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Case Report

Cystinuria as a Cause of Abdominal Pain in Children

MWS ***Yu,*** CC ***Shek,*** WKY ***Chan,*** KW ***Lee***

Abstract Urolithiasis is an uncommon renal problem in paediatrics. Once identified, however, a thorough investigation should be performed to look for the underlying cause. Children with renal stone may present as haematuria, recurrent abdominal pain and urinary tract infection. Since abdominal colic is a common reason for medical consultation, rare cause like renal stone can be easily overlooked. We reported an infant presented as recurrent abdominal pain and positive urine culture. Subsequent work up revealed the diagnosis of Type A cystinuria.

Key words Cystine; Cystinuria; Urolithiasis

Case Report

A 21-month-old girl born by nonconsanguinous parents with good past health consulted a private paediatrician for recurrent abdominal pain. In some occasions the child could locate the pain as originating from the loin regions or from dysuria, but in most of the time she could not describe the nature of pain verbally. Nevertheless, her parents observed that she was restless, frequently changing her posture or rocking from side to side on her bed during the pain attacks. Severe episodes of pain were frequently associated with vomiting. No passage of stone or sand was noticed in the urine. She was afebrile all along.

Department of Paediatrics, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong, China

MWS **Yu** (余詠詩) *MBBS, MRCPCH (UK), FHKAM (Paed)*
WKY **Chan** (陳桂如) *MBBS, FHKAM (Paed), FRCP (Eding)*
KW **Lee** (李國偉) *MBBS, MRCP (UK), FHKAM (Paed)*

Department of Pathology, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong, China

CC **Shek** (石志忠) *MBBS, FRCPath, FHKAM(Path)*

Correspondence to: Dr MWS **Yu**

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Physical examination was unremarkable. Urine microscopy showed pus cells of 170/uL (normal <15), red blood cells of 18/uL (normal <20). Urine culture grew E-coli with bacterial count $>10^5$/mL. She was diagnosed to have urinary tract infection and responded well to oral antibiotic. Renal ultrasound revealed normal-sized kidneys with shadows of hyper-echogenicities measuring 5 to 20 mm over the central sinus of both kidneys. The findings were consistent with bilateral staghorn stones. She underwent one session of extracorporeal shock wave lithotripsy (ESWL) on the right kidney but the result was unsatisfactory. She was then referred to us for further management.

Prior to her assessment, she was hospitalised again through the Accident and Emergency Department for severe abdominal pain, which required surgical consultation. Physical examination revealed that she was nontoxic and afebrile. Her blood pressure was 100/64 mmHg. Her growth parameters were along the 75th percentile for her age and her development was normal. Her abdomen was soft and no abnormal mass was palpable. Blood investigations showed: white cell 7 x 10^9 /L, haemoglobin 12.0 g/dL, urea 3.9 mmol/L, creatinine 37 umol/L, and uric acid 0.16 mmol/L. Blood gas showed normal pH of 7.35. KUB showed bilateral staghorn stones (Figure 1). Urinalysis showed pH of 6.2; there were presence of white cells but no red cells or crystals were detected. Calcium to creatinine ratio was 0.17 mmol/mmol creatinine (Cr) (normal <0.78);

fractional excretion of sodium was 0.32 % (normal <1%). Urine oxalate was 0.09 mmol/day (normal <0.5). There was significant rise in the excretion of dibasic amino acids: cystine 430 umol/mmol Cr (normal 1-23); ornithine 139 umol/mmol Cr (normal 1-15); arginine 1046 umol/mmol Cr (normal 0-15); lysine 2934 umol/mmol Cr (normal 4-37). The diagnosis of cystinuria was made.

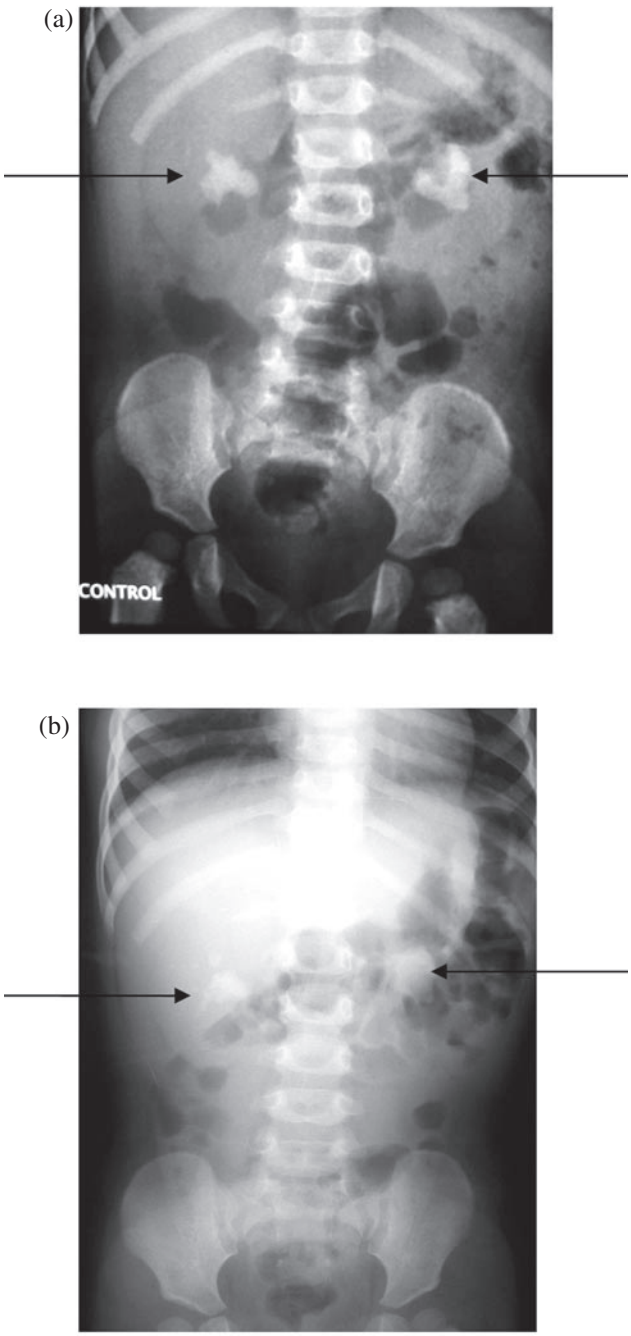

Figure 1 (a) KUB taken before private IVP and before ESWL. Arrows showing the bilateral staghorn stones. (b) KUB taken after ESWL and when complained of severe abdominal pain. Arrows showing persistence of staghorn stones.

Genetic study for the solute carrier family (SLC3A1) gene identified 2 mutations: R365W and IVS7+2T>A. R365W is a known disease-causing mutation for cystinuria, whereas the latter was a novel splice site mutation.

Medical treatments in terms of hydration therapy and urine alkalinization by potassium citrate were started. The child was encouraged to take fluid of up to 2-3 L daily, including citrus fruit drinks like orange juice. Parents were educated on the use of urine pH paper for checking urine pH after every void. A spot urine sample would also be sent to the laboratory for pH measurement during follow up. We aim to keep the range of urine pH between 7 and 7.5. Septrin prophylaxis was started for the presence of bilateral staghorn stone and recurrent urinary tract infection. Percutaneous nephrolithotomy was performed to remove the staghorn stones; septrin was then stopped. She is now taking potassium citrate 1.35g three times daily with a urinary pH of 7.54 (laboratory tested) and has been followed up for 1.5 years without any recurrence of renal stone.

Discussion

Cystinuria has been described as one of the most common genetic disorders in amino acid transport. Overall prevalence has been reported to be 1 in 7,000 in general population of Europe and America.[1] Figures in the Chinese population are lacking. It accounts for 6-8% of urinary stones in paediatric patients and 1-2% of urinary stones in adults.[2,3]

Cystinuria has been recognised in the medical history for almost two centuries. It was first described by Wollaston,[4] who identified a different type of human urinary stone composed of flat hexagonal crystals in 1810. He named it 'cystic oxide' because the calculi were found in the urinary bladder. Subsequently it was found that the stone was not an oxide, though it was mistakenly thought to be originated from the bladder. It was not until 1817 when cystine stones were recognised to actually form in the kidney, and in 1951 when Dent and Rose[5] postulated the cause of cystinuria being a defective common transport mechanism of the dibasic amino acids (including cystine, lysine, arginine and ornithine) in the renal tubules. With the recent advancement of molecular genetics and cellular biology, not only the underlying genetic defects of cystinuria are now identified, we are also able to have a better understanding of the

underlying pathophysiology of cystinuria.

Traditionally cystinuria was classified into 3 subtypes basing on the (a) excretion of cystine and dibasic amino acids in the urine of the parents i.e. obligate heterozygotes; and (b) plasma cystine level in the homozygotes after an oral cystine loading test. Type I heterozygotes showed a normal amino acid urinary pattern and no change in plasma cystine level in the homozygotes. Both types II and III heterozygotes have raised urinary excretion of the dibasic amino acids – but type II homozygotes have normal plasma cystine while type III homozygotes have elevated plasma cystine after oral cystine loading.[6] After the identification of genes responsible for cystinuria, there were problems trying to fit the phenotypes with the genotypes. A new classification based on genetic defects was then proposed in the International Cystinuria Consortium: Type A cystinuria (formerly known as type I cystinuria) are patients carrying mutations in both alleles of the SLC3A1 gene. This gene encodes a protein called r-BAT, which was identified in 1992 and was mapped to short arm of chromosome 2.[7] Type B cystinuria (formerly called type II and III or type non-I) are patients with mutations in both alleles of SLC7A9.[7] This gene encodes a glycoprotein BAT1 that associates with r-BAT to form the active transporter for cystine. The locus of this gene was on chromosome 19 (Table 1). Genetic study for the SLC3A1 gene in our patient identified 2 mutations: R365W and IVS7+2T>A. R365W is a known disease-causing mutation for cystinuria and had also been reported in Chinese patients.[8] The latter was a novel splice site mutation that has not been described so far.

Pathophysiology of Cystinuria

In normal kidney, amino acids are readily filtered by the glomeruli and undergo almost complete reabsorption in the proximal renal tubules. To date, studies by various authors have identified at least 2 transport systems for cystine reabsorption in the proximal renal tubules: (1) a high-affinity system that is shared by all dibasic amino acids; (2) a low-affinity system which is solely used by cystine. These systems are located at the brush border membrane.[9] A defect of the high-affinity system is believed to be the cause of cystinuria.

In a normal kidney, only around 1% of the filtered cystine and dibasic amino acids is excreted into the urine. On the contrary, cystinuric patients may have cystine clearance up to 1 to 2 folds the glomerular filtration rate.[9] This suggests the presence of other modes of defect like hyperexcretion or enhanced membrane permeability in cystinuria, mechanisms of which are yet to be determined.

The defect in cystinuria leads to the accumulation of dibasic amino acids in urine. The main culprit is cystine, which is a dimer of the amino acid cysteine, with a disulfide bond (Figure 2). It has low solubility at physiological pH

Table 1 Clinical and genetic classification of cystinuria

Classification	**Type A** [a]	**Type B** [a]		**Type AB** [a]
	Type I [b]	Type non-I [b]		
		Type II [b]	Type III [b]	
Urinary excretion of cystine and dibasic amino acids in heterozygotes	Normal	Elevated	Moderat elyelevated	Normal (rare < than 1.6% of patient,[6] mild phenotype)
Homozygotes plasma Cystine level after oral Cystine load	Not elevated	Not elevated	Elevated	
Gene locus	Chromosome 2 (SLC3A1)	Chromosome 19 (SLC7A9)		Chromosome 2 & 19 SLC3A1 & SLC7A9
Mutation	Mutations in both alleles of SLC3A1	Mutations in both alleles of SLC7A9		One mutation in each gene
Protein encode	rBAT [C]	BAT1 [C]		

[a] Classification based on genetic mutation as reported by Dello et al.[7]

[b] Classification based on phenotypes as reported by Rosenberg et al.[6]

[c] The protein products of SLC3A1 (rBAT) and SLC7A9 ($b^{0,+}$ AT) form the heterodimeric amino acid transporter system $b^{0,+}$, which is responsible for the uptake of cystine and dibasic amino acid in the renal tubules and intestinal epithelial cells.

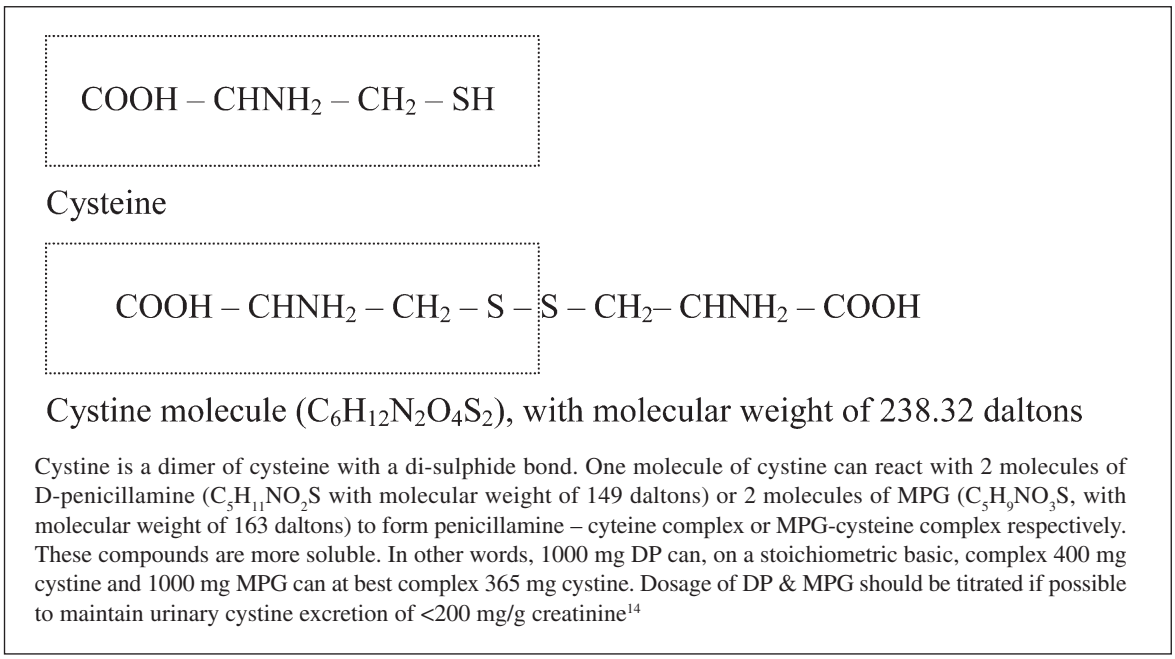

Figure 2 The molecular structure of cysteine and cystine molecules.

of urine. At a higher pH of >8, the solubility of cystine is greatly increased.[10] Hence, alkalinization of urine becomes a goal of pharmacotherapy. Cleavage of disulfide bond of cystine to form 2 cysteine molecules, which is more soluble in physiological urine, is another important target of treatment.

Clinical Presentation and Diagnosis

Cystinuria is basically a renal disease. Patients usually present with symptoms related to various complications of urolithiasis as in our patient. These include renal colic with or without acute obstruction, recurrent urinary tract infections, and macroscopic/microscopic haematuria. Rarely there might be spontaneous passage of stone, or the stones were incidentally detected by X-rays, which were planned for other purposes. Cystinuric patients, when symptomatic, can form stones since their early lives. More than 80% of these patients will have their first stone identified in the first 2 decades of life.[7] Stones formation recurs throughout their lives and the life time risk of having bilateral urolithiasis can be as high as 75%.[11,12]

A first-voided morning urine specimen may yield hexagonal cystine crystals under microscopic examination. However, this is present in only 20-25% of patients.[11,13] In the past, cyanide nitroprusside test had been used as a screening test. Cyanide cleaves cystine into cysteine; the nitroprusside then binds with the sulfide moiety of cysteine, producing a purple colour when cystine excretion exceeds 75 mg/L. The test is sensitive in picking up homozygous cystinurics who excrete more than 250 mg/g creatinine (0.12 mmol/mmol creatinine) but false positive results are found in homocystinuria, acetonuria, and patients taking ampicillin or other sulfur-containing medication.[11] With the advancement of other investigation modalities, this test has been out of favour.

A 24-hour urine specimen for ion exchange chromatography will show a rise in cystine and other dibasic amino acids. Cystine excretion exceeding 250 gm/g creatinine usually indicates homozygous cystinuria.[11] Of course, the presence of cystine in stones that have been passed spontaneously or surgically removed provide a definitive diagnosis. Mixed stones are commonly found. This can be due to urinary tract infection or urine alkalinization, which is part of the therapeutic regimen. Cystinuria also associates with other metabolic disorders like hypercalciuria, hyperuricosuria and hypocitraturia.[9] It is also important to exclude other causes of excess urinary cystine excretion including isolated cystinuria, tubular immaturity in infants <6 months, and generalised aminoaciduria in Fanconi syndrome.[11]

Cystine stones are radiopague because of its sulfur content. They are classically described to be more rounded

and homogeneous in appearance, but they can also attain a staghorn shape and size as in our patient. Nowadays, intravenous urogram is rarely needed to delineate the degree of obstruction. Both ultrasound and CT scan can delineate the size of stones and the degree of urinary obstruction with good results.

Management

There is no inhibitor of cystine crystallization. The main determinant of cystine crystallization is urinary supersaturation. One can prevent urolithiasis by maintaining the urinary cystine concentration below its solubility limit of 250 mg/L[9] (~1 mmol/l) at urine pH 7. This can be achieved by (1) reducing substrates for cystine formation, (2) decreasing cystine concentration in urine, (3) increase solubility of cystine, (4) converting cystine to a more soluble form.

Methionine is a metabolic precursor of cystine. It is found in protein-rich food like red meat, poultry, fish and dairy products. A low methionine diet is almost a vegetarian diet, and inevitably will lead to low compliance. Taking into account the potential detrimental effect on growing children, it is not recommended in paediatric patients.

Adequate hydration is of utmost importance in diluting cystine in urine. A daily fluid intake of up to 3 liters in children and 4-5 L in adults may be required in order to maintain an urine output of 1.5-2 liter/m^2/day and free cystine excretion <200 mg/L (0.8 mmol/L).[13] Fluid intake should be evenly distributed throughout the day and night to ensure adequate overnight diuresis. This is particularly important because physiologically urine would decrease in volume and become more acidic at night. Patients should be instructed to drink before bed and at least once during the night. Large volume fluid intake, however, can be a compliance problem especially for young children. Our patient's parents reported that she could only take around 1.5 L each day. She was willing to drink orange juice and beverages like Ribena, both providing extra source of citrate.

Both adult[14] and children[15] studies revealed that a reduction in dietary sodium intake could reduce urinary cystine excretion. The proposed mechanism is that reduced dietary sodium intake will result in enhanced reabsorption of sodium in the proximal renal tubule, which will result in coupled reabsorption of amino acids including cystine. In line with this aim to reduce sodium intake, alkalinization of urine should therefore be achieved with potassium-based alkali instead.

The solubility of cystine is greatly increased in alkaline urine. However, alkali source from diet alone is unable to achieve a desirable urinary pH. Alkali medications in the form of potassium citrate or bicarbonate can increase urinary pH more consistently. Citrate or bicarbonate at 1-2 mEq/kg/day[11] is usually required and dosage will be adjusted according to the urinary pH. Urinary pH must be meticulously maintained at 7 to 7.5 because a higher pH would lead to precipitation of calcium phosphate.[11] In our hospital, potassium citrate mixture at a concentration 3 gm/10 ml is available. Each 10 ml of mixture provides 9.24 mmol of citrate from potassium citrate and 2.39 mmol of citrate in the form of citrate acid, i.e. total 11.62 mmol of citrate. Our patient has a most recent body weight of 14.5 kg. She is currently taking potassium citrate 1.35 gm three times daily, i.e. 1.1 mol/kg/day of citrate.

If unfortunately the above measures fail, with recurrent stone formation, one may consider the use of chelating agents. D-penicillamine (DP) and α-mercaptopropionylglycine (MPG) or Tiopronin, are sulfhydryls. They cleave each cystine into 2 cysteine units to form a mixed disulphide that is 50 times more soluble than cystine (Figure 2). DP is less tolerable for patients because of its side effects, including skin rashes, arthralgia, pemphigus, proteinuria, nephrotic syndrome, loss of taste, lupus-like syndrome and potentially life-threatening agranulocytosis and thrombocytopenia. DP may also induce pyridoxine depletion and pyridoxine supplementation is needed. The mechanism of action and side effects of MPG is similar to DP but it is preferred because of its lower toxicities. The recommended starting dose of MPG in children is 15 mg/kg/day divided into 3 doses.[9,11,13] The dosage of DP in children is 15-40 mg/kg/day divided into 2 to 3 times daily.[11] Both drugs can be adjusted to around 20-40 mg/kg/day, aiming to reduce cystine concentration to <250 mg/L (1 mmol/L). Captopril is an angiotensin-converting enzyme inhibitor that also has a chelating property. It has an additional role in hypertensive cystinuric patients. However, its chelating effects have not been confirmed by some authors.[9,11,13] Efficacy of medical treatment can be monitored by the disappearance of cystine crystals in the first voided morning urine and a 24-hour free cystine excretion of <200 mg/L. Recurrence of stones should be monitored by serial ultrasound examination.[16]

Cystinuric patients are bound to have recurrent stone formation throughout their lives. Minimally invasive procedures are preferred to minimise the cumulative morbidity from repeated surgeries.[10] The size of the stone is one of the most important determining factors for the

choice of treatment modality. The crystal structure of the stone limits the efficacy of ESWL as compared to calculi of other types. This is best illustrated in our patient who underwent 1 session of ESWL at the right kidney, which resulted in fragmentation of the staghorn stone that remained within the renal pelvis without passage.

Nowadays, most centres would choose ESWL for pyelocaliceal or upper ureteral stones smaller than 1.5 cm.[17,18] Percutaneous nephrolithotomy (PCNL) coupled with intracorporeal ultrasonic stone fragmentation would be used for stones larger than 1.5 cm. For more complex ones, including staghorn calculi, PCNL is shown to be safer than ESWL in terms of stone-free rates, less need for re-treatment and ultimately lower number of general anaesthesia required. Stones which are in lower ureters can be managed by retrograde endoscopic removal. Regarding the largest and most complex or extensively branched stones, a 'combination endourological sandwich approach' can be used. Initial procedure involves PCNL debulking, then ESWL for residual inaccessible stones, followed by a second look nephroscopy if necessary. The potential risks of PCNL and ESWL are higher when used to treat larger stones, which include bleeding, sepsis, and renal damage. In ESWL there is also an uncommon complication called Steinstrasse, which means the impact of small stone particles in the lower ureters forming a 'stone street'.[18] Open lithotomy is only very occasionally required in infected or obstructing stones which could not be removed by other means.[11]

Prognosis

Stone event frequency does not correlate with the amount of cystine or other dibasic amino acids excreted.[6] This, together with family studies in which siblings shared the same mutations and nurtured under the same environment but with very different clinical outcomes, suggested that there might be other cofactors for lithogenesis. Renal failure is uncommon and occurs in less than 5% of cystinuric patients, but up to 1/3 of patients may have some degree of impaired renal function.[11] One study showed that cystinuric patients tend to have higher serum creatinine levels than calcium oxalate stone formers and they are at more risk for renal loss.[19] Patients who undergo renal transplant would have no recurrence of cystinuria after transplantation.

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