Understanding Rare Kidney Stone Diseases: A Review

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Rare kidney stone diseases typically present with nephrolithiasis or nephrocalcinosis in childhood or adolescence. Affected individuals might face kidney injury and even kidney failure related to associated complications. Screening blood and urine tests recommended for patients with nephrolithiasis and/or nephrocalcinosis help guide further evaluation, and the increased availability and decreased costs of genetic testing can facilitate the diagnosis of hereditary stone conditions. Genetic testing should be considered when there are clinical clues of an increased likelihood of an inherited condition such as consanguinity, nephrolithiasis in young children, nephrolithiasis in multiple family members, repeated episodes of nephrolithiasis, or kidney failure with nephrolithiasis or nephrocalcinosis. Adult and pediatric nephrologists and urologists should have a basic understanding of monogenic rare kidney stone diseases and their associated diagnoses, treatments, and complications. In many disorders, early detection allows for the initiation of tailored therapies that may alter the natural history of the disease, preserve kidney function, and modify extrarenal manifestations.

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Nephrologists use the term "rare kidney stone diseases" for inherited conditions such as primary hyperoxaluria (PH), Dent disease, cystinuria, and adenine phosphoribosyltransferase (APRT) deficiency. These conditions often present during childhood or adolescence with nephrolithiasis or nephrocalcinosis, and affected individuals may face considerable risk of kidney failure related to metabolic perturbations altering urinary mineral salt excretion.[1] More recently, inherited variations in the kidney homeostasis of calcium, phosphate, uric acid, and magnesium have been found to underlie other kidney stone conditions or interplay with monogenic variants identified in rare kidney stone diseases.

Because of the low incidence and phenotypic variability, the diagnosis of a rare kidney stone disease is often delayed, and an actual or perceived lack of effective therapy decreases any sense of diagnostic urgency. In fact, the population prevalence of gene variants underlying rare kidney stone diseases significantly exceeds the reported clinical prevalence of these conditions, underscoring that barriers to diagnosis exist.[2,3] Moreover, systematic genetic testing in referral stone clinics has led to estimates of the incidence of monogenic disorders ranging from 11.4% in adults to 29% in children, suggesting that these conditions are highly prevalent in specific patient populations.[4,5] Given the broader availability of genetic testing, definitive diagnosis of rare kidney stone diseases is now possible. As exemplified by advances in PH treatment, new therapeutic options render the early and accurate diagnosis of stone disorders even more important to alter disease course, preserve kidney function, and address extrarenal manifestations when applicable.

Consequently, clinicians frequently evaluating patients with kidney stones need to be cognizant of the clinical hallmarks of rare kidney stone diseases so appropriate genetic testing ensues (Box 1). Similarly, there needs to be familiarity with results from screening blood and urine tests recommended in all patients with nephrolithiasis or nephrocalcinosis that increase the index of suspicion for the diagnosis of one of these conditions. A list of key genes, rare kidney stone disease diagnoses, and associated findings are summarized in Table 1.

In the next sections, the most clinically relevant rare kidney stone diseases will be reviewed with an emphasis on pertinent pathophysiology, clinical manifestations, natural history of the disease, and recommended treatment or management to reduce the risk of disease-related sequelae.

Key Rare Kidney Stone Diseases

PH

PH, a family of disorders of hepatic glyoxylate metabolism, results in hyperoxaluria and risks of nephrolithiasis, nephrocalcinosis, systemic oxalate deposition, and progressive kidney failure. PH stems from variants in one of 3 genes and is inherited in an autosomal-recessive fashion. The 3 types of PH are also differentiated by changes in urinary or plasma levels of oxalate and specific metabolic precursors as listed in Table 1.[6]

A recent consensus algorithm summarizes the best diagnostic practice for PH, including critical reliance on a laboratory with expertise measuring urinary and plasma oxalate levels.[7] In children, 24-hour urine oxalate excretion must be corrected to body surface area for interpretation, and, in the absence of risk factors for secondary hyperoxaluria, daily urinary oxalate excretion >0.5 mmol (45 mg)/1.73 m^2 is consistent with PH. When a 24-hour urine collection cannot be obtained, spot levels of urinary oxalate and its metabolites can be sent from a single urine sample and compared versus age-appropriate normal ranges.[7,8] When increased urine or plasma oxalate levels have been found, genetic testing for PH variants confirms a diagnosis. The risk of kidney failure is highest and occurs earlier in life in PH type 1 (PH1) than in PH2. Reported cases of kidney failure in PH3 have been rare, but limited

Box 1. Clinical Presentation That Should Raise Suspicion for the Presence of Rare Kidney Stone Diseases

- Kidney stones or nephrocalcinosis detected in infancy, childhood, or adolescence
- Multifocal kidney stone disease
- Recurrent urolithiasis (ie, more than one episode)
- Progressive chronic kidney disease/end-stage kidney disease of unknown cause
- Family history of stone disease, especially if presentation occurs in infancy, childhood, or adolescence
- Consanguinity with stone disease

longitudinal data from patients with genetically confirmed PH3 limits a definitive risk assessment.[9-12]

Treatment for PH includes high fluid intake and crystallization inhibitors such as potassium citrate or bicarbonate. For some specific PH1 variants, pyridoxine decreases oxalate production significantly, and empiric pyridoxine therapy is therefore recommended for all with suspected PH1 while awaiting genetic confirmation of the diagnosis.

Two subcutaneously administered RNA interference (RNAi) therapies for PH1 have attained regulatory approval in the United States and Europe. Lumasiran (Oxlumo), targeting glycolate oxidase, reduces urine and plasma oxalate in individuals of all ages with normal kidney function, chronic kidney disease (CKD), or dialysis dependency.[13-16] Nedosiran (Rivfloza), targeting lactate dehydrogenase, has been shown to lower urinary oxalate levels in PH1 in individuals >9 years of age with a glomerular filtration rate (GFR) of ≥30 mL/min/1.73 m^2, and studies are ongoing in younger children, in advanced CKD, and in persons who are dialysis-dependent.[17-19] Early RNAi therapy outcomes data suggest that its use may mitigate GFR loss in PH1, with the hope that such therapy will prevent progression to kidney failure. Studies that assess RNAi efficacy in PH2 or PH3 are ongoing.[20]

As GFR decreases in PH, kidney oxalate clearance decreases, and plasma oxalate levels subsequently increase. Plasma oxalate levels >30-45 μmol/L, occurring typically with a GFR <30 mL/min/1.73 m^2, result in systemic oxalate deposition, most markedly in the eye, bone and bone marrow, heart, skin, and nerves. Infants with PH1 are at particularly high risk of kidney failure in the first months of life (ie, infantile oxalosis) and often manifest failure to thrive.

Regardless of residual GFR, intensive hemodialysis 6-7 times weekly is indicated in PH1 when plasma oxalate levels are >30-45 μmol/L to attenuate systemic oxalate deposition. Peritoneal dialysis does not clear sufficient oxalate and is not the preferred modality for kidney replacement therapy in PH1 unless hemodialysis is not available. Dialysis is often a bridge to transplant. Consensus guidelines for the management of kidney failure in PH are available.[7,8]

Except in patients with pyridoxine-sensitive PH1 variant, isolated kidney transplant used to be avoided in patients with PH1 with kidney failure because of the inevitable failure of the allograft from rapid oxalate deposition.[21] Because the primary pathologic processes in PH stem from anomalies in hepatic oxalate metabolism, kidney transplant alone does not address the etiology of the hyperoxaluria and does not address the excess oxalate production in the pathophysiology of kidney failure. Liver/kidney transplant performed in a combined or sequential fashion was the mainstay of PH1 transplant treatment for several decades, with the transplanted liver correcting the metabolic disorder. With the advent of RNAi therapy that abates pathologic hyperoxaluria, isolated kidney transplant can be considered, with the expectation that RNAi therapy will continue on a long-term basis after transplant.[22] In patients without reliable access to such effective oxalate-lowering therapies, liver/kidney transplant remains the recommended treatment.[6]

Cystinuria

Cystinuria, an autosomal-recessive disorder stemming from variants in SLC3A1 or SLC7A9, results in decreased proximal tubular reabsorption and excessive urinary excretion of the dibasic amino acids cystine, ornithine, lysine, and arginine. SLC3A1 encodes the heavy subunit of the cystine transporter rBAT, whereas SLC7A9 encodes the light subunit. The cystine transporter is a heterodimer, and subunits are needed for the transport system to function. Of the dibasic amino acids, only excessive urinary cystine results in nephrolithiasis given its very limited solubility (<250 mg/L at urine pH <7).[23-25]

Cystinuria typically presents with nephrolithiasis, and stones may often be quite large. Most commonly, patients are diagnosed as adolescents or adults as a result of recurrent stones, but infants and small children may also present with cystine stones, especially if at-risk children experience a dehydrating illness or urinary tract infection. Because the cystine transporters are also present in the intestine, rare patients may be referred for findings of a hyperechoic colon on prenatal imaging, with confirmation of potential cystinuria occurring after birth.[26]

Cystine crystals in the urine (Fig 1) are pathognomonic of cystinuria, and a cystine urinary screen is available as part of some 24-hour urine stone profiles. Quantification of random urine amino acids can also confirm the diagnosis. Genetic testing is typically reserved for patients without readily confirmable cystinuria. Identification of the specific cystinuria genotype does not change the approach to treatment and follow-up because the clinical phenotype is similar with either variant.[24]

Treatment of cystinuria is grounded on hyperhydration, with the goal to maintain cystine solubility <250 mg/L. Reducing dietary sodium intake and resulting urinary sodium excretion also decreases cystine excretion. High-protein diets should be avoided to moderate methionine

Table 1. Important Genes in Rare Kidney Stone Diseases

Gene	Disease	Inheritance	Associated Findings
AGXT	Primary hyperoxaluria type 1	AR	Increased urine and/or plasma oxalate, increased urine glycolate in many cases
GRHPR	Primary hyperoxaluria type 2	AR	Increased urine and/or plasma oxalate, increased urine L-glycerate
HOGA1	Primary hyperoxaluria type 3	AR	Increased urine and/or plasma oxalate, increased 4-hydroxy-2-oxoglutarate
APRT	Adenine phosphoribosyltransferase deficiency	AR	2,8-DHA crystals; orange/brown staining in diaper
ALPL	Hypophosphatasia; low alkaline phosphatase; bone disease	AD/AR	Low alkaline phosphatase
CLCN5	Dent disease	XR	Tubular proteinuria, hypercalciuria (with/without aminoaciduria, hypophosphatemia, acidosis)
OCRL	Lowe syndrome/Dent disease 2	XR	Tubular proteinuria, hypercalciuria (with/without aminoaciduria, hypophosphatemia, acidosis)
CLDN16	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	AR	Hypomagnesemia hypercalciuria
CLDN19	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis; ocular abnormalities	AR	Hypomagnesemia, hypercalciuria
CYP24A1	Vit D 24 hydroxylase deficiency, infantile hypercalcemia	AR	Hypercalcemia, increased 1,25-dihydroxyvitamin D, abnormal 1,25–to–24,25 vitamin D ratio, suppressed PTH
SLC3A1	Cystinuria	AR	Hexagonal cystine crystals, increased dibasic urinary amino acids
SLC7A9	Cystinuria	AR	Hexagonal cystine crystals, increased dibasic urinary amino acids
SLC34A1	Hypophosphatemic rickets with hypercalciuria/, NL/NC infantile hypercalcemia	AR/AD	Variable hypophosphatemia, variable hypercalcemia as infant, increased 1,25-dihydroxyvitamin D, decreased PTH
SLC34A3	Hypophosphatemic rickets and hypercalciuria	AR/AD	Variable hypophosphatemia, increased 1,25-dihydroxyvitamin D
ATP6V0A4	Distal RTA	AR	Acidosis, alkaline urine
ATP6V1B1	Distal RTA, deafness	AR	Acidosis, alkaline urine
CA2	Carbonic anhydrase II, osteopetrosis with RTA	AR	Acidosis, alkaline urine
SLC4A1	Distal RTA	AR/AD	Acidosis, alkaline urine
SLC12A1	Bartter syndrome type 1	AR	Hypokalemia, hypercalciuria
KCNJ1	Bartter syndrome type 2	AR	Hypokalemia, hypercalciuria
CASR	Hypocalcemia	AD	Hypocalcemia
HPRT1	Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome	XL	Developmental delay, hyperuricemia
SLC22A12	Renal hypouricemia	AD/AR	Hypouricemia
SLC2A9	Renal hypouricemia	AD/AR	Hypouricemia
UMOD	Familial juvenile hyperuricemic nephropathy, medullary cystic kidney disease type 2	AD	Hyperuricemia
VDR	Idiopathic hypercalciuria; vitamin D–dependent rickets	AD	Hypocalcemia, hypophosphatemia, increased 1,25-dihydroxyvitamin D
XDH	Xanthinuria type 1	AR	Low uric acid, orange/brown staining in diaper
MOCOS	Xanthinuria type 2	AR	Low uric acid, orange/brown staining in diaper

Abbreviations: AD, autosomal-dominant; AR, autosomal-recessive; DHA, dihydroxyadenine; NL/NC, ephrolithiasis/nephrocalcinosis; PTH, parathyroid hormone; RTA, renal tubular acidosis; XDH, xanthine dehydrogenase; XL, X-linked; XR, X-linked recessive.

intake, which can increase cystine excretion. However, there have been no specific clinical trials to better understand the specific benefits of these dietary changes.

Alkalinization of the urine increases cystine solubility, and potassium citrate or potassium bicarbonate should be taken 3-4 times daily, aiming for a urine pH consistently between 7 and 8. Thiol-binding drugs can be used for patients who continue to be at stone risk based on quantification of cystine excretion or other 24-hour urine parameters and in those in whom stones continue to form despite the aforementioned measures. Thiol-binding drugs include tiopronin and D-penicillamine.[23-25]

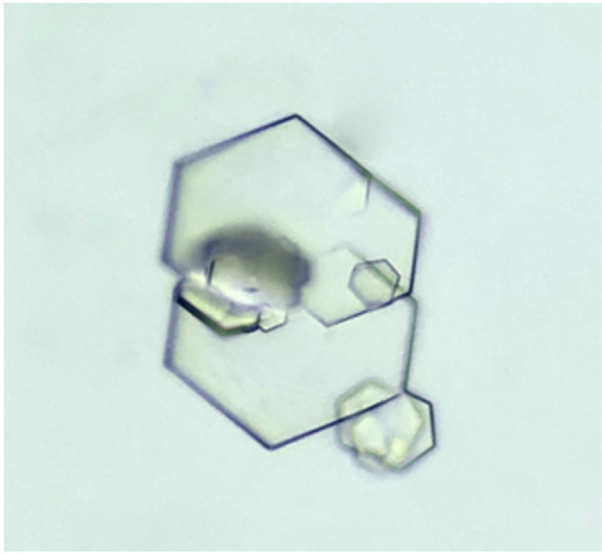

Figure 1. Cystine crystal in the urine. Such hexagonal crystals are pathognomonic of cystinuria. Reproduced from Shastri et al.[85]

Dent Disease and Lowe Syndrome (Oculocerebrorenal Syndrome)

Dent disease is a rare X-linked renal tubulopathy characterized by low-molecular-weight proteinuria, hypercalciuria, and nephrocalcinosis, and is commonly associated with nephrolithiasis, variable proximal tubular defects, and CKD.[27]

Dent disease 1, caused by variants in the CLCN5 gene, makes up 60% of cases. CLCN5 encodes the Cl^-/H^+ exchange transporter 5 (CIC-5) that is primarily expressed in the proximal tubule, thick ascending limb, and intercalated cells.[28,29] Dent disease 2 occurs in 15%-20% of cases and is caused by variants in the OCRL1 gene that encodes the inositol polyphosphate-5-phosphatase (OCRL1) expressed more widely in kidney and other tissues.[30,31] These genes play important roles in cell signaling, and variants lead to impairments in endocytic pathways and decreased proximal tubular reabsorption.[27,32] Compared with Dent disease 1, patients with Dent disease 2 are more likely to have extrarenal involvement, including mild cognitive impairments and short stature.[27,30]

OCRL1 gene variants are also seen in Lowe syndrome (oculocerebrorenal syndrome), a rare disease characterized by a more severe clinical phenotype including congenital cataracts, hypotonia, intellectual disability, and progressive kidney failure beginning in early childhood. Compared with Dent disease, patients with Lowe syndrome more commonly have Fanconi syndrome with more generalized aminoaciduria and renal tubular acidosis. It remains unclear why certain patients with OCRL variants develop the Lowe syndrome phenotype and others develop Dent disease 2.[31]

Diagnosis of Dent disease should be considered in any child or young adult presenting with high levels of low-molecular-weight proteinuria, especially if the individual is male or the proteinuria is associated with nephrocalcinosis or CKD. Female carriers may have low-molecular-weight proteinuria, hypercalciuria, and nephrolithiasis, but they rarely develop CKD.[33] The majority of patients with Dent disease exhibit focal global glomerulosclerosis on kidney biopsy, although focal segmental glomerulosclerosis can be seen, and therefore Dent disease should be considered in the differential for male individuals presenting with focal segmental glomerulosclerosis.[34-36]

Laboratory evaluation includes assessment of kidney function and blood chemistries and screening for low-molecular-weight proteinuria: increased urine β_2 microglobulin levels may be a good screening method, but the gold standard for diagnosis is specific increases in urine retinol binding protein and urine α_1 microglobulin levels. Patients with Dent disease typically have incomplete Fanconi syndrome with variable presentations of hypokalemia, hypophosphatemia, acidosis, hypouricemia, glycosuria, and aminoaciduria.[27,37] A 24-hour urine sample or spot urine calcium-creatinine ratio in younger children should be obtained to quantify hypercalciuria, which is present in most patients.[38,39] Genetic testing is available to confirm CLCN5 and OCRL variants. A negative genetic test result does not rule out the diagnosis because significant heterogeneity exists, and a lack of an identified variant may occur in many with the Dent disease phenotype.[40-42]

Most male individuals with Dent disease will develop GFR loss over time. Progression to kidney failure occurs later in life, typically between the ages of 30 and 50 years.[37,43,44] There is no specific treatment targeting the molecular defects causing Dent disease. Management is focused on reducing hypercalciuria to mitigate nephrolithiasis and nephrocalcinosis. High fluid intake, a low-salt diet, and thiazide diuretic agents are mainstays of therapy, along with close monitoring for hypokalemia or hypotension with thiazide initiation or dose adjustments. Renin-angiotensin system inhibitors have been used with unclear effects on CKD progression, as the proteinuria in Dent disease is primarily tubulointerstitial in nature.[35-37,45] There may be benefits in select patients with focal segmental glomerulosclerosis and increased glomerular proteinuria, but the efficacy of renin-angiotensin system inhibitors remains to be elucidated.[46,47] There are also limited data on the use of SGLT2 inhibitors. Kidney transplant is ultimately curative without the risk for disease recurrence.

APRT Deficiency

Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal-recessive disorder of purine metabolism that leads to recurrent nephrolithiasis and CKD.[48] APRT is required for proper recycling of adenine, and, in its absence, adenine is instead broken down by xanthine dehydrogenase to 2,8-dihydroxyadenine (DHA). DHA is

highly insoluble in the urine, and affected individuals develop crystalluria and recurrent stones with GFR loss secondary to crystalline nephropathy.[48-50]

The APRT gene is located on chromosome 16q24, and deficiency occurs through a loss-of-function mechanism. More than 50 pathogenic variants have been reported from more than 25 countries, with most reported cases in France, Iceland, and Japan.[47,48]

Clinical presentation varies widely, and many affected individuals remain asymptomatic and undiagnosed for decades.[50] Radiolucent nephrolithiasis in childhood is the most common presentation, with reddish-brown diaper stains with acute kidney injury from bilateral obstructive calculi, recurrent urinary tract infections, and hematuria also reported.[48,49,51-53] Reddish-brown stains occur beyond the first few months of life, are often recurrent, and are not associated with volume depletion, allowing for differentiation from the more common uric acid crystals of infancy. The kidney and urinary tract are the only confirmed organ systems affected by APRT deficiency, with sporadic reports of corneal involvement requiring further investigation.[47,50,54]

Untreated, APRT deficiency leads to CKD, with approximately 20% of adults developing kidney failure, most commonly in the fifth decade of life.[50] Some adults first present with the need for kidney replacement therapy,[48,49] and, in others, diagnosis is delayed until allograft dysfunction occurs after kidney transplant.[55,56]

A diagnosis of APRT can be made with routine urine microscopy if the characteristic round, brown DHA crystals are seen (Fig 2).[48,53] Confirmatory testing is established with absent APRT enzyme activity in red cell lysates or with genetic testing identifying biallelic pathogenic variants in the APRT gene.[47]

The mainstays of treatment include xanthine dehydrogenase inhibition with allopurinol, increased hydration, and a low-purine diet.[47] Febuxostat can also be used for those with allopurinol intolerance. Pharmacologic intervention is effective in reducing nephrolithiasis and preventing kidney failure.[48-50,57,58]

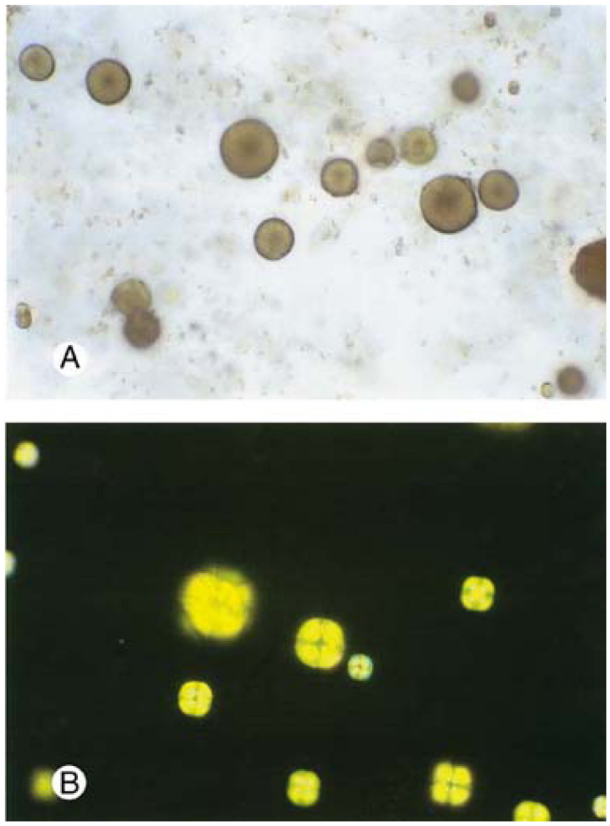

Figure 2. 2,8-Dihydroxyadenine (DHA) crystals in the urine. (A) Light microscopy shows red/brown DHA crystals. (B) Polarized light microscopy shows DHA crystals with Maltese crosses (original magnification, ×400). Reproduced from Edvardsson et al.[48]

Phosphate Abnormalities Associated With Hypercalciuria and Nephrocalcinosis/ Nephrolithiasis

Hereditary hypophosphatemic rickets with hypercalciuria results from a disordered sodium phosphate transporter (NPT2c) due to a variant in SLC34A3.[59,60] In most patients, the serum phosphorous level is low, urine phosphate excretion is inappropriately high, 1,25-dihydroxyvitamin D levels are high, and hypercalciuria is present. Bone disease may also be present with rickets or osteomalacia and fractures. Children may present with nephrolithiasis or nephrocalcinosis. Kidney cysts have been reported in some families with SLC34A3 variants.[61,62]

Initial treatment is phosphate supplementation, with addition of a thiazide diuretic agent if hypercalciuria persists. Bone health evaluations are performed, and alkaline phosphatase levels are followed.

Most inherit this disorder in an autosomal-recessive fashion, although some heterozygous carriers also have an increased incidence of nephrolithiasis or nephrocalcinosis, with laboratory abnormalities that can be similar to homozygous cases. Bone disease in heterozygotes is variable.

Nephrolithiasis or nephrocalcinosis and osteomalacia may also stem from an SLC34A1 variant affecting the sodium phosphate transporter NPT2a.[63] This disorder has homozygous and heterozygous presentations, and the gene variant has been reported in idiopathic infantile hypercalcemia presenting in the first few months of life.[64,65] This disorder presents with hypophosphatemia, inappropriately high urine phosphate excretion, and increased 1,25-dihydroxyvitamin D levels mediating hypercalciuria and bone disease. The mainstay of treatment is phosphate supplementation.

Hypercalcemia, Hypercalciuria, and Increased 1,25-Dihdroxyvitamin D

CYP24A1 variants result in the loss of function of 24-hydroxylase, with decreased degradation of 1,25-

dihydroxyvitamin D and resulting hypercalcemia and hypercalciuria predisposing to nephrolithiasis and nephrocalcinosis. In infants, this disorder is associated with hypercalcemia of unclear cause.[65,66] Children may present with relatively normal serum calcium levels, increased 1,25-dihydroxyvitamin D levels, and nephrocalcinosis or nephrolithiasis.[60,61] Kidney cysts have also been reported.[67] Later in life, increased sun exposure and exogenous vitamin D supplementation may unmask this condition with ensuing hypercalcemia and hypercalciuria.[68]

Treatments include vitamin D and calcium restriction, limiting sunlight exposure, and consideration of drugs such as rifampin, ketoconazole, and fluconazole that induce enzymes that help to inactivate 1,25-dihydroxyvitamin D.[69-72]

Familial Hypomagnesemia With Hypercalciuria and Nephrocalcinosis

Hypomagnesemia in the setting of nephrolithiasis, nephrocalcinosis, and kidney function impairment of unknown cause should lead to the consideration of claudin 16 or 19 variants (familial hypomagnesemia with hypercalciuria and nephrocalcinosis). Familial hypomagnesemia with hypercalciuria and nephrocalcinosis is an autosomal-recessive disorder, and patients develop hypomagnesemia and hypercalciuria due to tubular losses, resulting in nephrocalcinosis and kidney failure. Recurrent urinary tract infection, polyuria, polydipsia, and nephrolithiasis have also been reported. In some patients with kidney failure, magnesium levels may normalize with GFR loss. Magnesium supplementation is used as needed, along with hydration, crystallization inhibitors such as potassium citrate or bicarbonate, and thiazide diuretic agents.

Claudin 19 is also expressed in the retina, and some individuals may have eye and vision changes. Kidney cysts have also been reported. Hypercalciuria may be marked and lead to early hyperparathyroidism, amelogenesis imperfecta, and chondrocalcinosis. Progression to kidney failure is variable, and kidney transplant is considered curative.[73-75]

Uric Acid Disorders

Uric acid disorders in pediatric populations are uncommon and may represent disorders in uric acid production, reabsorption, or secretion. Hypouricemia and increased renal urate excretion are associated with variants in SLC2A9 and SLC22A12.[76-78] Hyperuricemia, low fractional excretion of urate, gout, and renal cysts are associated with variants in UMOD and are a form of autosomal-dominant tubulointerstitial kidney disease.[79]

Lesch-Nyhan syndrome is a very rare X-linked recessive disorder associated with hypoxanthine-guanine phosphoribosyl transferase deficiency that results in uric acid overproduction. Lesch-Nyhan disorder may present with developmental delays and severe self-destructive behaviors. Children with Lesch-Nyhan syndrome may form uric acid stones, and parents may report orange crystals in the diaper beyond early infancy. Allopurinol or febuxostat, high fluid intake, and potassium citrate to alkalinize the urine are used for stone prevention.[80]

Xanthinuria

Genetic causes of xanthinuria consist of variants in *XDH* and *MOCOS* genes. Xanthinuria type 1 stems from variants in xanthine dehydrogenase, causing hypouricemia, hypouricosuria, and an increase in xanthine production, resulting in xanthinuria. Affected individuals are at risk for nephrolithiasis and associated kidney failure. Xanthinuria type 2 results from inactivating variants in *MOCOS* (molybdenum cofactor sulfurase) leading to hypouricemia, hypouricosuria, and increased xanthine production with xanthinuria. In addition to concerns for nephrolithiasis and kidney failure, affected individuals may have myositis. Treatment for either type of xanthinuria includes high fluid intake and a low-purine diet.[81,82]

Renal Tubular Acidosis

Renal tubular acidosis results from impaired urinary acidification leading to hyperchloremia, metabolic acidosis, hypocitraturia, variable hypokalemia, and nephrocalcinosis or nephrolithiasis. Untreated, renal tubular acidosis may be associated with risk of kidney failure and bone disease. Some forms of renal tubular acidosis are associated with deafness. Treatment includes sodium or potassium citrate supplementation and potassium chloride if needed.[83]

Conclusions

As with many less commonly encountered clinical conditions, rare kidney stone diseases are often misdiagnosed or significantly delayed in diagnosis, which may lead to suboptimal clinical management and predispose to serious sequelae that may lead to kidney injury or failure. Clinicians who treat patients with nephrolithiasis with any frequency need to be aware of which aspects of clinical history or presentation and results of screening imaging and laboratory testing should raise the index of suspicion for a rare kidney stone disease. Because there are significant similarities among the phenotypic expressions of many rare kidney stone diseases, clinicians also need to recognize which findings should prompt genetic testing to make a definitive diagnosis. Given this phenotypic overlap, outside of those cases in which initial diagnostic evaluation pinpoints a very likely specific diagnosis such as increased urine oxalate (ie, PH) or tubular proteinuria (ie, Dent disease), targeted genetic testing may be a less successful diagnostic strategy than broader genetic testing with a nephrolithiasis and nephrocalcinosis panel.[84] Clinicians also need to understand which findings should prompt genetic testing to make a definitive diagnosis.

When a definitive diagnosis has been made, given that clinical experience with many of these rare kidney stone disease conditions can be limited, referral to physicians or

medical centers with specific disease expertise may also be needed to complement ongoing local resources, especially in this era when novel therapeutic platforms allow for the ongoing development of more disease-specific therapies.

Care may be best delivered in the context of a multidisciplinary stone clinic involving nephrologists, urologists, and other health professionals with training and expertise in stone disease. Given the chronicity of these conditions, the need for longitudinal patient care and access to clinicians with disease expertise should be anticipated. As with many rare clinical conditions, disease-specific advocacy groups can play an important role for patients, families, and clinicians as clearinghouses for relevant disease information, including new research findings, ongoing therapeutic trials, and identification of clinical centers of excellence for disease-specific care.

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