

Pediatric Cystine Calculi in West of Iran

A Study of 22 Cases

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Introduction: Cystinuria is an autosomal recessive disorder which clinically presents as cystine calculi. In this study, we reviewed cystine calculi cases in the west of Iran to determine their common presentations and response to different therapeutic modalities.

Materials and Methods: Between 1999 and 2005, we had 22 pediatric patients (11 boys and 11 girls) with cystine calculi. The demographic characteristics and clinical data of the patients as well as the treatment results were reviewed.

Results: The mean age of the patients was 34.20 ± 42.99 months (range, 4 to 156 months). They were followed for a mean duration of 23 months (range, 3 to 70 months). Thirteen patients (59.1%) had bilateral and 9 (41%) had unilateral kidney calculi. The sizes of the calculi were between 2 mm and 20 mm. Nine patients (41%) had renal atrophic changes and 1 (4.5%) had obstructive acute renal failure. Hydration and urinary alkalinization were administered to all of the patients which yielded an excellent result in 54.5% and a poor response in 27.2%. Captopril started for 5 patients was effective only in 1. D-penicillamine had no favorable response. Extracorporeal shockwave lithotripsy was successful in 5 attempts and failed in 4. Surgical interventions were performed for 13 patients (59.1%) and 6 (27.2%) required more than 1 surgical operation.

Conclusion: We recommend metabolic workup of childhood urolithiasis and appropriate medical management of its underlying disease. We also recommend minimally invasive urologic techniques including shockwave lithotripsy only when there are clear indications for nonmedical procedures.

Keywords: cystine, child, urinary calculi, treatment

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INTRODUCTION

Cystinuria is an autosomal recessive disorder in reabsorptive transport of cystine and other dibasic amino acids (lysine, ornithine, and arginine) in the kidney and the small intestine.^(1,2) Thus, there is excessive urinary excretion of dibasic amino acids. But, only cystinuria is of clinical significance due to its insolubility in the normal urinary pH. It has also the highest tendency to be crystallized and cause recurrent urolithiasis.⁽³⁾

Cystinuria may be particularly more important in children, firstly because

it accounts for 6% to 8% (in some reports up to 10%) of pediatric urinary calculi compared with 1% to 2% in adults⁽²⁾; secondly, if the underlying problem is not properly diagnosed and treated, there is a high risk of damage to the kidney due to its recurring nature.⁽⁴⁻⁶⁾ In this study, we describe 22 cases of cystine calculi in pediatric patients and evaluate their common presentations and response to different therapeutic modalities.

MATERIALS AND METHODS

Between 1999 and 2005, 22 pediatric

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patients with cystine calculi had presented to pediatric nephrology clinic of Razi hospital in Kermanshah. We retrospectively reviewed their medical records. The demographic characteristics and clinical data of the patients were studied focusing on the initial presentations, number of the calculi, bilateral or unilateral involvement of the kidney, complications of the calculi, the treatment, and the outcome. Cystinuria was confirmed in the patients by one or a combination of the following criteria: detection of cystine crystals in the first morning urine sample, positive cyanide nitroprusside test, and analysis of the calculi.

All of the patients were managed by our conservative treatment protocol including hydration (2 L/m²/d of oral water intake), urine alkalization (potassium citrate oral solution, 2 meq/kg/d in 3 divided doses), and dietary sodium restriction. Adequacy of the alkali therapy was evaluated according to the urine pH measured by urine pH meter and proper hydration was monitored by maintaining urine specific gravity around 1.010.

Physical examination and laboratory evaluations including ultrasonography, urine pH, and urine specific gravity were performed monthly for follow-up. An excellent response to treatment was defined as no calculus formation after the treatment regarding ultrasonographic results; a partial response was defined as less than 3 calculi per year; and a poor response was defined as 3 or more calculi per year.

For the patients with a poor response to this initial protocol, captopril (0.5 mg/kg/d to 1 mg/kg/d) was added and their response to the treatment was re-evaluated. D-penicillamine (20 mg/kg to 40 mg/kg) was started for the patients with a poor response to captopril and the efficacy of this drug was also evaluated regarding the promotion of further calculus formation. In special cases, such as large symptomatic calculi or obstruction, we referred the patients to a pediatric urologist for performing extracorporeal shockwave lithotripsy (SWL) or surgical intervention.

RESULTS

Of 22 patients, 11 (50%) were boys and 11 (50%) were girls. Thirteen patients (59.1%) were younger than 2 years of age at presentation. The mean age

Table 1. Number of Calculi and Clinical Presentations in Patients with Cystine Calculi*

Characteristics	Number of Patients [†]
Initial clinical presentation	
Nonspecific	13 (59.1)
Urinary tract infection	7 (31.8)
Hematuria	1 (4.5)
Failure to thrive	1 (4.5)
Number of calculi	
≥ 4	14 (63.6)
2 or 3	4 (18.2)
1	4 (18.2)

*Values in parentheses are in percents.

†Because of rounding, percentages may not all total 100.

of the patients at presentation was 34.20 ± 42.99 months (range, 4 to 156 months). They were followed for a mean duration of 23 months (range, 3 to 70 months). The initial presentations of the patients and number of their calculi are summarized in Table 1. Thirteen patients (59.1%) had bilateral and 9 (41%) had unilateral kidney calculi. The calculi were detected in the kidneys, the kidneys and the ureters, and the bladder and the kidneys in 17 (77.3%), 3 (13.6%), and 2 (9.1%) patients, respectively. The sizes of the calculi were between 2 mm and 20 mm. Complications occurred in 10 patients (45.5%), mostly before the initiation of the treatment. Nine patients (41%) had renal atrophic changes and 1 (4.5%) had obstructive acute renal failure.

All of the patients were first treated conservatively and excellent response was achieved in 12 (54.5%). Their response to the treatments and the next measures are shown in Table 2.

Shockwave lithotripsy was performed for 8 patients (36.4%). Two did not return for the follow-up and the 6 remaining underwent an overall of 9 sessions of SWL which was successful in 5 cases (55.6%).

Surgical interventions were performed for 13 patients (59.1%) and 6 (27.2%) required more than 1 surgical operation. For 12 (54.5%), 4 (18.1%), and 1 (4.5%) patients, open lithotomy (18 times), percutaneous nephrolithotomy, and transureteral lithotomy were performed, respectively. Three patients (13.6%) required a combination of these surgical methods.

DISCUSSION

The incidence of cystinuria and cystine calculi varies

Table 2. Patients' Response to Medical Treatments*

Treatment Modality	Outcome				
	Excellent Response	Partial Response	Poor Response	Lost to Follow-up	Discontinuation of Treatment
Conservative	12 (54.5)	0	6 (27.3)	2 (9.1)	2 (9.1)
Captopril	1 (4.5)	2 (9.1)	2 (9.1)	0	0
D-penicillamine	0	0	2 (9.1)	0	0

*Values in parentheses are in percents.

according to geographic areas. Newborn screening programs have estimated a prevalence of 1:2000 in the United Kingdom, 1:4000 in Australia, 1:15 000 in the United States, and 1:2500 in Libyan jews.⁽²⁾ More than 50% of cystinuric patients develop cystine calculi during their lifetime.⁽⁴⁾ In children, review of the literature on the composition of urinary calculi yields different contributions of cystine calculi in various populations. For example, in Croatia, up to 10% of the pediatric urolithiasis cases are cystine calculi,⁽⁷⁾ while this rate is 2%, 2%, 2.4%, and 2% in Armenia,⁽⁸⁾ Turkey,⁽⁹⁾ Kuwait,⁽¹⁰⁾ and the United States,⁽¹¹⁾ respectively. Only 1 published study of childhood urolithiasis has been performed in Iran in which cystinuria has been detected in 6 of 125 patients (4%).⁽¹²⁾

In the present study, we described 22 cases of cystine calculi in children in the west of Iran during a 6-year period (1999 to 2005). In our case series, the numbers of boys and girls were equal. In a study of urolithiasis in Tunisian children, there were 4 cases of cystine calculi, 3 of whom were boys and only 1 was girl.⁽¹³⁾ In another study in Jordan on 20 patients with cystine calculi, 16 were male and 4 were female, but only 4 patients were younger than 14 years.⁽¹⁴⁾ In another study in Italy, the female-male ratio (especially in adults) was 0.64:1.⁽¹⁵⁾

The early presentation of the cystine calculi was one of the most interesting findings in our patients. The peak age of onset of urolithiasis is the third decade of life;⁽²⁾ however, in our patients, mean age of the disease onset was 34 months and we had even a 4-month-old patient with cystine calculus. This implies that cystinuria should be considered as a likely etiology of urolithiasis even in very young patients. Therefore, metabolic workup of cystinuria is mandatory in young children presenting with urinary calculi. In addition, significant differences in the age of presentation of cystine calculi in various reports could be due to the genetic factors in the cystinuric

patients who had been studied.⁽¹⁾

Thirteen out of 22 cases in our series were detected during the evaluation of nonspecific symptoms by ultrasonography. This allows us to speculate that some cases of cystine calculi in adulthood are the undiagnosed cases since infancy and childhood. Urinary tract infection was present in 32% of our patients. This finding emphasizes the consideration for the underlying metabolic disorders in such conditions.

Bilateral nephrolithiasis was detected in 59% of our patients, and 14 patients (63.6%) had more than 4 calculi. The presence of multiple calculi together with the recurring nature of the cystine calculi predispose the patients to renal parenchymal damage. On the other hand, in 9 (41%) patients, only 1 kidney was involved. Some other reports of cystine calculi have also mentioned this laterality of the cystine calculi in adults.⁽¹⁶⁾ We have no clear explanation for this laterality, but it could be due to minor anatomical differences between the 2 kidneys or some undetermined factors.

Our patients had a rather high rate of complications (45.4%). Nine (41%) of them had atrophic changes in the kidneys mostly at presentation and before any therapeutic intervention. This finding indicates the importance of the early diagnosis and treatment of cystine calculi before any irreversible kidney damage.

All of our patients were initially treated by hydration, dietary sodium restriction, and alkali therapy. Of the patients, 12 (54.5%) showed excellent response to this method of treatment, which is indicative of the efficacy of conservative treatment. Interestingly, in spite of undesirable taste of the alkali solution, we had a low rate of noncompliance even in young infants. This is in contrast to some reports of adult patients with high rates of noncompliance to the conservative treatment.⁽¹⁷⁾ Captopril was started on for 5 patients; 1 had excellent response, 2 had partial

response, and 2 had poor response to captopril. There are conflicting reports of captopril efficacy in cystinuria. Some researchers have found it to significantly decrease urinary cystine excretion and calculus formation, especially in adults. In contrast, several reports have failed to show a significant effect of this drug, mostly in children.⁽¹⁸⁾ Our results indicate that, at least in children, captopril cannot be assumed as a very effective treatment of cystine calculi and should be tried in case of noncompliance and poor response to conservative treatments. We started D-penicillamine for 2 patients, but no decrease was seen in the calculus formation; however, we did not find any significant side effect either.

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Finally, SWL was successful in 5 attempts and failed in 4. This is in agreement with other reports indicating that the stone-free rates after SWL are significantly higher in children comparing to adults;⁽⁴⁾ nonetheless, it may depend on the localization of the calculi.⁽¹⁹⁾ Surgical interventions were required in the majority of our patients (59%). About 27% of them underwent more than one operation and many of these operations were performed before starting the medical management. This trend can impose a significant financial burden on the patient's family and the medical system and also a higher risk of renal parenchymal damage. Conservative and pharmacologic treatment may decrease the need of surgical intervention significantly and should be tried initially.

CONCLUSION

In pediatric urolithiasis, we recommend metabolic workup, appropriate medical management of the underlying cause, and using minimally invasive urologic techniques including SWL when there are clear indications of nonmedical procedures.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Goodyer P, Saadi I, Ong P, Elkas G, Rozen R. Cystinuria subtype and the risk of nephrolithiasis. *Kidney Int.* 1998;54:56-61.

2. Shekarriz B, Stoller ML. Cystinuria and other noncalcareous calculi. *Endocrinol Metab Clin North Am.* 2002;31:951-77.
3. Rutchik SD, Resnick MI. Cystine calculi. Diagnosis and management. *Urol Clin North Am.* 1997;24:163-71.
4. Knoll T, Zollner A, Wendt-Nordahl G, Michel MS, Alken P. Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. *Pediatr Nephrol.* 2005;20:19-24.
5. Kirsch-Noir F, Thomas J, Fompeydie D, Debre B, Zerbib M, Arvis G. Cystine lithiasis: study of a series of 116 cases. *Prog Urol.* 2000;10:1135-44.
6. Tekin A, Tekgul S, Atsu N, Sahin A, Bakkaloglu M. Cystine calculi in children: the results of a metabolic evaluation and response to medical therapy. *J Urol.* 2001;165:2328-30.
7. Biocic M, Saraga M, Kuzmic AC, et al. Pediatric urolithiasis in Croatia. *Coll Antropol.* 2003;27:745-52.
8. Sarkissian A, Babloyan A, Arikoyants N, Hesse A, Blau N, Leumann E. Pediatric urolithiasis in Armenia: a study of 198 patients observed from 1991 to 1999. *Pediatr Nephrol.* 2001;16:728-32.
9. Ozokutan BH, Kucukaydin M, Gunduz Z, Kabakcioglu M, Okur H, Turan C. Urolithiasis in childhood. *Pediatr Surg Int.* 2000;16:60-3.
10. el-Reshaid K, Mughal H, Kapoor M. Epidemiological profile, mineral metabolic pattern and crystallographic analysis of urolithiasis in Kuwait. *Eur J Epidemiol.* 1997;13:229-34.
11. Sternberg K, Greenfield SP, Williot P, Wan J. Pediatric stone disease: an evolving experience. *J Urol.* 2005;174:1711-4.
12. Kheradpir MH, Bodaghi E. Childhood urolithiasis in Iran with special reference to staghorn calculi. *Urol Int.* 1990;45:99-103.
13. Kamoun A, Daudon M, Abdelmoula J, et al. Urolithiasis in Tunisian children: a study of 120 cases based on stone composition. *Pediatr Nephrol.* 1999;13:920-5.
14. Bani Hani I, Matani Y, Smadi I. The value of family screening for patients with cystine stone disease in northern Jordan. *Br J Urol.* 1998;81:663-5.
15. Trinchieri A, Dormia G, Montanari E, Zanetti G. Cystinuria: definition, epidemiology and clinical aspects. *Arch Ital Urol Androl.* 2004;76:129-34.
16. Purohit RS, Stoller ML. Laterality of symptomatic cystine calculi. *Urology.* 2003;62:421-4.
17. Pietrow PK, Auge BK, Weizer AZ, et al. Durability of the medical management of cystinuria. *J Urol.* 2003;169:68-70.
18. Joly D, Rieu P, Mejean A, Gagnadoux MF, Daudon M, Jungers P. Treatment of cystinuria. *Pediatr Nephrol.* 1999;13:945-50.
19. Slavkovic A, Radovanovic M, Siric Z, Vljakovic M, Stefanovic V. Extracorporeal shock wave lithotripsy for cystine urolithiasis in children: outcome and complications. *Int Urol Nephrol.* 2002-2003;34:457-61.

EDITORIAL COMMENT

I read, with great interest, the article by Dr Seyedzadeh and his colleagues. The authors described the medical management and prevention of the cystine calculi. Previous studies from our country have suggested that captopril regimen and strict urinary alkalization could prevent the recurrence of the cystine calculus in 34 children.⁽¹⁾ Furthermore, based on our experience, we propose a therapeutic algorithm for patients with cystine nephrolithiasis. Hyperdiuresis, alkalization (optimally by potassium citrate and simple urinary pH measurement every 6 hours for citrate dosage adjustment), and diet precautions (moderate animal protein and salt intake) should be initially presented to all patients as the basic therapeutic regimen. Thiol derivatives should be considered early perioperatively or to dissolve preexisting stones in patients with a heavy cystinuria of 800 mg or greater daily, or high metabolic calculus activity of more than 1 calculus yearly. Thiols should also be administered when basic measures fail to inhibit calculus recurrence or the significant growth of preexisting calculi. In any case, hyperdiuresis and alkalization should not be neglected.

To our knowledge, our report represents the largest single-center study (516 patient-year) of the long-term results of medical therapy for cystine urolithiasis to date, and the 17 years' follow-up will be published soon for clarifying the long-term durability, effectiveness, feasibility, and cost-effectiveness of these strict measures. Certain comparable single-center studies using a similar therapeutic schedule have been reported.⁽²⁾ The study of Chow and Strem included 16 adults followed for 104 patient-year

with a minimum follow-up of 6 months (average, 6.5 years). Results in our patients generally confirm those of Chow and Strem and highlight the difficulty of arresting calculus formation in patients with homozygous cystinuria even when treated by a homogeneous dedicated team that performs frequent clinical, radiological, and laboratory follow-up studies. We observed that the overall compliance and longevity of the treatment success in our patient population are optimal.

Interestingly patient perception of the degree of compliance corresponded poorly to the physician perception, educational status, as well as to the results of 24-hour urine samples. While patients who achieved therapeutic success considered themselves compliant, similar self-perceptions were noted in noncompliant patients. This lack of insight portends obvious difficulties in those with uncontrolled cystinuria. These difficulties noticed by our patients clearly suggest avenues for improving future medications and dose regimens.

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REFERENCES

1. Kajbafzadeh AM, Vejdani K. Captopril and strict urinary alkalization for the prevention of cystine stone recurrence in children. *J Endourol.* 2002; 16:A108.
2. Chow GK, Strem SB. Medical treatment of cystinuria: results of contemporary clinical practice. *J Urol.* 1996;156:1576-8.