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SYMPOSIUM PAPER

# Cystinuria: the South Indian experience

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**Abstract** Cystinuria is reportedly a rare condition affecting the stone patients in India. This paper presents the occurrence of cystine-related abnormality in the population of stone patients reporting to the hospitals in South India. Two thousand and eight hundred urine samples from 1,300 patients attending the urinary stone clinic during the period 2004–2008 were assessed for cystinuria by performing the nitroprusside test on the early morning urine and random samples on the day of attendance. Urinary deposits were also studied in all the patients. Stones retrieved from 800 stone patients were analysed qualitatively and by Fourier Transform infra red (FTIR) spectroscopy. Cystinuria was identified in only three patients. None of these patients showed cystine crystals. Three other patients out of the 1,300 showed presence of cystine crystals in the urine deposit. FTIR spectroscopy of the stones retrieved from the patients showed presence of cystine in 19 out of the 800 stones analysed (2.375%). None of the patients with cystine in the stones had either cystine crystals in the urine or positive nitroprusside test for cystine. All the patients who had positive cystine, cystine crystals or cystine in stone analysis had other biochemical abnormalities. They were medically managed with appropriate biochemical corrective chemotherapy and had control of stone disease process. All the patients were advised purine restriction in the diet. It is concluded from the study that cystinuria is a rare entity in South India. It, however, exists in a small percentage of stone patients. Specific treatment with D-penicillamine was not administered to the patients in view of the high cost, nonavailability and possible toxicity. The patients considered above did not have intractable stone disease which was not amenable to usual modalities of directed medical therapy.

**Keywords** Cystinuria · Urolithiasis · Cystine crystal · Cystine stone · D-penicillamine

## Introduction

Cystine is a dibasic amino acid formed by the linkage of two cysteine molecules via a disulfide bond. Cystinuria is an inherited autosomal recessive [1] metabolic disorder characterized by inadequate reabsorption of cystine and the amino acids ornithine, arginine, and lysine from the renal proximal tubule and small intestine resulting in an excessive concentration of this amino acid in the urine. The only manifestation of cystinuria is cystine urolithiasis, which often recurs throughout a patient's lifetime. Cystine may precipitate out of the urine, if the urine is neutral or acidic, and form crystals or stones in the kidneys, ureters, or bladder. Mutations in the SLC3A1 and SLC7A9 genes cause cystinuria. These genes give instructions for producing the two parts of a transporter protein that is made primarily in the kidneys. The defects prevent proper reabsorption of basic, or positively charged amino acids such as histidine, lysine, ornithine, arginine and cystine [2]. Cystinuria is reportedly a rare condition affecting the stone patients in India. No significant report is available in literature on this problem from India. The objective of this paper is to assess the relevance of cystine metabolism in the stone population

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in South India. This paper presents the occurrence of cystine-related abnormality on the population of stone patients reporting to a stone clinic.

## Materials and methods

2,800 urine samples from 1,300 patients attending the urinary stone clinic during the period 2004–2008 were assessed for cystinuria by performing the nitroprusside test on the early morning urine and random samples on the day of attendance. Urinary deposits were also studied in all the patients. Stones retrieved from 800 stone patients were analysed qualitatively and by Fourier Transform infra red (FTIR) spectroscopy. Metabolic study including 24-h urine calcium, phosphorus, creatinine, uric acid, magnesium, sodium, potassium, oxalate and citrate and serum calcium, phosphorus, creatinine, uric acid and magnesium were assessed and compared between the three groups of patients and statistical significance of difference tested using ANOVA.

## Observations

Cystinuria was identified by nitroprusside test in only three patients. None of these patients showed cystine crystals on repeated urine examination. Three patients out of the 1,300 showed presence of cystine crystals in the urine deposit. None of the six patients had stone passage, radiological stone identification or stone retrieval. On analysing the 800 stones obtained from the patients, FTIR spectroscopy showed presence of cystine in 19 out of the 800 stone analyses done (2.375%). None of the patients with cystine in the stones had either cystine crystals in the urine or positive nitroprusside test for cystine. All the six patients who had either positive cystine or cystine crystalluria and the 19 patients with cystine-positive stone analysis had other biochemical abnormalities. There was, however, no significant variation between the biochemical values of the three groups (Table 1). All the patients were medically managed with appropriate biochemical corrective chemotherapy and had control of stone disease process for a period of follow-up ranging from 6 months to 3 years. Specific treatment with D-penicillamine was not administered to the patients in view of the high cost, nonavailability and possible toxicity. All the patients were advised to consume plenty of oral fluids, particularly lime juice and purine restriction in the diet.

## Discussion

Cystine stone formation is directly related to the level of cystine saturation of the urine. Cystine saturation is a function of cystine solubility, cystine excretion, and urine flow rate; the last two factors determine the urine cystine concentration. Therapy to reduce stone formation is focused on lowering urinary cystine concentration or increasing cystine solubility [1]. Worldwide, the overall prevalence of cystinuria is 1 person per 7,000 population [3, 4]. The prevalence has been reported to vary from 1 case in 15,000 in United States, 1 in 18,000 in Japan, 1 in 2,500 in Israel, 1 in 2,000 in Great Britain, 1 in 4,000 in Australia, 1 in 1,900 in Spain, 1 in 2,500 in Libyan Jews, and 1 in 100,000 in Sweden. A similar population study does not

**Table 1** Urine and serum biochemical parameters of patients with cystinuria, cystine crystals and cystine stones

| No. | Parameter | Cystinuria ($n = 3$) | Cystine crystals ($n = 3$) | Cystine stones ($n = 19$) | $P$ value |
|---|---|---|---|---|---|
| 1 | 24-h urine volume ($cm^3$) | 1,670 | 1,874 | 1,830 | NS |
| 2 | 24-h urine calcium (mg/day) | 256 | 275 | 258 | NS |
| 3 | 24-h urine phosphorus (mg/day) | 1,786 | 2,110 | 1,690 | NS |
| 4 | 24-h urine creatinine (mg/day) | 1.36 | 1.26 | 1.34 | NS |
| 5 | 24-h urine uric acid (mg/day) | 795 | 690 | 715 | NS |
| 6 | 24-h urine magnesium (mEq/day) | 6.3 | 8.1 | 7.5 | NS |
| 7 | 24-h urine sodium (mEq/day) | 167.3 | 156.9 | 180.4 | NS |
| 8 | 24-h urine potassium (mEq/day) | 56.7 | 49.7 | 57.3 | NS |
| 9 | 24-h urine oxalate (mg/day) | 78.3 | 89.7 | 70.4 | NS |
| 10 | 24-h urine citrate (mg/day) | 234 | 286 | 267 | NS |
| 11 | Serum calcium (mg%) | 8.6 | 9.6 | 90.7 | NS |
| 12 | Serum phosphorus (mg%) | 4.3 | 4.7 | 4.2 | NS |
| 13 | Serum creatinine (mg%) | 1.2 | 1.2 | 1.1 | NS |
| 14 | Serum uric acid (mg%) | 7.3 | 6.6 | 5.9 | NS |
| 15 | Serum magnesium (mEq/L) | 1.63 | 1.73 | 1.96 | NS |

appear to have been done so far in India. The Quebec Genetic Network Neonatal Screening Program reported the incidence of persistent cystinuria as 562 cases per million infants, a rate 7 times higher than for clinically manifested cystinuria in the adult population of Quebec. This suggests that many cystinuric individuals may not form stones. The findings of the present study indicate that the incidence of cystinuria is very low in South India. The presentation widely differed in the few cases encountered.

Cystinuria may be of three subtypes: Rosenberg I, II, and III. Type I heterozygotes show normal cystine levels. Types II and III often manifest cystinuria without cystine calculi and may be at increased risk for other types of urolithiasis. Type III shows an increase in plasma cystine concentration. The three types of patients encountered in the present series of patients may include any of the types describes above. A proper classification is not possible, as urine and serum cystine estimations were not performed. Cystinuria may be classified based on the urinary cystine level as phenotype I (recessive), phenotype II (dominant) and phenotype III (partially dominant). Cystinuria can also be classified based on the age at which symptoms first appear (i.e. infantile, juvenile and adolescent).

The most common symptom of cystinuria is formation of cystine kidney stones; in 10%, hypertension may occur. Unusual presentations include renal insufficiency, recurrent urinary tract infections, or kidney damage (sometimes called renal Fanconi syndrome) and hypophosphatemic rickets [5, 6]. Diagnosis is usually made when a patient develops a renal stone. Urinalysis will often show cystine crystals in the urine. Nitroprusside test is beneficial to detect cystine in urine. In the present study, diagnosis was made only on the positive nitroprusside test, presence of microscopic cystine crystals or the presence of cystine peaks in the FTIR analysis of stones.

The principle of treating cystinuria is to prevent renal stone formation. This can be achieved by reducing the urinary concentration of cystine [7] by high fluid intake, alkalinisation [8] or D-penicillamine [9]. The urine volume should reach 4 l per day. Mineral water and citrus juice are preferred [10]. A low methionine diet by avoiding animal proteins such as milk, eggs, cheese, and fish will help reduce the production of cystine in the body. Sodium intake may be reduced and dietary fibre increased [11]. Potassium citrate may reduce urine acidity [12, 13]. Medicines like D-penicillamine, alpha-mercaptopropionylglycine, captopril, or bucillamine bind to cystine and reduce the amount of cystine in the urine. In the present study, as the patients did not have intractable problems related to either stone or cystinuria, none of them required any of the above specified drug regimes. Nonavailability of the drug, high cost and possible side effects dissuaded prescription by the author.

## Conclusions

It is concluded from the study that cystinuria is a rare entity in South India. It, however, exists in small percentage of stone patients. Specific treatment with D-penicillamine was not administered to the patients in view of the high cost, nonavailability and possible toxicity. None of the patients considered above had intractable stone disease. They were amenable to usual modalities of directed medical treatment of the stone disease.

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