Cystinuria : Cause of Recurrent Renal Stones in a 4-Year-Old Girl

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Abstract

This paper presents the case report of a 4-year and 6-month old girl with cystinuria. She clinically presented with recurrent radiopaque renal stones since the age of 3 years. She received 2 subsequent operations of pyelolithotomy combined with ureterolithotomy at the age of 3 years 6 months, and pyelolithotomy alone at the age of 5 years. She was initially diagnosed as having cystinuria by the presence of hexagonal plate crystals in her acidified urine and positive for the urinary cyanide-nitroprusside test. The diagnosis was confirmed by urinary amino acid analysis using quantitative ion-exchange chromatography which revealed increased amounts of cystine and dibasic amino acids of lysine and ornithine. In spite of maintaining a high fluid intake and alkalinizing urine by giving potassium citrate after the first operation, recurrent renal stones were found. Therefore, after the second operation, D-penicillamine was additionally introduced. During the 18-month follow-up, although there were recurrent renal stones, the rate of stone formation was slower. To the authors' knowledge, this is the first case report in Thailand.

Key word : Recurrent Renal Stones, Cystinuria, D-Penicillamine, Alkalinization

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Cystinuria is an autosomal recessive genetic defect of transepithelial transport of cystine and the other dibasic amino acids in the kidney and intestine (1,2). The renal transport defect is expressed by the excessive urinary excretion of cystine, the least soluble amino acids, which results in cystine crystallization and subsequent formation of a cystine stone. Cystinuria is the cause of 1 per cent to 2 per cent of renal stones observed in adults(3,4) and about 6 per cent to 8 per cent of pediatric urinary calculi in Western countries(5,6). As the genetic transport defect exists since birth, stone formation begins in the first decade of life and continues life long. The majority of patients with cystinuria will suffer recurrent renal stone disease during their lifetime(7) with subsequent urinary tract obstruction, infection and possible renal insufficiency(7). Cystine stones are poorly fragmented by extracorporeal shock wave lithotripsy (ESWL) and hence operative lithotomy is often necessary. To prevent recurrent renal stone formation, regular medical treatment is of particular importance in affected patients(8).

CASE REPORT

A 4-year and 6-month-old girl was referred to the Pediatric Nephrology Unit, Ramathibodi Hospital for the management of recurrent renal stones. Her past medical history included recurrent abdominal pain and urinary tract infections at the age of 3 years. Her intravenous pyelography revealed bilateral hydronephrosis, right radiopaque renal stones and left distal ureteric stones. Right pyelolithotomy and lower left ureterolithotomy were successfully performed at the age of 3 years and 6 months. She had been doing well since the calculi were removed. One year post-operatively, she developed recurrent bilateral renal stones. Ultrasonography showed bilateral hydronephrosis, 2 small stones in the right upper and middle calices and a large one in the lower calyx, about 2.2 cm in diameter and a left lower pole renal stone, about 0.8 cm.

On physical examination, the patient was a healthy-looking child in no acute distress. The only abnormal finding was surgical scars on the right flank area and left lower abdomen. Laboratory studies revealed normal complete blood count ; blood urea nitrogen 11 mg/dl, serum creatinine 0.5 mg/dl, sodium 138 mmol/L, potassium 4.53 mmol/L, chloride 110 mmol/L, total CO_2 20.7 mmol/L, calcium 10.0 mg/dl,

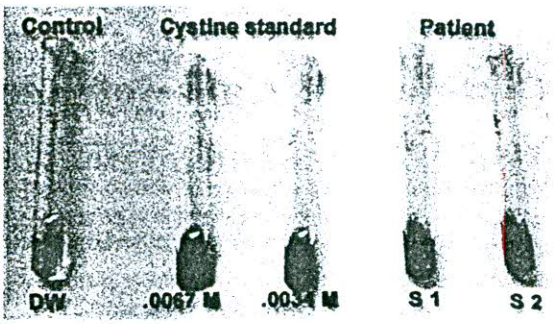

Fig. 1. The urine cyanide-nitroprusside test of the patient (S_1 and S_2) revealed magenta color compared with cystine standard and control using distilled water.

phosphate 4.8 mg/dl and uric acid 4.5 mg/dl. Urinalysis revealed yellowish color, pH 5, specific gravity 1.020, markedly positive blood, WBC 5-10/HPF, RBC >100/HPF, no casts and few hexagonal crystals. The 24-hour urine calcium was 0.19 mg/kg/day. The cystine test was performed on the patients fresh and first-morning-voided urine using cyanide-nitroprusside. After adding sodium cyanide and nitroprusside, a purple red or magenta color was revealed which was suggestive of the presence of cystine (Fig. 1). Subsequently, urinary amino acid analysis by quantitative ion-exchange chromatography revealed increased amounts of cystine and dibasic amino acids of lysine and ornithine (Table 1).

Her mother had also had a right ureteric stone which was removed at the age of 26 years. She has been doing well and no recurrence of renal stone was found during the 9-year follow-up. There was no family history of consanguinity. No other family member had history of renal stones. Laboratory findings for her mother including complete blood counts, serum electrolyte, blood urea nitrogen, serum creatinine, calcium, uric acid and urinalysis were within normal limits. The 24-hour urine calcium was 73 mg/day. Her urine cyanide-nitroprusside test was negative for cystine. There was no radiopaque stone on a recent abdominal radiograph. The urinary amino acid analysis of the mother revealed 25 per cent

Table 1. The urinary amino acid analysis of the patient and her mother by the quantitative ion exchange chromatography.

Amino acids	Normal range in children[a] (mg/g creatinine)	Patient's values[b]	Normal mean ± SD in adults (mg/g creatinine)	Mother's values[c]
Cystine	4.3-48.0	286.5	16.5 ± 6.9	30.0
Ornithine	4.6-44.3	440.1	1.3 ± 0.5	2.2
Lysine	10.4-184.5	549.7	21.0 ± 17.2	3.3
Arginine	1.5-110.0	5.3	1.7 ± 0.7	2.7

a : N = 13, 1-13 years
b : All urine amino acids except cystine and dibasic amino acids were within normal limits
c : All urine amino acids except cystine were within normal limits

increased amounts of cystine but amounts of dibasic amino acids were within normal limits compared with the control (Table 1).

At the age of 4 years and 6 months after revealing recurrent renal stones, the patient had been encouraged to maintain a high fluid intake and a low salt diet. Potassium citrate had been given for alkalinizing urine in order to increase cystine solubility. Her serial urine specific gravity ranged from 1.010 to 1.015 and urinary pH invariably exceeds 7.0. She had been doing well without abdominal pain and urinary tract infection. Six months after receiving stone preventive treatment, repeated abdominal ultrasonography revealed an increase of the stone size from 0.8 cm to 1.3 cm in the left kidney and a large stone 2.2 cm in the right kidney. Moderate right hydronephrosis and mild left hydronephrosis were evidenced. She underwent the second operation of right pyelolithotomy, at the age of 5 years. Stone analysis proved cystine stone. Because the high diuresis and urine alkalinization failed to slow down the cystine stone formation, D-penicillamine was added after the second operation in order to increase cystine solubility. One year later, at the age of 6 years, repeated abdominal ultrasonography showed mild hydronephrosis of the right kidney and no hydronephrosis of the left kidney. There were two new small stones at the lower pole of the right kidney, measuring about 0.3 cm. Fortunately, the left renal stone of 1.3 cm had decreased to 0.3 cm diameter.

At her last visit when she was 6 years and 6 months old, the recent abdominal ultrasonography showed the same size of multiple stones in both kidneys measuring 0.3 cm without obstruction. Her recent serum creatinine was 0.6 mg/dl. She had done very well in the elementary school with medical preventive treatment for cystine stone.

DISCUSSION

Cystinuria is not an uncommon cause of pediatric renal stones reported from Western countries[5,6]. Cystine stones are particularly prevalent in the second or third decade of life but occur infrequently in infancy[9]. In Thailand, the prevalence of pediatric renal stone is unknown and cystinuria is a rare cause in childhood. Because cystine stone is moderately radiopaque secondary to the presence of the sulfur atom in the molecule, it may be misdiagnosed as being a calcium containing stone which delays the diagnosis of cystinuria. The presented patient developed bilateral renal cystine stones in first few years of life with subsequent obstruction and recurrent urinary tract infections requiring right pyelolithotomy and left ureterolithotomy at the age of 3 years and 6 months. Due to the undiagnosed cause of her renal stones and lack of medical preventive treatment for cystine stones, she had recurrent stone formation within 1 year after the first operation.

Urinary excretion of cystine in a normal individual is less than 20 mg/g creatinine. Patients of homozygous cystinuria excrete more than 400 mg/day or more than 250 mg/g creatinine[8,10]. The major lithogenic factor in patients with cystinuria is the high concentration of cystine in the urine, because of its relative insolubility, crystallizes at the usual urine pH (5.5-6.5). Dent and Senior reported that the solubility of cystine in the urine sharply rises with higher pH, up to 500 mg/L in urine pH above 7.5[11]. The presence of hexagonal cystine crystals in fresh and first-morning-voided urine may be a pathognomonic for cystinuria but this is seen only in a minority of cases[12,13]. In the presented patient, hexagonal crystals of cystine were not found in repeated urinalysis until her urine was concentrated and pH was low to 5.0. Also, the positive for urinary cyanide-

nitroprusside test is suggestive of the presence of cystine excretion exceeding 75 mg/L[9,14] which is a rapid and simple screening test for patients with cystinuria. It may also detect asymptomatic patients and some patients with heterozygous cystinuria[15]. The presence of urinary hexagonal crystals and the positive cyanide-nitroprusside test indicate the presumptive diagnosis of cystinuria. Her subsequent urinary amino acid analysis by the quantitative ion exchange chromatography documenting elevated levels of cystine, 286.5 mg/g creatinine and dibasic amino acids of lysine and ornithine confirms the diagnosis of cystinuria.

Cystinuria is an amino acid transport disorder, transmitted as an autosomal recessive inheritance[1]. Rosenberg et al[16] described 3 types of classic cystinuria of obligate heterozygotes in the proband's family according to the urinary phenotype. Type I heterozygotes shows normal aminoaciduria, whereas type II and III heterozygotes show high or moderate excretion of cystine and dibasic amino acids, respectively. Heterozygotes for cystinuria generally do not excrete enough cystine into the urine to be at increased risk for cystine calculi, but they may be at increase risk for calcium oxalate stone formation when compared with normal control groups [17,18]. In the present report, the patient's mother had negative results of cyanide-nitroprusside test and her urinary amino acid chromatography showed only mild elevation of cystine but normal excretion of dibasic amino acids. The finding is consistent with type I heterozygotes of cystinuria. She also had experience of a ureteric stone which has not recurred.

The objective of medical treatment is to reduce the urinary cystine concentration below its solubility limit which would prevent recurrent cystine stone formation. Manipulations of urinary pH to optimal alkalinity and maintenance of adequate urine volumes to prevent cystine crystallization represent realistic and pragmatic means of cystine stone chemoprevention[4,7-9]. The goal of alkali therapy by means of sodium citrate and/or potassium citrate is to maintain urine pH up to 7.5[8]. Due to the sodium-induced enhancement of urinary calcium and cystine excretion, potassium citrate is preferable[8-9, 19]. After the first operation, the presented patient has been encouraged to maintain high fluid intake and high diuresis and has taken potassium citrate for urine alkalinization since the presumptive diagnosis of cystinuria. Her urine specific gravity has been maintained at 1.010 to 1.015 and urinary pH up to 7.5-8.0. However, the above treatments were not sufficient enough for dissolving pre-existing stones or preventing new stone formation. Therefore, after the second operation of right pyelolithotomy, additional therapy of D-penicillamine was initiated. D-penicillamine is a cystine-binding agent composed of a thial group which is able to bind the sulfide moiety of cystine. D-penicillamine-cystine complex is 50 times more soluble than cystine itself[20]. However, after 18 months of D-penicillamine administration, the patient still had new stones but the rate of stone formation is much slower and the dissolution of the pre-existing stone was also evidence.

In summary, cystinuria is a rare cause of renal stone in early childhood. If the recurrent radiopaque renal stones are found soon after the operation, the diagnosis of cystinuria should be suspected. Screening for cystinuria by looking for urinary hexagonal crystals and performing the cyanide-nitroprusside test is suggested. Medical intervention in patients with cystinuria is essential not only for preventing new stone formation but also protecting renal impairment.

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ซิสตินยูเรีย : สาเหตุของการเกิดนิ่วที่ไตชนิดเป็นซ้ำในเด็กหญิงไทยอายุ 4 ปี

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รายงานผู้ป่วยเด็กโรคซิสตินยูเรีย อายุ 4 ปี 6 เดือน ผู้ป่วยได้รับการตรวจพบว่ามีก้อนนิ่วที่ไตตั้งแต่อายุ 3 ปี ผู้ป่วยได้รับการผ่าตัดเพื่อเอานิ่วที่ไตออก 2 ครั้ง คือเมื่ออายุ 3 ปี 6 เดือน และอายุ 5 ปี ตามลำดับ ผู้ป่วยได้รับการวินิจฉัยเบื้องต้นว่าเป็นโรคซิสตินยูเรีย จากการตรวจพบผลึกลักษณะ hexagonal plate ในปัสสาวะที่ทำให้เป็นกรด และการตรวจทดสอบ urine cyanide–nitroprusside พบว่าได้ผลบวกสำหรับโรคซิสตินยูเรีย ต่อมาได้วิเคราะห์หาปริมาณ amino acids ในปัสสาวะโดยวิธี quantitative ion–exchange chromatography พบว่ามีปริมาณของ cystine และ dibasic amino acids ชนิด lysine และ ornithine เพิ่มขึ้น จึงให้การวินิจฉัยได้ว่าเป็น cystinuria ผู้ป่วยได้รับการรักษาเพื่อทำให้สาร cystine ในปัสสาวะละลายได้ดีขึ้น โดยการให้ยา potassium citrate เพื่อทำให้ปัสสาวะเป็นด่าง ร่วมกับการดื่มน้ำเป็นปริมาณมาก นิ่วในไตทั้ง 2 ข้าง ยังคงมีเพิ่มขึ้นและขนาดใหญ่ขึ้น ดังนั้นหลังการผ่าตัดครั้งที่ 2 ผู้ป่วยได้รับการรักษาเพื่อป้องกันการกลับเป็นซ้ำของนิ่ว cystine ด้วย การให้ยา D–penicillamine เพิ่มขึ้น ร่วมกับการดื่มน้ำปริมาณมากและ urine alkalinization ได้ติดตามการรักษาดังกล่าวในระยะเวลา 18 เดือนต่อมา พบว่ายังมีนิ่วที่ไตเกิดขึ้นใหม่แต่นิ่วมีขนาดเล็ก และจากการสืบค้นพบว่ารายงานนี้เป็นรายงานผู้ป่วยเด็กโรค cystinuria รายแรกในประเทศไทย

คำสำคัญ : นิ่วที่ไตชนิดเป็นซ้ำ, ซิสตินยูเรีย, ยาเพนิซิลลามีน, ปัสสาวะเป็นด่าง

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