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Case Series

Evaluating the efficacy of triple therapy incorporating low-dose D-penicillamine in pediatric patients with cystinuria: A case series analysis

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Abstract
Cystinuria is a hereditary disorder characterized by recurrent kidney stone formation, which poses significant challenges to affected individuals and their families. This study examines four pediatric cases of cystinuria referred to the Shahrekord Pediatric Nephrology Clinic in southwestern Iran over different time periods. Due to the presence of large and numerous stones, these patients experienced substantial renal injury, necessitating multiple surgical interventions and stone fragmentation procedures. Following the initiation of a medical treatment regimen that included low-dose D-penicillamine capsules (10 mg/kg daily), vitamin B6 tablets (4 mg/kg daily), and potassium citrate (1 mL/kg daily), none of the patients required further surgical intervention, underwent stone fragmentation, or experienced new renal damage. Additionally, no adverse effect related to the treatment was observed during several years of follow-up. The patients underwent routine laboratory tests and general ultrasound examinations every three months, and no drug-related complications were noted throughout the follow-up period.
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Introduction

Inherited transport defects result in the formation of cystine stones due to excessive excretion of the amino acid cystine in the kidneys, leading to a condition known as cystinuria. This disorder causes supersaturation in the renal system, significantly increasing the risk of stone formation and accounting for approximately 1% to 2% of all kidney stones in adults (1,2). Management of cystinuria typically involves a combination of interventions, including urinary dilution, alkalinization, and pharmacotherapy, along with regular monitoring of urinary pH (3). The standard recommended dose of D-penicillamine for pediatric patients is 30 mg/kg, administered in two or three divided doses daily. However, this treatment is associated with several serious complications, including aplastic anemia, renal toxicity, proteinuria, and nephrotic syndrome (4). To mitigate the need for frequent and invasive surgical procedures, as well as to alleviate pain and reduce the financial burden on patients and their families, this case series study evaluates the effectiveness of medical treatment using low-dose D-penicillamine in pediatric patients with cystinuria.

Case Presentation

All cases were referred by a urologist due to the presence of multiple renal stones and a history of multiple lithotripsy procedures. Additionally, the nitroprusside reaction test and baseline urine cystine levels were positive in all patients. In this study, D-penicillamine was administered at a dosage of 10 mg/kg/d, one-third of the standard recommended dose, to treat four patients with cystinuria who were referred to the Shahrekord Pediatric Nephrology Clinic. The patients were monitored every three months through ultrasound examinations and blood and urine tests. All patients received a three-drug regimen, which included low-dose D-penicillamine capsules (10 mg/kg/d), vitamin B6 tablets, and potassium citrate. Furthermore, the normal 24-hour urinary cystine level in children is considered to be a maximum of 30 mg.

Case 1

A 6-year-old patient diagnosed with cystinuria in 2017 presented with a large staghorn calculus in the left kidney, which necessitated open surgical intervention. Due to the recurrent formation of stones and subsequent surgeries, multiple scars developed in the left kidney, resulting in reduced renal size. Since the initial surgery in 2017, the patient has been monitored every three months through blood tests and ultrasound examinations. At baseline, imaging revealed one stone measuring 13 mm in the upper calyx, two stones measuring 12 mm and 11 mm in the middle calyx, and one stone measuring 8 mm in the lower calyx of the left kidney. Notably, no stone or hydronephrosis was detected in the right kidney.

Following 24 months of treatment with a triple therapy, a stone measuring 9 mm was identified in the middle calyx of the left kidney, while the right kidney remained completely normal.

Case 2

A 6-year-old patient diagnosed with cystinuria in 2016 experienced the formation of large and numerous kidney stones. The patient was treated several times with extracorporeal shock wave lithotripsy (ESWL) by a urologist. The patient also underwent bladder surgery at 9 months of age. From 2016 to 2023, the patient was managed with a three-drug regimen and did not require any surgical interventions or ESWL during this period. The patient was monitored every three months through blood tests and ultrasound examinations. At the time of admission, a 5 mm stone was identified in the upper pole of the left kidney without associated hydronephrosis. Additionally, a 5 mm stone was noted in the middle calyx of the right kidney, accompanied by mild hydronephrosis due to a 10 mm stone located in the distal ureter. After 10 months of treatment, a 4 mm stone was observed in the upper calyx of the left kidney, while the right kidney was free of stones and any pathological masses.

Case 3

A 2-year-old patient diagnosed with cystinuria in 2016 presented with bilateral reflux, resulting in multiple injuries and scars in both kidneys, as well as recurrent stone formation. In 2016, the patient underwent open surgery for a staghorn calculus in the right kidney. The patient had a history of stone formation since the age of one and had previously undergone ESWL. From 2016 to 2023, the patient was managed with a three-drug regimen and monitored every three months through blood tests and ultrasound examinations. During this period, the patient did not maintain continuous medication, but neither ESWL nor surgical interventions were repeated. At the time of the patient's visit, caliceal stones were identified in the upper to lower thirds of the right kidney, with diameters of 8 mm, 9.5 mm, 10 mm, 8.5 mm, and 7 mm, respectively. Additionally, stones measuring 1.6 mm and 2.3 mm were observed in the middle and lower calyx of the left kidney, respectively. After 8 months of treatment with the triple therapy, no stone or hydronephrosis was detected in either kidney. However, a small cyst measuring 7 mm in diameter was noted.

Case 4

A 4-year-old female patient diagnosed with cystinuria underwent two surgical procedures in 2019 for the treatment of staghorn calculus. The first procedure was a percutaneous nephrolithotomy, followed by a transurethral lithotripsy (TUL). In 2021, the patient required another TUL due to the presence of multiple stones and obstruction of the right ureter. During this time, she was treated with a triple regimen. At the time of her visit, hydronephrosis and calyceal dilation were observed in the right kidney, attributed to two stones measuring 4 mm and 4.5 mm located at the ureteropelvic junction. No stones or pathological masses were detected in the left kidney. Following 24 months of treatment, the kidneys showed no evidence of stones or hydronephrosis. In summary, the details of the examined cases, along with the treatment processes and associated side effects, are presented in Table 1.

The side effects of the drug were monitored using a D-penicillamine side effects checklist, with evaluations conducted every three months through periodic examinations and blood and urine tests. The follow-up included two patients from 2016, one patient from 2017, and one patient from 2020, all of whom were receiving this treatment regimen. Among the four patients studied, no side effect was observed during the treatment and follow-up periods. Additionally, all existing stones in the kidneys were eliminated. In three of the patients, no new stone formation occurred; however, one patient experienced the formation of new stones, which did not necessitate surgical intervention.

Discussion

In this case series, we found that a medical regimen consisting of low-dose D-penicillamine capsules (10 mg/kg daily), vitamin B6 tablets (4 mg/kg daily), and potassium citrate (1 mL/kg daily) effectively prevented the need for additional surgeries, stone fragmentation procedures, and kidney damage, all without any observed side effects. In a previous case report, despite successful treatment outcomes, the lack of regular follow-up and poor patient compliance contributed to the recurrence of stones (5). The treatment strategy for cystinuria focuses on preventing stone formation and is implemented in a step-by-step manner. It begins with conservative measures, including increasing fluid intake, reducing dietary sodium and animal protein consumption, and alkalinizing the urine (6). According to previous studies, initial management typically includes these conservative approaches, characterized by heightened fluid consumption and dietary modifications. In cases of stone recurrence, the next step involves the use of medications to elevate urine pH, followed by the introduction of thiol-based drugs that bind to cystine (7). However, another study reported that although the long-term use of sulfhydryl agents for preventing kidney stone formation can be effective, these treatments often result in frequent side effects, which may lead to the discontinuation of therapy (8). For patients who continue to experience recurrent cystine nephrolithiasis despite conservative measures, pharmacotherapy with cystine-binding thiol drugs may be considered, provided there is close monitoring. Monitoring of patients with cystinuria involves regular assessments of serum and urine chemistries, as well as periodic renal imaging (6). In a study involving a 4-month-old girl, the diagnosis of cystinuria was confirmed through urinary calculus

Table 1. Patient characteristics and treatment regimens

Cases	Age (y)	Gender	Familial history of cystinuria	Weight (kg)/height (cm)	Blood pressure	Cystine levels		Treatment	Follow-up
						Stone analysis test (urinalysis)	Urinary cystine level		
Case 1	6	Male	No	18/115 cm	85/55 mm Hg	80%	176 mg/24 h	D-penicillamine capsules (10 mg/kg, daily) + vitamin B6 tablets (4 mg/kg, daily) + potassium citrate (1 mL/kg).	2017-2023
Case 2	6	Male	No	19/110 cm	80/50 mm Hg	80%	188 mg/24 h	D-penicillamine capsules (10 mg/kg, daily) + vitamin B6 tablets (4 mg/kg, daily) + potassium citrate (1 mL/kg).	2016-2023
Case 3	2	Male	No	10/85 cm	75/45 mm Hg	50%	132 mg/24 h	D-penicillamine capsules (10 mg/kg, daily) + vitamin B6 tablets (4 mg/kg, daily) + potassium citrate (1 mL/kg).	2016-2023
Case 4	4	Female	No	15/100 cm	90/60 mm Hg	75%	142 mg/24 h	D-penicillamine capsules (10 mg/kg, daily) + vitamin B6 tablets (4 mg/kg, daily) + potassium citrate (1 mL/kg).	2021-2023

analysis and urinary amino acid analysis.

The treatment regimen for this patient included urine alkalinization using sodium hydrogen carbonate at a dosage of 100 mg/kg/d, along with cystine-chelating drugs, specifically Tiopronin at a dosage of 40 mg/kg/d. Following treatment, the patient experienced resolution of occult hematuria, which subsequently reoccurred, while small kidney stones persisted (9). In another case report conducted by Hiraoka et al including a 12-year-old girl, it was determined that to prevent the recurrence of stone formation and its associated complications, it is essential to increase the solubility of cystine in the urine (10).

Conclusion

In this case series study, a multi-year treatment regimen including low-dose D-penicillamine capsules, vitamin B6, and potassium citrate in children with cystinuria successfully prevented the need for invasive medical procedures, all without any observed side effects.

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Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

Informed consent was obtained from all patients' parents. Additionally, the study protocol was registered under the code IR.SKUMS.REC.1403.031 at Shahrekord University of Medical Sciences.

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