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REVIEW

Cystinuria: mechanisms and management

Donna J. Claes · Elizabeth Jackson

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Abstract Cystinuria is a relatively uncommon cause of pediatric stone disease, but has significant morbidity if not properly controlled because of its significant stone recurrence rate. Cystinuria is caused by the inability of the renal tubules to reabsorb filtered cystine, which is poorly soluble at a typical urine pH <7. Although many advances have been made in the understanding of the genetic and physiological basis of cystinuria, the cornerstones of treatment still involve stone prevention with dietary measures and pharmacological therapy, coupled with surgical interventions for stone removal. Pharmacological treatments can carry significant side effects that must be monitored and can limit therapy as well as impede compliance. Most patients will require surgical intervention for stone removal, although compliance with prevention strategies reduces the need for intervention.

Keywords Cystinuria · Kidney stones · Genetic · Stone prevention · Pharmacologic · Therapy · Surgical therapy

Introduction

Cystinuria is an autosomal recessive disease that accounts for 1–10% of all pediatric stone disease according to various reports [1–3]. Although cystinuria is a relatively rare disease, it is important to understand as patients with cystinuria have a lifelong history of recurrent stone formations that can lead to multiple surgical interventions and mild renal insufficiency. However, compliance with medical therapy can significantly reduce stone recurrence and provide renal protection.

D. J. Claes (✉) · E. Jackson
Division of Pediatric Nephrology and Hypertension,
Cincinnati Children's Hospital Medical Center,
3333 Burnet Avenue,
Cincinnati, OH, USA
e-mail: donna.claes@cchmc.org

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Epidemiology

The world-wide prevalence of cystinuria is estimated at 1:7,000, with significant ethnic variation. Prevalence ranges from 1:2,500 in the Libyan Jewish population to 1:100,000 in Sweden; the US prevalence is estimated to be about 1:15,000 [1–4]. Patients typically present with a symptomatic stone between 2 and 40 years of age with a median age of onset of 12 and 15 years in female and male subjects respectively [3]. The diagnosis of cystinuria prior to age 2 should be made carefully, as there can be falsely elevated urine cystine levels in heterozygote carriers due to immaturity of the amino acid transporters within the renal tubular membrane during the first 2 years of life [4].

Patients with cystinuria have a greater than 50% chance of stone formation during their lifetime, with the likelihood of bilateral stone formation seen in over three-quarters of patients [1]. Repetitive stone formation is the typical course of disease, with a recurrence rate as high as 60%. Male subjects tend to present earlier with more aggressive disease, forming a new stone on average every 3 years, compared with every 5 years in women [5]. In a study by Worcester et al., patients with cystinuria required significantly more procedures for stone removal, both prior to and after aggressive medical management, than non-cystine stone formers [6].

Pathophysiology

Cystine is an amino acid that is composed of two cysteine molecules joined by a disulfide bond. Cystinuria is due to

defective trans-epithelial transporters for the dibasic amino acids cystine, ornithine, lysine, and arginine ("COLA amino acids") in both the renal proximal tubules and the intestinal tract. Owing to its low solubility at physiological urinary pH, over-excretion of cystine in the kidney leads to the super-saturation of cystine within the urine and formation of cystine crystals and eventually stones. In general, overall stone formation is thought to develop secondary to one of the following three pathways:

1. Overgrowth on interstitial apatite plaques
2. Formation of crystal deposits within renal tubules
3. Due to free solution crystallization [7]

Stone formation in cystinuria is due to the third pathway; cystine crystals form freely within solution and typically plug the ducts of Bellini, but are easily mobile and wash away when surgically exposed; other cysteine stones are found free within the renal pelvis [7, 8].

There is no pathological association of the urinary excretion of ornithine, lysine or arginine, as these three amino acids have normal solubility within the urine. There is also no associated gastro-intestinal (GI) pathology from decreased intestinal absorption of these amino acids as, with the exception of lysine, these amino acids are classified as non-essential, and all four of these dibasic amino acids may be absorbed in their di-peptide forms from the GI tract [3].

Genetics and classification

Cystinuria is an autosomal recessive disease; however, some heterozygote carriers have an autosomal dominant, incomplete penetrance appearance with elevated, but typically non-pathological urinary cystine excretion. Due to this abnormality, prior to genetic analysis cystinuria patients were phenotypically classified as either type I or non-type I (type II or type III) based on urinary excretion and GI absorption of cystine in the parents (obligate heterozygotes) of patients, as seen in Table 1 [1–4]. Non-type I carriers can present with symptomatic cystine stones, although rarely.

The physiology of cystine absorption is thought to involve specific amino acid transporters within the kidney and GI tract. Cystine and the dibasic amino acids are absorbed from the urinary lumen into the proximal tubules by covalently linked heterodimer amino-acid transporters—rBAT and B(0,+) AT—found on the luminal side of both the GI tract and the proximal tubules of the kidney [2, 3, 9–11]. Once inside the proximal tubule, cystine is hydrolyzed into two cysteine molecules; cysteine is then absorbed into the bloodstream through the baso-lateral membrane to promote continued absorption down its concentration gradient. The

Table 1 Phenotypic classification of cystinuria based on parental (heterozygote) findings

Phenotypic classification	Urinary excretion of cystine (μmol/g creatinine) in heterozygotes	Genetic inheritance pattern of heterozygotes
Type 1	< 100	Autosomal recessive
Non-type 1 (type II)	>1,000	Autosomal dominant, incomplete penetrance
Non-type 1 (type III)	100–1,000	Autosomal dominant, incomplete penetrance

rBAT and B(0,+) AT sub-units belong to a whole family of heterodimeric amino acid transporters (HAT family), which modulate the near complete absorption of several amino acids within the kidney and GI tract; genetic abnormalities in various other HAT subunits are associated with aminoaciduria disorders such as Hartnup disorder and lysinuric protein intolerance (LPI) [11].

Genetic studies of cystinuria patients later found defects in two genes—solute carrier protein 3 (*SLC3A1*) on chromosome 2 and solute carrier protein 7 (*SLC7A9*) on chromosome 19—which encode for the sub-units rBAT and b(0,+) AT respectively. The b(0,+) AT protein is the transport channel, while the rBAT protein modulates the activity of b(0,+) AT protein [2, 4, 9]. Based on these genetic findings, a modern and more appropriate classification of cystinuria has been proposed by the International Cystinuria Consortium (ICC) [5], as seen in Table 2. Patients with two defective genes for *SLC3A1* have Type A cystinuria; whereas, patients with two defective genes for *SLC7A9* have Type B cystinuria. All heterozygote *SLC3A1* carriers and 14% of the heterozygote *SLC7A9* carriers have the phenotype of the probands for type I patients (i.e. no detectible urinary cystine excretion); while the remainder of heterozygote carriers of *SLC7A9* phenotypically correspond to the non-type I carriers (i.e. elevated urinary cystine levels).

The advantage of the new genetic-based classification is that it has created the possibility of classifying patients with concomitant genetic abnormalities in both the *SLC3A1* and

Table 2 Genetic classification of cystinuria

	Genetic mutations of alleles	Affected protein	Previous phenotypic classification of heterozygote carriers
Type A	SLC3A1, SLC3A1	rBAT	Type I
Type B	SLC7A9, SLC7A9	b(0,+) AT	Non-type I (86%), Type I (14%)[1]
Type AB (possible)	SLC3A1, SLC7A9	Both	Non-type I

SLC7A9 genes. This Type AB genotype is extremely rare, seen in 1.6% of a study population. Despite genetic differences between type A and type B patients, there is no clinical difference in their disease in terms of onset of illness, stone formation, aggressiveness of disease, or need for surgical intervention for stone removal [5].

Over 100 mutations in *SLC3A1* and 60 mutations in *SCL7A9* have been discovered [12], and these mutations have ethnic predilections. However, this classification system does not explain the disease in all patients. Especially in pediatric cystinuria patients, a lower prevalence of detected variants within the *SLC3A1* and *SLC7A9* genes has been seen, raising the suspicion for other unknown genes responsible for cystinuria [13, 14].

Of interest, a spectrum of three related, but distinctive genetic syndromes have been associated in patients with cystinuria Type A: 2p21 deletion syndrome, hypotonia–cystinuria syndrome (HCS), and atypical HCS [3, 15, 16]. In all three of these syndromes, contiguous genes on chromosome 2 are deleted or disrupted. As well as the formation of cystine stones, all three of these syndromes are associated with neonatal hypotonia, poor feeding, growth retardation, facial dysmorphisms, mental retardation, as well as abnormalities of the respiratory chain complex. The severity of each disease depends on the number of genes deleted.

Diagnosis

Laboratory diagnosis

A quick microscopic evaluation of the urine can be helpful, as up to a quarter of patients with cystinuria will have the pathognomonic hexagonal urinary cystine crystals on routine urinalysis. A screening test for cystinuria is the cyanide-nitroprusside test, which is a qualitative, colorimetric test that displays a red–purple color change when the reduced sulfhydryl groups (formed from mixing cystine and cyanide) react with nitroprusside. This test is not specific, being positive in patients with Fanconi's syndrome, homocystinuria, in heterozygote carriers of cystinuria, or patients taking various medications—including ampicillin or sulfa-containing medications. Because this test cannot differentiate between homozygous and heterozygous patients and is not specific for cystinuria, this test seems to have fallen out of favor.

In today's practice, when a patient presents with a new urinary stone, most clinicians will immediately send a 24-h quantitative urine evaluation to various private companies who measure multiple urinary components associated with urinary stone formation, including cystine excretion. Normal urine cystine excretion is 30 mg/L per day (0–100 μmol/g creatinine); homozygotes excrete more than 300–400 mg/L per day of urinary cystine while non-type I heterozygotes show intermediate urinary cystine excretion [1, 3]. Stones should be sent for composition analysis as well. In young patients from whom it is difficult to obtain 24-hour urine collections, sending a spot urine cystine (which can be obtained through urine amino acid quantification) to creatinine ratio may be helpful, but is not ideal as urinary cystine saturation changes throughout the day with regard to urine pH, urinary concentration, and volume. Although genetic testing can be done, it does not offer any clinical therapeutic benefit at this point.

Imaging

Cystine stones are less radio-opaque than calcium stones, and a KUB (kidney, ureter, bladder) may have limited ability to detect cystine calculi. However, regular surveillance KUBs (once or twice yearly) are helpful in following stone growth, especially in detecting increases or decreases in size and/or number of stones over time. They may also be helpful in verifying stone eradication after surgical interventions. Ultrasound is ideal for detecting all types of urinary stones, and can be especially important for following new stone development and/or stone resolution over time in conjunction with KUBs [1–3]. Helical computed tomography (CT) is becoming popular for characterizing cystine stone appearance as either rough or smooth to predict the likelihood of success of stone dissolution with extracorporeal shock wave lithotripsy, as described elsewhere in this article.

Treatment

The cornerstone of treatment for cystinuria is to prevent stone growth and reduce the number of urological procedures needed. This is achieved primarily by dietary interventions, urinary alkalinization, and therapy with cystine-binding thiol medications.

Dietary therapy

A urine volume of 2–3 L per day in adults is highly recommended, and in a study by Barbey et al. was found to be the prognostic factor associated with reduction of the stone formation rate [17]. In children, these values may be adjusted to promote 24-h urine volumes of $\geq$2 L per 1.73 m^2 [18]. Hydration prior to bedtime and upon awakening decreases the saturation of cystine within the urine. Urinary cystine has been found to promote calcium stone formation [19], and cystinuria patients can form non-cystine urinary stones in addition to cystine stones [3, 17]; apatite deposits within the inner medullary collecting ducts have been demonstrated in patients with cystinuria, which can increase the risk of calcium stone formation [7, 8]. Thus, all patients with cystinuria benefit from

a low-sodium diet and other standard, non-pharmacological maneuvers recommended for any stone-forming person. Even with dietary cystine elimination, serum cystine levels will likely remain normal as cystine is produced endogenously from methionine. Adolescent patients with cystinuria may benefit from a low protein diet in order to prevent general stone formation, but this practice is not recommended in young children because of concerns regarding growth and development on restricted diets [1].

Urinary alkalinization

Urinary alkalinization with either potassium citrate or sodium bicarbonate, in addition to hydration, is one of the foundations of therapy for cystinuria. Since cystine is poorly soluble within a pH range of 5–7, the goal of alkalinization therapy is to increase the urinary pH to >7 to increase the solubility of cystine within the urine. Potassium citrate is the preferred agent, as it increases urine potassium and avoids the excess urinary sodium load from bicarbonate therapy to prevent mixed calculi stones.

In a small study of patients with both cystine and uric acid stones, adding a night-time dose of acetazolamide, a potential adjunct to citrate or bicarbonate therapy, helped to achieve overnight urinary alkalinization [20]. Acetazolamide's beneficial effects could also be secondary to increased urinary flow volumes owing to its mild diuretic effect. However, approximately half of the patients discontinued therapy with acetazolamide because of adverse drug effects. A disadvantage of aggressive alkali management is the risk of calcium phosphate stone formation.

Pharmacological therapy

For patients with continued stone disease despite hydration and alkalinization therapy, addition of a cystine-binding thiol medication is the next step toward preventing cystine stone formation (Table 3). The two most common thiol medications—d-penicillamine and tiopronin (alpha-MPG, or alpha-mercaptopropionylglycine)—exert their activity by reducing the di-sulfide bond of cystine into two molecules of cysteine (one molecule of cystine → two molecules of cysteine) within the urinary lumen. The bound thiol-containing medication cysteine molecule has greater urine solubility than cystine. Tiopronin and d-penicillamine in the treatment of cystinuria have never been directly compared with one another; however, both drugs appear to be effective.

Tiopronin appears to be the preferred treatment in the USA because its slightly decreased adverse drug profile. However, both medications have significant side effects, which can lead to non-compliance with medical therapy or require discontinuation. Adverse effect profiles of sulfhydryl compounds include alterations in taste perception, muco-cutaneous lesions, proteinuria due to immune-complex membranous glomerulopathy/nephrotic syndrome, and immune-mediated diseases such as a lupus-like drug reaction, myasthenia gravis-like disease, and skin eruptions such as pemphigus and elastosis perforans serpiginosa (EPS rash). Hematological reactions such as neutropenia and thrombocytopenia can occur, although rarely, as reported in the literature [21]. Disturbances with taste typically abate with time, but can be a common cause for treatment discontinuation; therefore, patients may need encouragement to continue treatment until this adverse effect subsides. Oral lesions and erythematous, pruritic rashes that occur during the first months of therapy respond to dose reduction or temporary drug withdrawal; the rash does not typically recur with re-initiation of the drug at a lower dose. However, other serious manifestations such as immune mediated diseases or aplastic anemia require discontinuation of the drug. Neutropenia and thrombocytopenia can be either idiosyncratic or dose-related. Although as a class all sulfhydryl medications can result in these side effects, they are not exclusive in that experiencing a particular adverse effect with penicillamine does not predict the same side effect with thiola, or vice versa.

Table 3 Dosing of cystine-binding thiol-containing medications (information derived from Micromedex, Lexicomp)

Medication	Dosing
d-Penicillamine	30 mg/kg/day in four divided doses; titrated as necessary to keep urinary cystine concentration <300 mg/L. Maximum dose: 4 g/day
Tiopronin/ alpha-MPG	15 mg/kg/day in three divided doses; titrated as necessary to keep urine cystine <300 mg/L. Adult dose: 800 mg/day divided into three doses
Captopril	Initial: 6.25–12.5 mg/dose every 12–24 h; titrate upward to a maximum of 6 mg/kg/day in 2–4 divided doses

These medications have chelating properties, and their use may result in zinc and/or copper deficiencies requiring pharmacological supplementation. Vitamin B6 activity is decreased with penicillamine therapy only, owing to penicillamine's antagonistic effects on the formation of vitamin B6 to its metabolically active form [22, 23]; thus, pharmacological supplementation of vitamin B6 is recommended to be given with penicillamine.

In order to improve compliance, the individualization of drug dosage throughout therapy helps to achieve low urinary cystine concentrations with fewer side effects. Younger patients often require a higher dose of either medication per body size compared with older patients [24]. A gradual dosage titration of d-penicillamine for a small cohort of pediatric patients resulted in only two significant toxicities over a 1,203-patient-month treatment period, with less than

Table 4 This table is extracted from a Litholink® report (used with permission) of a 16-year-old patient with cystinuria whom we follow. The patient was only on alkali therapy until March 2008; at that time tiopronin therapy was initiated. However, because of mouth ulcerations, tiopronin was switched for d-penicillamine without significant side effects. The patient continues on d-penicillamine at the present time and has required concomitant copper supplementation

Dates	Urine volume (24 h; L)	Cystine excretion (mg/24 h)	Cystine super-saturation	Capacity	pH	Urine sodium (mmol/24 h)	Urine urea nitrogen (g/24 h)	Protein catabolic rate
May 2010	2.2	513	0.85	47	7.036	233	7.28	1.2
August 2009	2.58	731	1.04	−10	7.013	251	8.95	1.6
January 2009	2.61	512	0.66	118	7.369	130	8.22	1.6
June 2008	2.87	740	0.91	43	6.940	87	10.4	2
March 2008	2.20	788	1.17	−37	7.251	135	6.92	1.5
June 2007	2.33	752	0.94	34	7.296	118	6.99	1.6
December 2006	2.02	732	1.04	12	7.384	76	6.05	1.4
December 2005	2.53	405	0.67	62	6.920	134	5.98	1.4

half of patients developing evidence of a new stone (by ultrasound or symptomatic stone crisis); in those patients with a stone crisis, non-compliance with drug therapy was the culprit, as noted by decreased urine penicillamine disulfide levels [25].

The ACE inhibitor captopril also has a thiol-containing functional group, and has been used with conflicting results in reducing urinary cystine levels [3, 17, 26]. However, because of its less toxic side effect profile, it may serve as an alternative therapy in patients unable to take either d-penicillamine or tiopronin, as well as in patients with concomitant hypertension and/or proteinuria.

Monitoring of pharmacological therapy

The goal of pharmacological therapy with cystine-binding thiol medications is to keep urinary cystine levels low while avoiding medication side effects. It is important to note that when using thiol-containing medication therapy, the total urinary cystine measurement is no longer useful in 24-hour urine as it measures both the bound and free urinary cystine. Also, techniques that can distinguish between cystine and the drug–cysteine complex require disruption of the cystine–medication complex, which makes it difficult to then determine the medication's efficacy in reducing urinary cystine levels [3]. Use of a solid-phase assay of urinary cystine is a reliable method for determining urinary cystine super-saturation and capacity in the presence of cystine-binding thiol medications [27]. Cystine capacity measures the ability of the urine to solubilize cystine (reflecting under-saturation, or positive capacity) or precipitate cystine (reflecting super-saturation, or negative capacity) when additional cystine is added to the urine [28]. This can be an excellent method for following a patient's response to therapy over time (see Table 4).

Patients on sulfhydryl medications also require frequent monitoring for development of adverse reactions, such as any rashes, arthralgias, or proteinuria; routine monitoring for neutropenia, thrombocytopenia and/or development of anemia; and monitoring for copper and zinc deficiencies.

Table 5 Recommended surgical treatment of cystine stones as defined by stone size

Stone size	Treatment
<12 mm[a]	Extracorporeal shock wave lithotripsy (ESWL)
12–20 mm	Ureterorenoscopy and holmium laser stone fragmentation
>20 mm	Percutaneous nephrolithotomy (PCNL)

[a] ESWL recommended if the stone is also visualized on KUB (kidney, ureter, bladder)

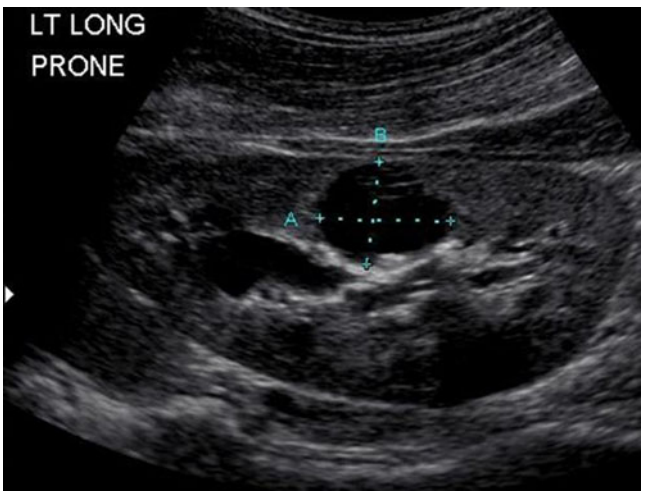

Fig. 1 Renal ultrasound was taken at 13 years of age in a female patient with cystinuria. She continues to have a persistent fluid-filled space at the site of open nephrolithotomy of the left kidney performed for removal of a large cystine stone at age 2

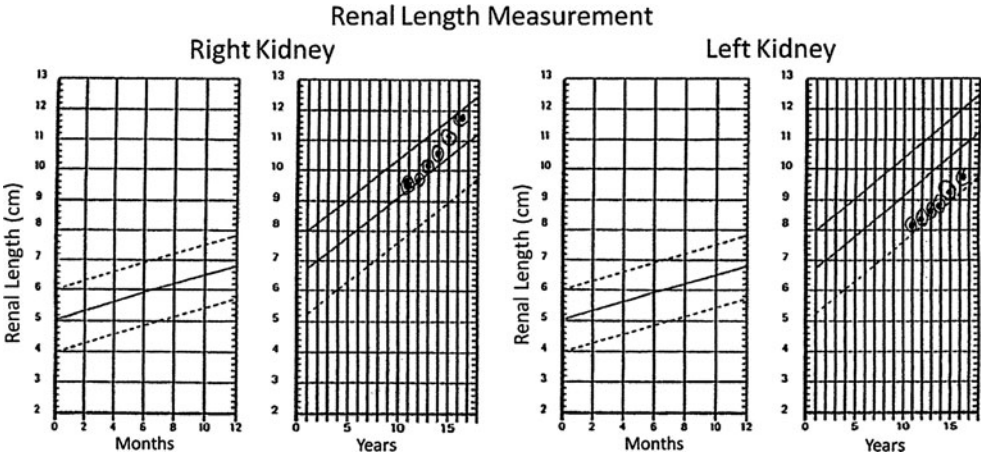

Fig. 2 This graph depicts renal growth over time in the same patient whose ultrasound appears in figure 1. Note that there continues to be a size discrepancy between the right and left kidneys

A monitoring schedule, as proposed by DeBerardinis et al., includes monitoring of urinary cystine once to twice yearly with surveillance imaging; daily urine protein monitoring; complete blood counts every 2 weeks for 6 months, then monthly; liver function tests every 6 months; and copper and zinc levels every 6 months [25].

Compliance with medical therapy

In a small study by Pietrow et al., only 15% of patients were able to maintain compliance with urinary cystine levels <300 mg/L, 42% were only intermittently compliant, and almost 20% had persistent urinary cystine levels >300 mg/L. However, self-reported compliance rates were similar among groups. Reasons for non-compliance included side effects as well as the large number of pills required to be administered per day [29]. However, in a pediatric study 79% of patients on either tiopronin or d-penicillamine were able to achieve target urinary cystine levels below 100 μmol/mmol of creatinine, with a reduction in the frequency of stone episodes from 0.28 per year to 0.03 per year [24]. This study focused on routine (up to 2–4 times per year) visits, with each visit including collection and calculation of urinary cystine values and ultrasound.

Surgical therapy

Due to the recurrent stone formation of cystinuria, many patients require surgical therapy to extract stones as well as the medical therapies. Minimally invasive techniques are preferred to reduce the risk of renal insufficiency compared with open surgical procedures [30]. Minimally invasive surgical therapies include extracorporeal shock wave lithotripsy (ESWL), ureteroendoscopy and holmium laser stone fragmentation, and/or percutaneous nephrolithotomy (PCNL).

Extracorporeal shock wave lithotripsy (ESWL) has not been as successful as other procedures for cystine stones [31]. However, others have found that the size of the cystine stone or characteristics of the stone determines the success rate for various surgeries. Using stone size, Ahmed and associates devised an initial approach [32], as referred to in Table 5.

Kim et al. found that cystine stones with areas of low attenuation (rough, or R-type) as demonstrated on helical CT were more easily fragmented with shock waves whereas those cystine stones that were homogeneous (smooth, or S-type) required significantly more shock waves irrespective of stone size [33]. Spontaneous passage of stones <5 mm in size occurs in only one-half of patients [2]; for this reason and because cystine stones can easily increase in size, many centers focus on an aggressive, proactive approach to rendering a patient stone-free [3]. It should be emphasized that combining therapeutic surgical options is quite common in order to render a patient stone-free.

Open nephrolithotomy is reserved for complex staghorn calculi or for patients with difficult anatomy, but can be done safely with effective results [1]. However, renal insufficiency is associated with the need for open surgical procedures for stone removal. For example, Figs. 1 and 2 show a renal ultrasound and renal length chart for the same 16-year-old patient from Table 4. This renal ultrasound was taken at age 13—notable is the persistent fluid-filled space at the site of open nephrolithotomy performed at age 2 for removal of a large cystine stone. At age 16, there is still a size discrepancy between the kidneys.

Long-term effects on kidney function

Many recent studies have shown that kidney stone formation is a risk factor for the development of chronic kidney disease, and patients with cystinuria as well as other hereditary diseases associated with kidney stone formation are at greatest risk [34, 35]. Renal insufficiency in cystinuria has been reported to be between 5 and 17% in the literature [3, 30]. Patients with cystinuria have a statistically higher serum creatinine compared with other stone formers [30], and

another study showed that cystinuria patients had a statistically lower creatinine clearance, as measured by 24-h urine collection, compared with non-cystine stone formers, including non-cystine stone formers who required a nephrectomy. In this study, there was no difference in blood pressure between cystine vs non-cystine stone formers [6]. Prognostic factors associated with renal insufficiency in cystinuria patients include male gender, increasing number of open procedures for stone removal, and history of nephrectomy [30]. In terms of understanding this relationship better, a study evaluating histopathological abnormalities in cystinuria patients revealed that cystine crystals form within the ducts of Bellini; however, only patients with abnormal obstruction of the ducts of Bellini had associated degrees of interstitial fibrosis, tubular atrophy, and glomerular pathology on renal biopsy [8]. Thus, it is postulated that medical prevention of stone formation could lead to improved renal function by preventing pathological changes of the renal parenchyma.

Conclusion

Patients with cystinuria can be frustrating to manage because of the chronicity of their disease coupled with necessary compliance with hydration, alkalization, and other pharmacological treatments. Yet, successful treatment is possible. Successful management focused on routine measurements of urinary cystine levels and/or capacity is associated with improved patient compliance and reduced need for surgical interventions [6, 16, 24, 25]. In terms of future therapies, a transient cystinuria type I model using antisense technology in a human kidney cell line has been reported in the literature [36], with hopes that its use could lead to better understanding, improved therapies, and a possible genetic cure for this illness. Another study published over the past couple of months by Rimer et al. showed that in vitro cystine stone growth was dramatically reduced by adding two different inhibitors of cystine crystallization to cystine-containing solutions in the laboratory setting [37]. More research is needed, but this could be a promising candidate for therapy in patients with cystinuria.

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