 mg/l at pH 7). More than 50% of patients develop bilateral UL and a frequently recurrent stone disease [48]. The risk for ESRD exists especially after unilateral nephrectomy and frequent surgical interventions.

As cystine is best soluble at a urine pH >8, urine alkalinization is the main goal of pharmacotherapy. Furthermore, chelating drugs (D-penicillamine and alpha-mercaptopropionylglycine, MPG) are administered, which cleave the disulfide bond of cysteine, and thus lead to the conversion to cysteine, a 50 times more soluble homodimer of cystine [49]. The spectrum of side effects, after all rash, arthralgia, thrombocytopenia, polymyositis and nephritic syndrome occur in 20–50% of patients, naturally limits the application. It is important to know that D-penicillamine reduces serum levels of vitamin B6, which must therefore be supplemented. The ACE inhibitor Captopril has a similar effect as MPG, but significantly fewer side effects [50]. High-dose ascorbic acid also reduces cystine to cysteine, but the effectiveness of the treatment is not clear and it could lead to increased endogenous oxalate production through the breakdown of vitamin C, and thus to hyperoxaluria. A methionine-reduced diet is important in cystinuria because it is metabolized to cystine in the body [51,52].

DEFECTS IN PURINE METABOLISM

Stones composed of uric acid, a metabolic end product of purine metabolism, are rare in childhood

(Table 4). As humans lack the enzyme uricase, uric acid salts cannot be further metabolized to the more soluble allantoin. Hyperuricosuria is found in purine-rich diets, myeloproliferative diseases, tumor lysis syndrome, or enzymatic defects. Many medications, for example, probenicid, high doses of salicylates or contrast agents also increase urinary uric acid excretion. An acid urine pH or a low urine volume are then the strongest risk parameters.

There are two known rare congenital defects of purine metabolism: hypoxanthine phosphoribosyltransferase (HPRT), which leads to hyperuricemia and hyperuricosuria and adenine phosphoribosyltransferase deficiency (APRT), which leads to accumulation of the poorly soluble adenine degradation product 2,8-dihydroxyadenine [53]. If untreated, APRT deficiency is associated with a high risk of ESRD, which can also lead to loss of the transplant kidney. Therapy with allopurinol is effective.

In patients with purine stones (uric acid, 2,8-dihydroxyadenine, xanthine), in addition to a high fluid intake, urine alkalinization with pH values >6.5 must be maintained. A high intake of animal protein should be avoided. If hyperuricosuria persists, inhibitors of xanthine oxidase, for example, allopurinol, are given. Of course, careful dosing is necessary, as secondary xanthinuria may occur [54]. Xanthine, in contrast to uric acid, is not readily soluble in alkaline urine, so alkali citrate therapy would not be useful. In patients with 2,8-dihydroxyadenine stones, urinary dilution and the administration of xanthine oxidase inhibitors in addition to dietary restrictions (adenine, purine) are the only therapeutic measures [53,54].

CONCLUSION

The stone is not the disease itself, it is only its first symptom. The metabolic and/or genetic reason for urolithiasis/nephrocalcinosis has to be found as early as possible to start treatment and to avoid problematic follow-up, being it repeated clinical events, multiple stone removing procedures, or even end-stage renal disease.

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None for C.H.. B.H. reports has had consultant contracts with Alnylam, Allena, Alexion and Oxthera AB over the last years, he is currently affiliated to Dicerna pharmaceuticals, Cambridge, USA.

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