REVIEW

# Cystine calculi: challenging group of stones

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Cystinuria is an autosomal recessive disorder in renal tubular and intestinal transport of dibasic amino acids, which results in increased urinary excretion of cystine, ornithine, lysine and arginine. It affects 1 in 20 000 people and is caused by a defect in the rBAT gene on chromosome 2. Development of urinary tract cystine calculi is the only clinical manifestation of this disease. Owing to recurrent episodes of stone formation, these patients require a multimodal approach to management. The role of medical management and minimally invasive surgery was reviewed for the treatment of cystinuria.

Cystine was described as an unusual chemical component in bladder calculi by Wollaston[1] about two centuries ago. He termed it cystic oxide. This nomenclature was later changed by Berzelius[2] to cystine because of the absence of an oxide component. The chemical structure of cystine was elaborated by Friedman[3] in the early 20th century. Cystinuria is recognised as increased urinary excretion of four amino acids—namely, cystine, ornithine, arginine and lysine. Among these, cystine is the only amino acid that is relatively insoluble in urine at normal pH. Thus, it predisposes to the formation of crystals and stones in the urinary tract at concentrations ⩾300 mg/l.

In general, cystine stones constitute 1–2% of urinary calculi.[4 5] The worldwide prevalence of cystinuria varies considerably, affecting 1 in 20 000 people. Cystine constitutes 6–8% of paediatric renal calculi.[6 7] Various studies showed that the peak age of onset of stones is in the third decade of life but can occur at any age. Most people with cystinuria have recurrent episodes of stones in their lifetime. Cystine stones are yellowish with a waxy appearance macroscopically and are characteristic flat hexagonal cystine crystals microscopically. Definitive diagnosis is made by a 24-h urine collection for cystine. Stone analysis provides definitive proof of the composition. Radiographically, cystine stones appear lightly opaque (due to the sulphur content) with homogeneous density, typically a ''ground-glass'' appearance.

The autosomal recessive pattern of cystinuria was first described by Harris *et al* in 1955.[8] Initially, three phenotypically distinctive groups of cystinuria, referred to as types I, II, and III based on the intestinal amino acid transport pattern,[9] were described. Later, this classification was criticised, as the widespread disparity of amino acids makes it difficult to differentiate type II cystinuria from type III. Two genes have been associated with type I (SLC3A1) and non-type I (SLC7A9) cystinuria, and multiple mutations of these genes have been identified. The type I form is completely recessive, whereas the non-type I form is incompletely recessive. Clinically, heterozygotes with type I mutations are silent whereas heterozygotes with non-type I (types II and III) mutations present with a wide range of urinary cystine levels; some even have symptomatic urolithiasis. Although the exact molecular basis for these differences is still under investigation, the future of medical management of cystinuria is based on molecular and gene therapy.

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## MEDICAL TREATMENT

As with all conditions predisposing to stone formation in the urinary tract, prevention rather than treatment of stones is the goal. In cystinuria the aim is to reduce urinary cystine levels below the solubility point. The natural history of cystinuria is marked by recurrent episodes of stone formation, which has been shown to be associated with chronic urinary tract infections, renal impairment and end-stage renal failure in some cases, requiring renal replacement. More than half of the people with cystinuria eventually develop stone disease, regardless of their age, and among them three quarters present with bilateral stone disease.[10]

### Hydration, dietary modification and urinary alkalinisation

The main aim of treatment is the prevention of new stones and the dissolution of existing ones. Hydration is the mainstay of the treatment. Patients are advised to wake up at night to drink water in addition to their daytime intake. Therefore, maintaining the urine output to keep up with cystine excretion helps the prevention of stone formation. To prevent nocturnal aggregation of crystals, 500 ml of water intake at bed time and another 300 ml overnight is advocated.[11] Others have stressed that patients should check their urine-specific gravity to maintain a level of ⩽1.010.[12]

Methionine, a component of high-protein foods, is a metabolic precursor of cystine; therefore, its restriction is advocated. Some have stressed the decreased intake of sodium, as it has been shown to be effective in reducing urinary cystine excretion.[13 14]

Urinary pH has a key role in the prevention of stone formation. Therefore, cystine stone formation can be reduced by increasing the pH level. Oral alkalinisation treatment is a safe and

**Abbreviations:** ESWL, extracorporeal shock wave lithotripsy; PCNL, percutaneous nephrolithotomy

effective way of keeping the urine pH between 7.5 and 8.0. Potassium bicarbonate is safer than the sodium compound (starting at 60–80 mEq/day).[15]

### Drug treatment

Failure of hydration, dietary modification and urinary alkalinisation requires the use of pharamacological treatment.

#### Penicillamine

A thiol derivative introduced in 1963, penicillamine cleaves the disulphide bond and creates compounds that are 50 times more soluble.[16] Adverse effects are mostly dose dependent and some authors have reported that they occur in ⩾50% of cases.[17] Side effects include gastrointestinal intolerance, rash, arthralgia, leucoplakia, proteinuria and nephritic syndrome. Vitamin $B_6$ deficiency due to thiol derivatives may need supplementation.[18]

#### α-Mercaptopropionylglycine

This drug has been in use since the late 1960s[19] and is less toxic than penicillamine, but has similar chemical action and mechanism of action to penicillamine and is 50% more effective.[20] α-Mercaptopropionylglycine has been reported to have achieved an 85% prevention rate (stone formation prevented in 23 of 27 patients) by Koide *et al*[21] The rate of adverse effects, although similar to penicillamine, is reported to be less (⩾50%).[22]

#### Captopril

The captopril–cystine complex formed as a result of binding of its thiol group to cystine is reported to increase cystine solubility by about 200 times.[23] Although the efficacy of captopril is still in question,[24] it is recommended as the drug of choice by Cohen *et al*[25] in patients with hypertension.

## UROLOGICAL INTERVENTIONS

Despite aggressive medical management, patients with cystinuria require 0.14–0.32 procedures per year.[26 27] Over the past few decades, minimal invasive techniques have markedly transformed the approach towards management of cystinuric stones.

### Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) is the primary treatment of choice for patients with stones measuring ⩽1.5 cm,[15] and the secondary treatment option after most of the instrumentation for larger stones. The success of ESWL is proportional to the number of shocks given at higher power, but treatment is limited to stones <1.5 cm.[15] More than one session of shock treatment may be required to breakdown the stones. ESWL may be used as an adjuvant to percutaneous nephrolithotomy (PCNL) and ureterorenoscopy.

### Percutaneous nephrolithomtomy

PCNL is considered the treatment of choice if ureteroscopy fails or stone load dictates the primary procedure. PCNL with ESWL gives acceptable results with respect to stone-free duration only if the entire stone load is taken out.[28 29] It is described by some authors as more problematic in stone treatment because of the hardness as well as the multiplicity of sites within the kidney, making the approach difficult. Multiple percutaneous procedures may be needed to remove the stone load.[30]

### Ureteroscopic management (retrograde)

Ureteroscopic manipulation of smaller distal-uretic and miduretic stones is an appropriate treatment option if the stone is accessible.[31] Lithoclast and holmium lasers (yttrium-aluminium-garnet) have improved the fragmentation of larger stones, which were difficult to handle with an electrohydraulic lithotripter. Holmium is considered superior to lithoclast as it produces smaller fragments with less chance of retrograde migration of the stone.[32 33]

## CONCLUSION

Patients with cystinuria are a challenging group of stone formers, best managed by a multidisciplinary approch whereby surgical and medical management go hand in hand. Despite advances in urological interventions, it remains a troublesome source of morbidity at urology centres. High stone-free rates can be achieved without the need for open surgery, and patients with cystinuria can benefit from contemporary interventions. Compliance of these patients with medical treatment is often poor, and most experience recurrent episodes of stone formation requiring multiple interventions. Frequent imaging of the patients with cystinuria should be carried out to identify early recurrence. Family members of patients with cystinuria should undergo screening.[34]

High fluid intake is advised during the day and overnight. Maintaining a daily urine output volume of ⩾3 litres is essential for therapeutic success regardless of drug treatment.[27] Medical treatment has its limitations, with a low success rate and a shorter stone-free duration. Closer vigilance by the doctor is required to maintain prophylactic management. These patients also require better insight into the disease process to improve compliance, which is important for medical management.

Although these stones are traditionally quite hard, some of the smaller, softer calculi will breakdown with ESWL and it is certainly worth attempting initially as it may prevent patients having more invasive interventions. The advent of flexible ureterorenoscopy and holmium laser has revolutionised the management of ESWL refractory cystine calculi, although these stones take longer to breakdown, and patience on the part of the surgeon is imperative. Multiple attempts at stone disintegration are often necessary. As cystinuria is a single gene defect, we can hope that, with genomic and proteomic advances, corrective intervention for the genetic anomaly may be available in the future.

Modern management of cystine stones should be with staged minimally invasive options to avoid the complications of multiple open procedures wherever possible in patients in whom stones are formed despite adequate medical treatment or as a result of poor compliance.

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## Jointzone.org.uk: rheumatology in a tablet form

As a medical student, house man and medical senior house officer, rheumatology was a scary and obscure subject for me. Rheumatology always required extra effort in revising for finals and membership exams of the Royal College of Physicians, as it is a subject that does not crop up frequently in everyday general medical practice. Until I came across the website www.jointzone.org.uk, sponsored by the Arthritis Research Campaign.

In its basic science area, the musculoskeletal and immune systems are explained in a simple and concise way, aided by diagrams.

It then takes you through the various disorders, explaining in an easy way all aspects of the disease with plenty of pictures, *x* rays and short video clips.

There follows a quick reminder of how to approach the patient, describing how to examine each joint, aided by a video demonstration. The main deformities are featured.

The website then proceeds to investigations. It briefly explains every test and its value in diagnosing a particular disorder. The imaging section provides samples of the tests and their interpretation, and even offers a small *x* ray quiz.

In the final section, the management of the various disorders is described, with special emphasis on pain control. Surgical treatment options are also discussed, as well as their outcomes and complications.

There is an interactive case studies section as well. In each case, you have the chance to choose which history questions to ask, examinations to do, investigations to order and treatments to give. Once completed, you can find out how well you did.

It is an excellent website, fun to go through, a valuable rheumatology revision tool for all medical students and junior medical trainees, and a useful reminder for our senior colleagues.

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