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Cystinuria: A Review of Inheritance Patterns, Diagnosis, Medical Treatment and Prevention of Stones

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Abstract

Cystinuria is a rare inherited renal stone disease. Mutations in two genes *SLC3A1* and *SLC7A9* underlie this condition, encoding proteins that facilitate dibasic amino acid exchange which are expressed in the gut and the proximal tubule of the kidney. Genetic studies now allow precise genotyping of patients who may have both autosomal dominant and autosomal recessive patterns of disease. The disorder is characterised by the urinary loss of cystine, lysine, ornithine, and arginine, and the insolubility of cystine gives rise to crystalluria and cysteine-containing renal stones. Although an inherited condition, it may present at any age. Clinical management combines lifestyle advice and preventative medical therapy. However, many patients require surgical interventions to remove problematic stones from the urinary tract. Preventative therapies include increased fluid intake, alkalinization of the urine, and the use of cystine-binding drugs, including penicillamine and tiopronin, which form soluble heterodimers with cystine.

Keywords: cystine, calculi, *SLC7A9*, *SLC3A1*, genetics, prevention, urine, crystal

1. Introduction

Cystinuria is an inherited metabolic disorder characterised by the abnormal transport of dibasic amino acids, cystine, lysine, ornithine and arginine, in the intestine and proximal renal tubule [1, 2]. In cystinuria patients these amino acids are excreted in excess concentrations in the urine due to a failure of reabsorption in the proximal tubule. Cystine is relatively insoluble; its presence in high concentrations in the urine predisposes to formation of urinary calculi, which are often large and can form staghorn calculi. On urine microscopy cystine

crystals appear as flat hexagonal crystals [2]. The recurrent formation of the cystine stones can lead to development of chronic kidney disease [3]. Ornithine, lysine and arginine are more soluble and therefore their excretion in excess concentrations in the urine does not produce clinical sequelae. There are currently no known clinical consequences of impaired absorption of these four dibasic amino acids within the intestine.

2. Diagnosis of cystinuria: historical and modern

Cystinuria may present with renal calculi at any age, but most patients will present before 30 years of age. Historically, cystinuria was diagnosed mainly through renal calculi analysis and this lead to an underestimation of the incidence of the condition [1]. As methods developed to analyse the cystine concentration in urine samples it became possible to detect cases with confirmed accuracy, and also provided a valuable screening tool. The cyanide-nitroprusside reaction, developed by Brand et al. in 1930, provided a qualitative method of measuring excessive urinary excretion of cystine [1]. This test is positive when the urinary cystine level is greater than 75 mg/g creatinine [2].

Modern diagnostic methods may utilise a combination of laboratory tests, stone composition analysis, radiological investigation and genetic testing. Urinary cystine levels may be precisely measured using mass spectrometry, and are significantly elevated in cystinuria patients [4]. Levels of urinary cystine has also been used historically to detect carrier status, but a molecular genetic diagnosis is more reliable in the modern era. On urine microscopy, hexagonal crystals can be visualised which are pathognomonic [3]. Cystine stones are faintly radio-opaque and have a homogenous, ground-glass appearance [4], but may be missed on plain X-ray imaging. Cystine stones are often 100% cysteine but may contain variable amounts of calcium. CT-scanning allows accurate detection and localisation of cystine stones within the kidney and urinary tract.

3. Incidence and outcomes

Cystinuria is a rare inherited metabolic disorder, with an estimated incidence of 1:7000 live births [3]. The condition requires lifelong treatment, with the aim of minimising urinary calculi formation. However, the treatments involving high fluid intake, dietary modification, and urinary alkalinisation may be burdensome for some patients and compliance may be difficult. In those patients who continue to form recurrent cystine stones there may be an associated decline in kidney function over time [5].

4. Genetics of cystinuria

Cystinuria is an inherited renal stone disorder. Traditionally, a classification system based upon phenotype grouped patients as type I, II or III according to the levels of urinary cystine excreted

by their parents, known to be obligate heterozygotes [5]. However, identification of the individual mutations underlying cystinuria, in addition to recognised limitations of the phenotype-based classification, has led to a new genotype-based classification system being introduced [6].

The heterodimeric amino acid transporter responsible for cystine absorption in the renal proximal tubule is formed by two proteins, $b^{0,AT}$ and rBAT, which are joined by a disulphide bridge [7]. The *SLC3A1* gene, located on chromosome 2, encodes rBAT and mutations in both alleles (homozygous or compound heterozygous) of this gene lead to type AA cystinuria. The *SLC7A9* gene, located on chromosome 19, encodes $b^{0,AT}$ and homozygous mutations in this gene produce type B cystinuria. Due to digenic inheritance of two or more mutant alleles there exist much rarer forms, including type AB, type ABB and type AAB cystinuria [8]. Such mutations account for only 2% of cases [7] (**Table 1**). Interestingly, patients with underlying mutations in *SLC3A1* and *SLC7A9* may sometimes present with calcium stones [9]. Genetic screening in paediatric stone formers may allow for precise diagnosis and earlier opportunities for therapeutic and preventative measures to be adopted [10].

Recently, a further membrane protein has been identified which is involved in cystine transport in the S3 (distal) part of the proximal tubule; mutations in the gene encoding this protein could account for further cystinuria cases. The AGT1 protein is encoded by the *SLC7A13* gene, and forms a heterodimer with rBAT to facilitate cystine reabsorption in the S3 part of the proximal tubule [11]. The discovery of AGT1 working alongside rBAT in the S3 section of the proximal tubule may help explain the previously recognised paradox of $b^{0,AT}$ and rBAT being predominantly expressed in different segments of the proximal tubule. It is known that $b^{0,AT}$ expression is highest in the S1 (proximal) segment of the proximal tubule, whilst rBAT expression is mostly in the S3 (distal) segment [11].

The clinical phenotype does not vary between the three recognised subtypes of cystinuria, although male gender and early age of stone onset have been suggested to be poor prognostic signs [1, 4]. As treatment options do not vary between genetic subtypes of cystinuria individual genotyping has not been routinely performed in clinical practice [4].

Gene	OMIM id	Inheritance pattern	Cystinuria type
SLC3A1	104614	Autosomal dominant and recessive	Type A and type AA
SLC7A9	604144	Autosomal dominant and recessive	Type B and BB
2p21 deletion	606407	Autosomal recessive	Hypotonia-cystinuria syndrome

Table 1. Known genetic causes of cystinuria.

5. Syndromes associated with cystinuria

There are three recessive contiguous gene syndromes associated with cystinuria. These are the hypotonia-cystinuria syndrome (HCS) [12], atypical hypotonia-cystinuria syndrome

[13] and 2p21 deletion syndrome [4]. Each of these syndromes includes the homozygous disruption of the *SLC3A1* gene, and therefore produce cystinuria type AA as part of their clinical phenotype.

Hypotonia-cystinuria syndrome arises from homozygous deletion of two genes, *SLC3A1* and *PREPL*, and has the least severe phenotype. The main phenotypical features are infantile hypotonia, poor sucking and associated feeding problems, growth hormone deficiency leading to growth restriction, mild facial dysmorphic features and cystinuria type AA [12]. Atypical hypotonia-cystinuria syndrome, which features disruption to three contiguous genes, *SLC3A1*, *PREPL* and *C2orf34*, produces an intermediate phenotype featuring mild to moderate intellectual disability in addition to the features of hypotonia-cystinuria syndrome [13]. The 2p21 deletion syndrome, resulting from homozygous loss of four contiguous genes, *SLC3A1*, *PREPL*, *C2orf34* and *PPM1B*, produces a more severe phenotype, as expected, owing to the higher number of genes affected [4]. Patients with 2p21 deletion syndrome may have neonatal seizures, severe developmental delay and lactic acidosis in addition to the typical features associated with hypotonia-cystinuria syndrome (**Table 1**).

6. Biochemistry and urine analysis

Confirmation of significantly elevated urinary cystine levels is key to establishing a diagnosis of cystinuria. The cyanide-nitroprusside test is a qualitative test traditionally used as a screening test for cystinuria; a positive result occurs when the urine turns red after the addition of the reagent, indicating a urinary cystine level >75 mg/g creatinine [2]. However, as the cyanide-nitroprusside test is designed to detect amino acids containing a free sulfhydryl or disulphide bond there is the possibility of obtaining a false positive result in cases of homocystinuria and acetonuria [4]. Precise quantitative measurement of urinary cystine levels is therefore always indicated in cystinuria patients, and homozygotes will often have grossly elevated levels of >300–400 mg/L, compared to the normal level of 30 mg/L [4]. In addition to measuring urinary cystine levels by mass spectrometry, urine microscopy may also be performed to look for the hexagonal colourless crystals which are pathognomonic for cystinuria [4].

7. Treatment of cystinuria

Cystinuria is an inherited metabolic disorder requiring lifelong treatment. In the absence of any specific treatment to reverse the abnormal dibasic amino acid transport, the target of therapy is to prevent cystine stone formation and thereby minimise complications of recurrent nephrolithiasis. Management of patients should ideally be undertaken in dedicated metabolic stone clinics [14]. Initial treatment is focussed on increased fluid intake, dietary modification and urinary alkalisation, but these interventions are cumbersome and patient compliance often limits their effectiveness. In refractory cases, a cystine-binding drug may be added to the treatment regime, although continued adherence to the initial conservative treatments is crucial for successful outcomes. Surgical intervention is reserved for large or symptomatic calculi which are causing obstruction, infection or pain.

7.1. Fluid

Maintaining a high fluid intake, aiming to produce at least three litres of urine per day, is the cornerstone of successful cystinuria treatment. Establishing a hyperdiuresis reduces the cystine concentration in the urine, thereby reducing the risk of nephrolithiasis [4]. The therapeutic target is to keep urinary cystine levels below 300 mg/L [15]. Nocturnal intake of fluid, both before bed and ideally at least once overnight, is an important factor, in order to avoid the increased risk of stone formation associated with the body's natural tendency to concentrate urine overnight [16]. However, it is hard for patients to comply with long-term [15]. Continued high fluid intake is a crucial factor in determining treatment success in cystinuria, both in isolation and in patients also taking thiol-binding drugs [15]; patient education regarding this is essential to achieve compliance with this burdensome intervention.

7.2. Diet

Dietary modification can help reduce the risk of stone formation in cystinuria. Patients are advised to follow a low sodium and relatively low animal protein diet. A low sodium diet is effective as dibasic amino acid reabsorption in the proximal tubule is partially sodium-dependent; a low sodium intake encourages reabsorption of cystine and sodium, thereby minimising excess urinary cystine excretion [4]. A low animal protein, or ideally vegan diet, is advised as this leads to a more alkaline urine being produced and also reduces the intake of the amino acid methionine, which is the precursor to cysteine [16]. Recipe books have been written especially for cystinuric patients that provide ideas regarding foods with high fluid content and low animal protein [17].

7.3. Urinary alkalinisation

Cystine solubility is increased in alkaline pH; a target urinary pH of 7.0–7.5 is recommended in cystinuria patients [16]. This can be achieved either by supplementation with potassium citrate or sodium bicarbonate, or through following a vegan diet. Potassium citrate is the preferred medication, but its use is limited in patients with chronic renal impairment due to the risk of hyperkalemia. It is important for the urine to remain within the target pH range, as over-alkalinisation can paradoxically increase the risk of calcium stone formation. Patients can use urine dipsticks to regularly check their urine pH [16].

7.4. Cystine-binding thiol drugs

Thiol-containing medications (penicillamine, tiopronin and captopril) can play a role in cystinuria treatment. These drugs bind to cystine in the urine, reducing the disulphide bond which forms cystine and producing two molecules of cysteine which are more soluble [4].

The use of penicillamine and tiopronin may be limited by their side-effect profile. Captopril, an angiotensin converting enzyme inhibitor, may be used as an alternative, although there is not strong evidence for its use in cystinuria [16]. Therapeutic success (reduction in stone events) is only likely to be achieved if conservative measures such as increased fluid intake are also followed simultaneously. Clinical trials using a new thiol binding drug called bucillamine are underway and will be completed by March 2018 [18].

7.5. Surgical therapies

Although stone prevention is the aim of cystinuria management, in cases where medical therapy has failed minimally-invasive surgical intervention can be required to break up and remove stones. This may be through lithotripsy (or extracorporeal shock wave lithotripsy), ureteroscopy or percutaneous nephrolithotomy [16]. These techniques are similar to those used for other types of renal stones. However, extracorporeal shock wave lithotripsy may be less successful in cystinuria patients due to the recognised increased resistance of cystine stones to fragmentation by shock wave lithotripsy [4]. Cystinuria is a recognised form of staghorn calculus which may require open surgical intervention and even nephrectomy in some cases.

8. Conclusion

Although a rare inherited condition, cystinuria remains an important cause of renal calculi. Establishing the diagnosis is crucial in order to prevent further calculi formation in these patients, whose treatment is distinctly different to patients with the commoner calcium-containing calculi. Our increasing understanding of the underlying genetic mutations causing cystinuria provides further information on the condition, and may eventually lead to treatments targeted at the underlying defect. However, at present, preventative medical treatment is the mainstay of treatment, reducing the calculi burden in cystinuria patients and aiming to avoid the risk of chronic renal impairment posed by recurrent calculi formation.

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