Case Report

Cystinuria: A rare cause of bladder stone

Amalu Marutholil Babu[1], Radhika Chemmangattu Radhakrishnan[2], Susan Uthup[3], Beena Sushamma Vasudevan[4]

From [1]Postgraduate, Department of Pediatrics, Department of Pediatrics, [2]Assistant Professor, Department of Paediatric Nephrology, [3]Professor, Department of Paediatric Nephrology, [4]Professor, Department of Pediatric Surgery, SAT hospital, Government Medical College, Thiruvananthapuram, Kerala, India

ABSTRACT

Cystinuria is an inherited metabolic disorder progressing with recurrent kidney stones due to impaired reabsorption of dibasic amino acids and arises from mutations in the SLC3A1 and SLC7A9 on chromosome 2. Here, we present the case of a 1-year 10-month-old male child with recurrent episodes of urinary tract infections. On evaluation, duplex kidneys and a large bladder calculus were found which was surgically managed. Stone analysis and the genetic study were suggestive of cystinuria.

Key words: Cystinuria, Aminoaciduria, Cystine, ornithine, lysine and arginine transporter, SLC7A9 gene

Cystinuria is an inherited autosomal recessive disorder, characterized by the impaired reabsorption of cystine, lysine, ornithine, and arginine in the proximal tubule with an increased urinary excretion, resulting in a risk of renal stone formation because of the low solubility of cystine in the urine. The average prevalence of cystinuria is reported to be 1 in 7000 births. It is caused by mutations in the SLC3A1 gene or SLC7A9 [1]. The clinical manifestations of cystinuria are those related to stone formation, such as flank pain, stone passage, and hematuria. The aim of the medical therapy is to maintain the cystine concentration in the urine below its solubility level, thereby preventing stone formation. The therapy is based on hydration therapy, urine alkalinization, and cysteine-chelating drugs [2]. When medical treatment is ineffective, surgery should be considered.

Here, we report the case of cystinuria that manifested in late infancy, and we aim to understand the need for a complete evaluation of such cases that can progress to chronic kidney disease (CKD).

CASE REPORT

A 1 year and10 months old male child, the second child of non-consanguineous marriage was referred to our center with complaints of painful micturition over the last 9 months and multiple episodes of urinary tract infection (UTI) since 8 months of age. The child had no family history of renal stones.

Initial evaluation revealed normal hemogram and renal functions. Urine analysis showed microscopic hematuria (Urine RBC–10-15/HPF). Coagulation parameters were within the normal range (International normalized ratio of 1.05, activated partial thromboplastin time of 30.6). Urine cultures for bacteria were negative. No hypertension and electrolyte abnormalities were found.

Ultrasound abdomen revealed bilateral moderate-to-severe hydroureteronephrosis and two large urinary bladder calculus, the larger one being 25 × 16 mm. A plain X-ray of the abdomen and pelvis revealed two large radiopaque stones in the bladder (Fig. 1a). The urine calcium creatinine ratio was 0.026. Micturating cystourethrogram was normal with no evidence of reflux. Intravenous urogram was done, which identified the duplex system.

Cystolithotomy was done and the stone was removed (Fig. 2). The left retrograde Double-J stenting was done (Fig. 1b). Stone analysis revealed a mixture of calcium oxalate and cysteine. Diethylene-triamine-pentaacetate renogram was done to assess residual renal function, which showed reduced renal function in the left kidney (28%) along with non-obstructed drainage.

By molecular analysis, a homozygous missense variant (Phenylalanine is substituted by Serine in the 140th position in Exon 4 of the SLC7A9 gene) was identified which is pathogenic for cystinuria. On the gnomAD database, p.Phe140Ser had an allele frequency of 0.00009799 in the South Asian population and 0.00008137 in the total population. No mutations were found in the SLC3A1 gene.

The child was treated with urine alkalinization with potassium citrate and now is on regular follow-up. After 6 months of the procedure, hematuria got resolved, his urine pH was 7.5, there were no further episodes of UTI, and the ultrasound revealed no new stone formation.

Access this article online	
Received - 01-May-2023 Initial Review - 11-May-2023 Accepted - 20-Jun-2023	Quick Response code
DOI: 10.32677/ijcr.v9i6.4023	

Correspondence to: Amalu Marutholil Babu, Marutholil House, Pallikavala, Kattappna, Idukki - 685 515, Kerala, India. E-mail: amalumbabu@gmail.com

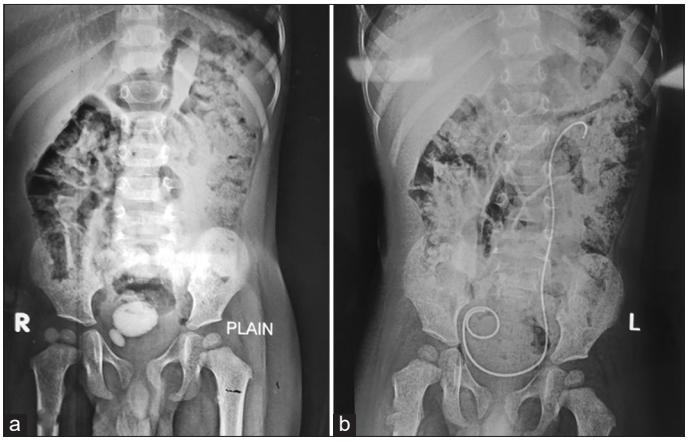

Figure 1: (a) Plane radiograph showing 2 bladder calculi; (b) radiograph after Double J stenting

Figure 2: Cystine stones removed after cystolithotomy

DISCUSSION

Cystinuria is an inherited amino acid transport defect that was first described by Garrod in 1908 [3]. Cystine stones account for only about 1–2% of all kidney stones but represent roughly 6–8% of all pediatric calculi. The cause of cystinuria is an inheritable, autosomal recessive genetic defect that affects the proximal renal tubular reabsorption of cystine which also affects ornithine, lysine, and arginine, but only cystine is clinically significant as it is the only amino acid in this group that will form stones owing to its low solubility [4].

Inborn errors of metabolism like cystinuria leading to nephrolithiasis should be suspected when there are early onset kidney stones, large or recurrent stones, a family history of renal stones, and consanguineous marriage. The two genes, the pathogenic forms of which are responsible for the disorder, are SLC7A9 and SLC3A1. While the former encodes (b0, + AT) protein, the translated protein product of the latter is rBAT. The aforementioned proteins form a dibasic amino acid transporter located in the apical membrane of proximal renal tubular epithelial cells which facilitate the transport of cysteine from inside the tubules back to the blood. The chromosomal locations of these two genes are at 2p16.3-21 and 19q13.1, respectively [5].

Cystinuria is divided into two main clinical subtypes according to the mutations and inheritance type. Cystinuria Type A is an autosomal recessive inherited disease and occurs as a result of a mutation in the SLC3A1 gene on the second chromosome, while Cystinuria Type B has an autosomal dominant inheritance and is caused by a mutation in the SLC7A9 gene on the 19th chromosome. Rarely, there can be two different mutant alleles on the same gene and this subtype of cystinuria is defined as Type AB [6].

Children suspected of having cystinuria require a quantitative 24-h urine test for cystine. In older children, cystinuria is usually defined as >315 mg cystine/g creatinine. In younger children who cannot perform 24-h collections, there are age-related standards for first-morning urine cystine concentration per gram of creatinine Normal cystine concentrations in younger children are as follows [7]: age <1 month: <80 mg cystine/g creatinine; age 1 month -1 year: <52 mg cystine/g creatinine; age >1 year: <35 mg cystine/g creatinine.

Management of cystinuria should be done with adequate hydration, urinary alkalinization using 3–4 mEq/day of potassium citrate or potassium bicarbonate (cystine solubility increases 3 folds in alkaline urine), and dietary restriction of sodium and animal protein. For resistant cases, thiol-containing drugs such as Tiopronin or D Penicillamine can be given. These drugs have sulfhydryl groups that can reduce the disulfide bond between two cysteine molecules, producing mixed drug-cysteine disulfides which are more soluble than homodimer cystine [8].

The response to therapy must be monitored both biochemically and radiologically. Initially, the monitoring of 24-h urine cystine, sodium, and calcium along with urine pH should be done every 3 months followed by every 6 months. Radiological monitoring with 6 monthly ultrasonography should be done to detect the new stone formations. Non-contrast computed tomography should be reserved for symptomatic patients with suspected ureteral stones missed on ultrasound or to better assess stone burden prior to surgery [8].

The prevalence of CKD in cystinuric patients is higher than that in the general population. A French study by Prot-Bertoye *et al.* in 2015 found that 27% of cystinuria patients (aged ≥16 years) had impaired renal function [9]. Furthermore, the prevalence of end-stage renal disease (ESRD) is also higher in these patients (0.4–4.3%). Cystinuria patients are more likely to develop CKD because of renal parenchyma damage, damage during nephrectomies performed for renal stone removal, recurrent UTIs, use of drugs with nephrotoxicity, and the obstruction of the collecting ducts by cystine crystals [9].

CONCLUSION

In the management of rare causes of nephrolithiasis such as cystinuria, it is critical to assess the potential impact of these stones on renal function in addition to promptly initiating medical management to reduce stone production. Early recognition of kidney injury resulting from recurrent obstructive stone formation can help delay or prevent the development of ESRD.

REFERENCES

1. Tunçbilek E. Clinical outcomes of consanguineous marriages in Turkey. Turk J Pediatr 2001;43:277-9.
2. Barbey F, Joly D, Rieu P, Méjean A, Daudon M, Jungers P. Medical treatment of cystinuria: Critical reappraisal of long-term results. J Urol 2000;163:1419-23.
3. Özgur A, Tanzer F, Cankorkmaz L, Koyluoglu G. Bir yaşındaki bir çocukta böbrekte taş nedeni olarak sistinüri. Çocuk Sağlığı ve Hastalıkları Derg 2005;48:158-63.
4. Gres AA, Nitkin DM, Juraha TM, Sivakow AA. Cystine as a risk factor of the stone formation in kidney: The reference value range of urinary excretion, the stage diagnosis of cystine metabolism disorder. Urologiia 2016;4:10-4.
5. Fazaeli S, Ashouri S, Kheirolahi M, Mohammadi M, Fazilati M. A novel mutation in SLC7A9 gene in cystinuria. Iran J Kidney Dis 2017;11:138-41.
6. Kim JH, Park E, Hyun HS, Lee BH, Kim GH, Lee JH, *et al.* Genotype and phenotype analysis in pediatric patients with cystinuria. J Korean Med Sci 2017;32:310-4.
7. Sadiq S, Cil O. Cystinuria: An overview of diagnosis and medical management. Turk Arch Pediatr 2022;57:377-84.
8. Daga S, Palit V, Forster JA, Biyani CS, Joyce AD, Dimitrova AB. An update on evaluation and management in cystinuria. Urology 2021;149:70-5.
9. Prot-Bertoye C, Lebbah S, Daudon M, Tostivint I, Bataille P, French Cystinuria Group, *et al.* CKD and its risk factors among patients with cystinuria. Clin J Am Soc Nephrol 2015;10:842-51.

Funding: Nil; Conflicts of interest: Nil.

How to cite this article: Babu AM, Radhakrishnan RC, Uthup S, Vasudevan BS. Cystinuria: A rare cause of bladder stone. Indian J Case Reports. 2023;9(6):179-181.