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Chronic Renal Failure in Boy with Bilateral Cystine Nephrolithiasis

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Abstract Cystinuria is a rare cause of stone disease and has a peak age of presentation in the third decade of life. However, it can also present during the first decade of life with acute renal failure, anuria or other symptoms. We present a case of a 13-year-old boy with multiple and bilateral cystine stones and high excretion of cystine in the urine (981 mg/24 h; 4082 µmol/24 h) producing chronic renal insufficiency grade 3 (creatinine clearance 55 ml/min). Medical treatment with potassium citrate, acetazolamide and captopril, and percutaneous nephrolithotomy and retrograde ureteroscopy were chosen for this case. Cystinuria is a rare condition, but when it does occur, timely diagnosis, appropriate treatment and close follow up are important to avoid severe clinical complications. Appropriate treatments include urine alkalinisation, decreasing cystine supersaturation and intake of 4 liters of water per day.

Key words Chronic renal failure; Cystine stones; Cystinuria; Paediatric age

Introduction

The worldwide prevalence of cystinuria is about 1:7000; however, it is regionally variable. Specifically, cystinuria occurs in the Mediterranean East Coast in approximately 1: 1887 persons. Although the peak age of onset of stones is in the third decade of life, the first symptoms usually occur between 2-40 years of age. In children, the cystine composition in the calculi is approximately 6-10%.[1] Cystinuria is a monogenic disorder in which there is a transepithelial transport defect in some of the amino acids, such as cystine, ornithine, lysine and arginine. This produces a decrease in the reabsorption of these amino acids in renal proximal tubule and intestine that can result in cystine supersaturation and crystal stone formation.[2] Commonly, the three subtypes of cystinuria have been described based on the level of urinary cystine in heterozygotes: Type I/I cystinuria; Type I/III cystinuria; and Type I/II cystinuria. Type I/I is genetically and phenotypically different from the other subtypes.[3] The urinary hyperexcretion of cystine is caused by the mutations in SLC3A1 and SLC7A9, and this is necessary for formation the calculi. However, other factors can influence cystine stone formation such as dietary intake of fluids, salt, and protein.[4] Timely diagnosis, individualised treatment and close follow up are essential for good therapeutic control and improved outcomes as medical treatment of cystinuria is often disappointing.[5]

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Case Report

A 13-year-old boy presented to the Emergency Department with intense left abdominal pain and oliguria for 24 hours. In the physical examination, the boy was thin appearing, with pain on palpation in the left quadrants of the abdomen and in the left lumbar flank. Blood and urine

tests were performed with creatinine 2.25 mg/dl (199 µmol/l, normal range 50-77 µmol/l), urea 80 mg/dl (29 mmol/l, normal range 4-18 mmol/l), C Protein Reactive 263.9 mg/L (2513 nmol/l, normal range 0-48 nmol/l), pH 7.415 (normal range 7.33-7.43), mild thrombocytopenia and mild coagulopathy. An abdominal radiograph (Figure 1) showed at least 12 left stones and 4 right stones. There was 1 stone in the left ureteropelvic junction. An abdominal-pelvic CT scan without contrast was performed after left ureteral stent was positioned (Figure 1). In Figure 1, multiple and bilateral stones can be seen with decreased visualisation of the renal parenchyma. A detailed social and medical history revealed patient's low socioeconomic status with parents of gypsy ethnicity with no medical history of stones and personal antecedents of bilateral nephritic colic with stone expulsion, which was not analysed by the primary care physician and received no medical treatment. Review of previous blood test showed a normal creatinine (0.87 mg/dl; 77 µmol/l) one year prior. More recent lab work including a complete metabolic study and 24 h urine study (Table 1) showed chronic renal insufficiency grade 3 (55 ml/min), mild hypercalcaemia and hyperkalemia, moderate hypocitraturia and severe cystinuria. Left rigid ureteroscopy was performed to extract the stone found in the ureteropelvic junction with analysis of the stone showing cystine composition by infrared spectroscopy and X-ray diffraction. The next planned procedure is for left percutaneous nephrolithotomy to treat the left lithiasic masses followed by a right percutaneous nephrolithotomy to treat right lithiasic masses. Patient was medically managed with 40 mEq of potassium citrate daily, 250 mg of acetazolamide daily and captopril 6.25 mg every 12 hours.

Comments

Clinical presentation of cystinuria is varied. Cystine levels in the urine can be measured with sodium-cyanide-nitroprusside test and with ion-exchange chromatographic quantitative analysis to confirm the diagnosis.[1] The normal range of excretion of cystine in the urine is up to 30 mg/24h (125 µmol/24 h); however, in type I heterozygotes excretion is less than 200 mg/24 h (832 µmol/24 h) and in non-type I heterozygotes excretion is between 200-400 mg/24 h (832-1665 µmol/24 h). On the other hand, homozygotes usually excrete more than 400 mg/24 h (1665 µmol/24 h) of cystine in the urine.[1,2] In the paediatric patient of this case report, the high excretion of cystine in the urine (981 mg/24 h; 4082 µmol/24 h) and the significant bilateral stone activity is consistent with cystinuria type I/I with high risk of stone formation in the first decade of life.[3] It is very probable that in this patient stone activity started in the first decade of life, but without metabolic control and medical treatment, the evolution has been rapid. The likely contributing factors leading to the poor control of his disease are his low economic and social status and inadequate training of the

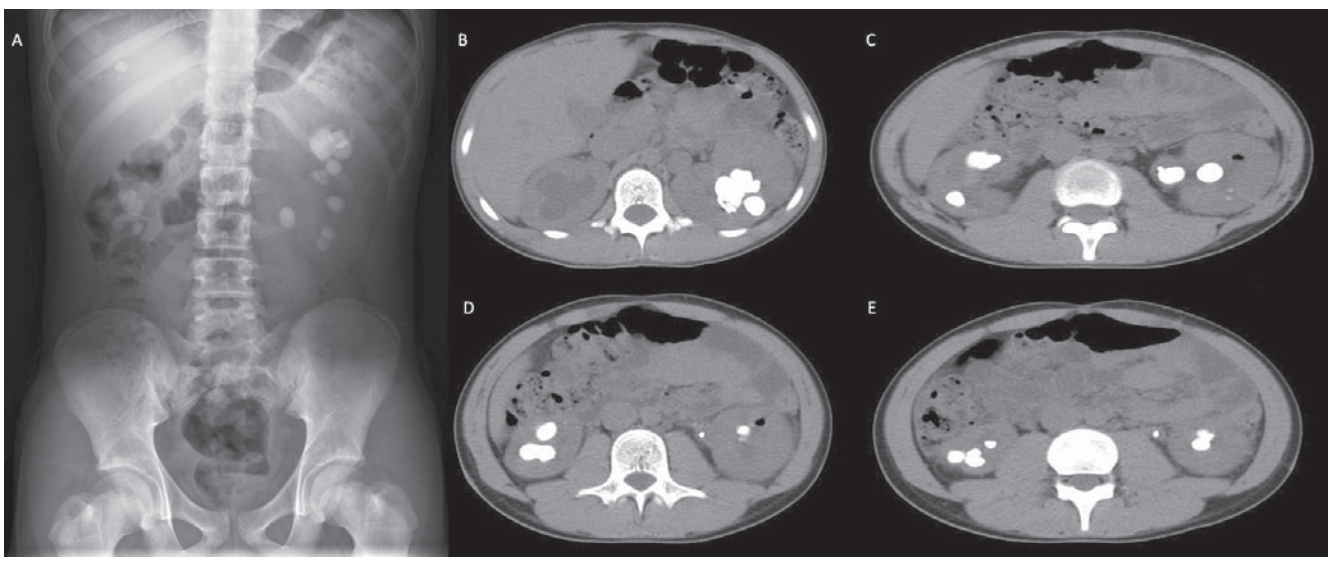

Figure 1 A (abdominal X-ray), at least 12 left radiopaque images projected onto the left renal silhouette and 4 right radiopaque images projected onto the right renal silhouette. These findings are compatible with stones. B, C, D and E (abdominal CT scan) images of multiple and bilateral stones, which were suspected in abdominal X-ray, with decrease in both kidney parenchymas.

primary care physician. Although renal failure and anuria.[6,7] can be consequences of cystinuria, it is very uncommon that cystinuria and cystine stones produce chronic renal insufficiency in children like the case presented. Once the patient has been diagnosed, medical and surgical treatment is paramount. The main objectives of medical treatment are to decrease cystine supersaturation in the urine and increase urine pH.[1,2,4] There are different options available for decreasing cystine supersaturation such as increasing fluid intake (4-5 liters/day in children), decreasing protein intake (<0.8 g of protein/kg/day)[1] and the use different drugs like D-penicillamine,[8] alpha-MPG or tiopronin[1] and captopril (specially used in patients with proteinuria).[1] Another concomitant option is urine alkalinisation since cystine solubility is greater with higher pH.[2] The urine alkalinisation can be achieved by taking potassium citrate, although with special attention is required with monitoring serum potassium,[1] and with acetazolamide that increase urine pH, although there is increased risk of calcium phosphate stones.[1,2] Other types of alkalinisation drugs are less preferable.[1] In this present case we preferred to use potassium citrate with acetazolamide and captopril due to our experience with these medications in adults with excellent results and good control of stone activity. Moreover, in many occasions, treatment with tiopronin or D-penicillamine is not well tolerated by the patients. Other treatment modalities include extracorporeal shock wave lithotripsy (in upper ureter and kidney stones <1.5 cm diameter), retrograde ureteroscopy, percutaneous nephrolithotomy, open nephrolithotomy and robotic pielolithotomy.[1,9] In our case, we first treated the ureteral stone with retrograde ureteroscopy and we are planning on future treatments with percutaneous nephrolithotomy and likely extracorporeal lithotripsy for the residual stones since it is effective in children. This case highlights that an uncontrolled cystine stone can produce renal insufficiency due to a severe lithogenic activity. It is important to increase urinary pH, reduce the cystine stone formation and increase water intake.

Table 1 Results of urinary and blood metabolic study in the boy with suspected cystinuria and cystine stones

	Levels (normal range)
Serum parameters	
Urea (mmol/l)	17 (4-18)
Creatinine (µmol/l)	86 (50-77)
Sodium (mmol/L)	140 (135-145)
Potasium (mmol/L)	5.3 (3.5-5)
Chloride (mmol/L)	96 (95-110)
Uric acid (µmol/l)	405 (202-416)
Calcium (mmol/l)	2.6 (2.1-2.6)
Phosphorus (mmol/l)	1.3 (1.0-1.9)
TSH (mIU/l)	2.65 (0.51-4.30)
iPTH (pg/ml)	16.7 (15-65)
25-OH-Vitamin D (ng/ml)	51 (50-175)
Urine parameters	
Fasting calcium/creatinine	0.05 (<0.11 or >0.11)
pH	6.5 (5-8)
Density	1013 (1005-1030)
24 h urine parameters	
Creatinine clearance (ml/min)	55 (71-151)
Calciuria (mmol 24 h)	1.3 (<6.5)
Uricosuria (µmol 24 h)	2256 (<4500)
Phosphaturia (mmol 24 h)	130 (130-423)
Natriuria (mmol 24 h)	152 (85-250)
Citraturia (µmol 24 h)	453 (>1665)
Oxaluria (µmol 24 h)	0.16 (<0.44)
Magnesuria (mmol 24 h)	3.9 (3-11)
Cystinuria* (µmol 24 h)	4082 (29-279)
Albuminuria (mg 24 h)	55.9 (30-299)

* Measured with liquid chromatographic technique (LC-MS/MS)

Declaration of Interest

The authors declare no conflict of interest and no funding.

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