Urol Res (2007) 35:129–132
DOI 10.1007/s00240-007-0089-1

ORIGINAL PAPER

# The impact of new technology in the treatment of cystine stones

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Received: 25 February 2007 / Accepted: 9 March 2007 / Published online: 18 April 2007


**Abstract** Cystinuric patients frequently require stone removing procedures because of their high tendency to have recurrent urinary calculi. In the last 20 years the morbidity of stone treatment has been reduced by the introduction of endourologic procedures and shock wave lithotripsy (SWL), but cystine stones are not amenable to all minimally invasive procedures. The aim of our study was to assess the impact of new technology in the treatment of cystine stones. The records of patients observed at our institutions from 1978 to 2005 were reviewed. We retrospectively analysed the previous stone histories of all the patients who presented at our institutions for stone treatment who resulted to be cystinuric at our metabolic work up. Patients were divided in two groups according to the date of our first observation: group A comprised patients observed from 1978 to 1989 who mainly experienced traditional stone treatment and group B patients observed from 1990 to present who were preferentially treated with minimally invasive therapeutic modalities. A total of 48 cystinuric patients were observed (31 in group A and 17 in group B). The mean age ($38 \pm 15$ vs. $36 \pm 13$ years), the age at stone onset ($21 \pm 11$ vs. $21 \pm 12$) and the annual recurrence rate ($1.34 \pm 2.38$ vs. $1.16 \pm 1.11$ stones/year/pt) were not significantly different in the two groups. The male/female ratio was 18/13 and 8/9, respectively, in group A and B. In group A 16 patients underwent open surgical treatment for a total of 29 procedures (0.93 for patient) and four of them had nephrectomy; in group B only eight underwent open surgery but other seven had percutaneous surgery ($0.47 + 0.41$ procedure/patient). In group B 37 SWL treatments were performed (2.17 for patient) whereas patients in group A underwent only four SWLs. Renal function was impaired in six patients (19%) in group A with a patient requiring haemodyalitic treatment and in one patient (6%) in group B. Compared to the traditional stone treatment, after 1990 fewer cystinuric patients required open surgery and none underwent nephrectomy or developed severe renal failure. Our results indicate that the actual care of patients with cystine stones should still be improved requiring a comprehensive approach in order to avoid inappropriate SWL treatments and more attention to early diagnosis and preventive measures.

**Keywords** Cystinuria · Lithotripsy · Urinary calculi · Renal function

## Introduction

Cystinuric patients frequently require stone removing procedures because of their high tendency to have recurrent urinary calculi. In the last 20 years the morbidity of stone treatment has been reduced by the introduction of endourologic procedures and shock wave lithotripsy, but cystine stones are not amenable to all minimally invasive procedures. The aim of our study was to assess the impact of new technology in the treatment of cystine stones.

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## Materials and methods

We reviewed the records of patients in whom stones were treated at our institutions from 1978 to 2005. In our stone patients the presence of cystinuria was routinely assessed by using cyanide-nitroprusside test (Brand's test). Patients with positive cyanide-nitroprusside test were further studied for identification of urine amino acids by quantitative ion-exchange chromatography. Pathological cystinuria was assessed in 48 (1.68%) out of 2,842 patients with renal stones.

At the first visit we recorded data including patient's sex and age, age at onset of symptom, number of stone episodes, modality of previous procedures for stone treatment and actual renal function.

Serum samples were taken from all patients and 24 h urine samples were collected for metabolic evaluation.

We retrospectively analysed the previous stone histories of all the patients who presented at our institutions for stone treatment who resulted to be cystinuric at our metabolic work up.

Patients were divided in two groups according to the date of our first observation: group A comprised patients observed from 1978 to 1989 who experienced traditional stone treatment and group B patients observed from 1990 to present who were preferentially treated with minimally invasive therapeutic modalities.

## Results

A total of 48 cystinuric patients were observed (31 in group A and 17 in group B) (Table 1).

The mean age of patients was $37.2 \pm 17.1$ years for group A and $36.0 \pm 13.3$ for group B ($P = 0.79$), whereas the age at stone onset was $21.7 \pm 12.1$ and $21.7 \pm 12.3$ ($P = 0.79$).

In most of the patients cystinuria was first diagnosed at presentation to our institutions (100% in group A, 71% in group B).

Renal stones were recurrent in 27 (87%) and 16 cases (94%), while other 4 and 1 patients were observed at their first stone. The male to female ratio was 1:0.72 and 1:1.12, respectively, in group A and B.

The mean number of stone episodes for patient was $20.3 \pm 39.0$ versus $12.1 \pm 12.7$ ($P = 0.40$) and the mean interval to first recurrence was $2.56 \pm 3.05$ versus $3.45 \pm 4.25$ years ($P = 0.46$). The recurrence rate 5 years after the first renal stone was 24/31 (77%) and 14/18 (78%).

The annual recurrence rate was $1.34 \pm 2.38$ and $1.16 \pm 1.11$, respectively, in group A and B.

Renal function was impaired in six patients (19%) and in only one patient (6%) in group A and B, with a patient requiring haemodyalitic treatment in group A.

Mean serum creatinine was not significantly different between the two groups ($0.77 \pm 0.77$ vs. $1.01 \pm 0.31$ mg/dl; $P = 0.372$).

In group A 16 patients necessitated open surgical treatment for a total of 29 procedures (0.93 for patient) and four of them had nephrectomy; in group B only eight underwent open surgery but other seven had percutaneous surgery (0.47 + 0.41 procedure for patient).

Patients in group A and B underwent, respectively, seven and eight retrograde endoscopic procedures including ureteroscopy, basket stone extraction, lithotripsy of vescical stone and chemolysis by irrigation of ureteral catheter or nephrostomy.

In group B a total of 37 extracorporeal shock wave treatments were performed (2.17 for patient) whereas in group A patients underwent only four treatments.

The annual rate of open procedures per patient in group A and in group B were, respectively, $0.091 \pm 0.125$ and $0.058 \pm 0.130$ ($P = 0.41$) whereas the annual rate of endoscopic procedures were, respectively, $0.013 \pm 0.032$ and $0.118 \pm 0.359$ ($P = 0.11$).

The annual rate of extracorporeal lithotripsy per patient was significantly ($P = 0.000$) lower in group A ($0.007 \pm 0.025$) with respect to group B ($0.312 \pm 0.409$).

Finally the total annual rate of procedures per patient was significantly ($P = 0.007$) lower in group A ($0.111 \pm 0.138$) than in group B ($0.493 \pm 0.740$).

## Discussion

Demographics of an inherited defect should remain stable during years, but surprisingly the male to female ratio of our patients with cystine stones was different in the group observed in more recent years with respect to the group observed 20 years ago.

Cystinuria is a genetic defect that may result in the formation of recurrent cystine calculi with about 3–59% of

**Table 1** Demographics of cystinuric stone patients

| Group | N° pt | M/F | Age (years) | Age onset (years) | Family history | Stone recurrence (stones/years/pt) |
|---|---|---|---|---|---|---|
| 1978–1989 | 31 | 18/13 | $37.2 \pm 17.1$ | $20.7 \pm 12.1$ | 11/31 (35%) | $1.34 \pm 2.38$ |
| 1990–2004 | 17 | 8/9 | $36.0 \pm 13.3$ | $21.7 \pm 12.3$ | 7/17 (41%) | $1.16 \pm 1.11$ |
| | | $P = 0.46$ | $P = 0.79$ | $P = 0.79$ | $P = 0.11$ | $P = 0.77$ |

patients with cystinuria developing renal stone during their lifetime.

Cystine stone formation is mainly related to the degree of urinary excretion of cystine (particularly elevated in homozygous subjects) but other unknown factors could play a minor role such as presence of concomitant anatomic or metabolic individual conditions or dietary habits and lifestyle. In fact relatives of patients forming cystine stones sometimes present with significant cystinuria but without stone formation. On the other hand patients with cystinuria tend to develop symptomatic calculi in cluster [1], with a slight predominance of stone formation after the age of 34 and a subset of patients forming exclusively unilateral calculi [2].

In general the incidence of nephrolithiasis is greater in males but it has been described that, within the past 25 years, there has been a progressive increase in the number of female renal stone formers.

This trend could be related to relatively low urine volumes and to recently acquired dietary habits of the female population that could trigger stone formation also in females with cystinuria.

Compared to the traditional surgical mode of stone treatment, after 1990 fewer cystinuric patients required open surgery and none underwent nephrectomy or developed severe renal failure.

However, the impact of new technologies seem to be less relevant for cystine stone patients with respect to what has been observed for patients with other type of stone disease.

Any type of stone today (except for the staghorn) requires less surgical procedures if compared to series conducted in the past.

Medical treatment maintains a pivotal role in the management of cystine stone disease because only active medical management seems able to decrease the incidence of surgical interventions in patients with cystinuria.

In fact a significantly fewer number of surgical procedures per year were requested by patients with cystinuria compliant with medical treatment with respect to those non compliant with treatment [3].

Although the genetics of cystinuria have been extensively investigated and explained during the last 15 years [4], the principles of medical treatment remain unchanged by many years.

It is now well demonstrated that cystinuria is related to mutations in SLC3A1 (type A) and SLC7A9 (type B). Furthermore many different mutations have been described and genotype–phenotype correlations were well explained.

Medical treatment still relies on hyperdiuresis, alkalinization and sulfhydryl compounds such as D-penicillamine and tiopronin [5].

In particular sulfhydryl agents are difficult to handle because of the potential risk of undesirable side effects. D-penicillamine has been applied for the dissolution of cystine stones in the urinary tract but its use has been strongly limited by potential toxicity. Alpha-mercaptopropionylglycine or tiopronin causes fewer side effects and it is more effective than D-penicillamine, but also can induce proteinuria with cases of nephrotic syndrome reported.

The medical management of cystinuria is challenging and adequate follow up is crucial.

Frequent clinical, radiological and laboratory surveillance is of primary importance in order to motivate patients to maintain compliance with treatment.

Our results indicate that the care of patients with cystine stones still requires more attention to preventive measures in order to avoid stone recurrence and invasive treatments.

Unfortunately the diagnosis of cystinuria is often delayed of many years from its clinical presentation owing to the absence of a reliable stone analysis or a screening test of the urine for cystinuria.

In fact most of the cystinuric patients observed in this study presented without a previous diagnosis of cystinuria and none was on pharmacological treatment with thiols.

The availability of less invasive modalities for stone treatment cannot justify the lack of an intensive search for the presence of cystinuria among all the patients presenting with renal stones. Urine testing for cystinuria and appropriate analysis of stones or stone fragments after lithotripsy is mandatory especially for patients with recurrent stones or presenting with stones in younger ages.

We previously reported that a significant reduction of stone formation can be achieved with tiopronin administration after the diagnosis of cystinuria [6, 7]. The efficacy of the treatment with thiols was similar in the patients observed by us in more recent years (unpublished data). Nevertheless a complete remission of the disease was never obtain due to insufficient compliance to treatment with thiols and to their side effects requiring withdrawal in about 25% of cases.

For this reason the care of patients with cystine stones still require particular skilfulness and dedication to motivate patients to continue treatment in order to avoid stone recurrence and invasive treatments.

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