Case Report

Cystinuria, an Atypical Presentation and Challenges of Establishing its Diagnosis in a Poor Resource Set Up

Bijaya Mishra,[1] Nisha Keshary Bhatta,[2] Anupam Pokhrel,[1] Madhab Lamsal[1]

[1]Department of Biochemistry, B.P. Koirala Institute of Health Sciences, Dharan, Nepal, [2]Department of Pediatrics and Adolescent Medicine, B.P. Koirala Institute of Health Sciences, Dharan, Nepal.

ABSTRACT

Cystinuria is an autosomal recessive defect in re-absorptive transport of amino acids: cysteine, ornithine, arginine and lysine from renal proximal convoluted tubules leading to urinary excretion of these amino acids. The phenotypic manifestations are recurrent urolithiasis, hematuria, flank pain and frequent urinary tract infection. An eighteen years old boy, diagnosed case of cystinuria at the age of two years is presented in this case report highlighting the atypical presentation of recurrent infections with multiple organ involvement. The challenges in establishing the diagnosis and the role of simple biochemical tests in confirming the diagnosis in a poor resource setup is highlighted. Performance of simple biochemical tests in the urine sample of this patient was done for the utility of these tests for future diagnostic purpose in any suspected cases of cystinuria in our set up.

Keywords: Case report; cystinuria; Nepal.

INTRODUCTION

Cystinuria is an autosomal recessive defect in reabsorptive transport of amino acids, particularly cystine, with the only phenotypic manifestation of recurrent cystine nephrolithiasis.[1] Symptoms vary from hematuria, flank-pain, frequent urinary-tract-infection, nephrolithiasis, hyperuricemia, and renal insufficiency. Significant delay in diagnosis and multiple urologic procedures adversely affects quality of life.[2] Diagnosis is based on renal calculi analysis, qualitative method of measuring urinary excretion of cystine, measurement of cystine concentration in urine by mass spectrometry, radiological investigations like CT scan and genetic-testing.[3] We present an eighteen-year-old boy, known case of cystinuria with atypical presentation of recurrent infections- pneumonia, meningitis, jaundice, pulmonary tuberculosis, renal calculi formation until and after his diagnosis was confirmed at age of two. During present follow-up, color reactions of amino acids and cyanide nitroprusside tests in urinary samples were performed; these tests were established for future testing in suspected cases of cystinuria in our laboratory.

CASE REPORT

An eighteen-year boy diagnosed with cystinuria at age of two, visited Paediatric OPD for follow-up after 7 years. He is apparently healthy with dietary restrictions, regular urinary alkalizer and pH monitoring. Patient was full-term baby, normal vaginal delivery with APGAR scores 7, 8 and 9 at 1, 5- and 10 minutes respectively. Six-days after birth, he developed high-grade fever, breathlessness, feeding refusal, decreased reflexes, and admitted with diagnosis of pyogenic meningitis, treated with IV antibiotics.

He developed recurrent episodes of bronchial pneumonia with high-grade fever treated with IV antibiotics at 1.5-, 3- and 6-months age. There was failure to thrive; poor sucking with NG-tube feeding. At nine months age, pulmonary tuberculosis was diagnosed and anti-tubercular treatment(ATT) was started and continued for nine months. At age of 14months, he developed high-grade fever with difficult micturition. X-ray KUB showed single vesicle and left ureteric calculi. Cystoureterolithotomy and circumcision were

Correspondence: Dr Bijaya Mishra, Department of Biochemistry, B.P. Koirala Institute of Health Sciences, Dharan, Nepal. Email: bjaya.mp@gmail.com, Phone: +9779849530325.

performed. At 16months age, bronchial pneumonia was treated with IV antibiotics. At age of 22months, suprapubic cystolithotomy performed for single bladder calculi. Stone analysis revealed cysteine and calcium oxalate stone.

One month later, patient redeveloped pain abdomen. At age of two, with impression of "Suspected metabolic disorder, recurrent urolithiasis with recurrent respiratory infection, with developmental delay, suspected post-meningitis complication resulting into feeding problem and recurrent aspiration pneumonia", he was referred to All India Institute of Medical Sciences(AIIMS), where in view of developmental delay and recurrent renal stone formation, diagnosis of "cystinuria" was made. Urine cyanide nitroprusside test was positive. Urine aminoacidogram (qualitative) showed positive for cysteine. Pulmonary work-up revealed right lung lower lobe collapse with calcification streaks. USG revealed bladder calculi and CT abdomen suggested microlithiasis in collecting-system and cystolithotomy performed. D-Penicillamine was started, with increased fluid intake, urinary alkalizer, dietary restriction of methionine and salt. Regular follow-up and urine pH monitoring was advised.

At age of eight, patient visited AIIMS for first follow-up. He was under regular intake of D-penicillamine, urine alkalizer. No calculi, no side effects of D-penicillamine; no signs of developmental delay. He was advised to continue same medication. Second follow-up was six-months later, where D-penicillamine was stopped. Since then, patient is continuously under urine alkalizer. At age of 10, patient was diagnosed with typhoid. At age of 18years, patient visited us for third follow-up. He was under regular urine alkalizer, urinary pH monitoring and seldomly performs X-ray KUB.

Patient has three siblings, all apparently healthy. According to parents, at AIIMS, they underwent few tests and results were normal, no documentation available.

Patient's chronological age is eighteen, height 158cm, weight 40kg, in tenth grade, with no signs of developmental, gross motor and IQ delay.

He was referred to Biochemistry Department, for investigations. However, there were no established investigations protocol for diagnosing/monitoring cystinuria in our laboratory. We started with simple urine tests, and also wanted to establish these investigations to diagnose cystinuria in suspected cases in future. We collected 24-hour and random urine sample.

In paper chromatography, both 24-hour and random urine sample showed positive ninhydrin test slightly above point of application, suggesting presence of amino acids. However, we were not able to differentiate them.

Color reactions in urine were performed. Sulphur test for cysteine/cystine was strongly positive in 24-hour urine sample and mild positive in random sample (Figure1). Sakaguchi test for arginine was mildly positive in both samples (Figure 2). Cyanide nitroprusside test was moderately positive in both samples, suggesting cystine in urine (Figure 3).

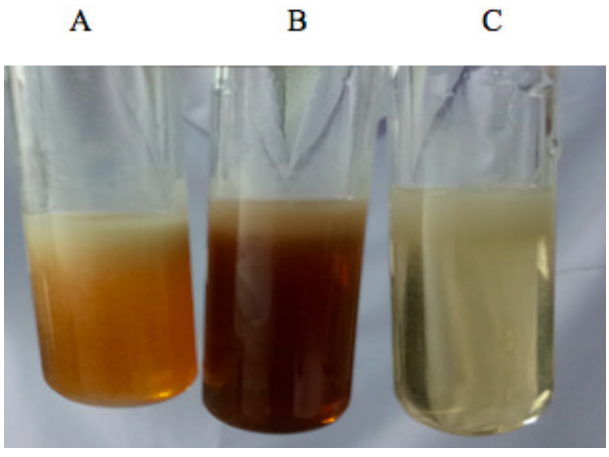

Figure 1. Sulphur test (A- random urine- patient, B- 24-hour urine-patient, C- control urine sample).

Figure 2. Sakaguchi test- 24-hour urine sample.

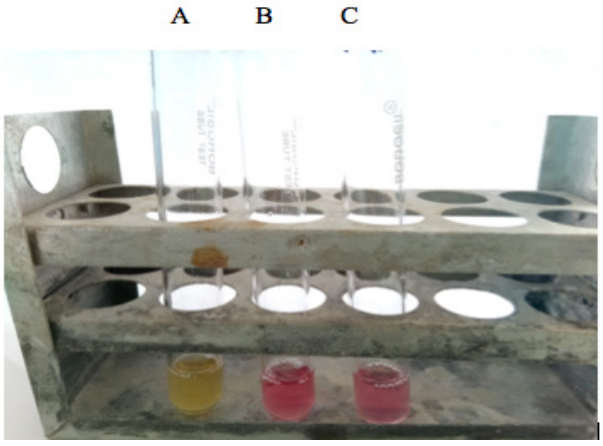

Figure 3. Cyanide nitroprusside test; A- control, B- random urine- patient, C- 24-hour urine- patient).

Random urine pH was 6.5. USG showed no calculi. All biochemical results were discussed with paediatrician; patient advised to continue urine alkalizer, plenty water, salt and dietary protein restriction.

DISCUSSION

Cystinuria, an inherited metabolic disorder with defect in reabsorptive transport of amino acids: cysteine, ornithine, arginine and lysine, typically presents with urolithiasis, hematuria, flank pain and frequent urinary tract infection.[4] In our patient there were no evidence of renal complications associated with cysteine calculi; atypical clinical presentation of recurrent infections- meningitis, pneumonia and tuberculosis has been highlighted. Mutation in two protein subunits of amino acid transporter, rBAT encoded by *SLC3A1* and $b^{0,+}$AT encoded by *SLC7A9* can lead to cystinuria.[5,6] We couldn't perform genetic tests to detect these mutations due to unavailable infrastructure. Diagnosis of cystinuria is commonly based on urinary microscopic finding of cysteine stone showing characteristic cysteine crystals, usually hexagonal, translucent and white.[7] Stone analysis of our patient post-cystolithotomy at age of 22months revealed cysteine and calcium-oxalate stone. Sodium cyanide nitroprusside test is rapid, simple, and qualitative determination of cystine concentrations. Cyanide converts cystine to cysteine, nitroprusside then binds, causing purple hue in 2-10minutes. This test detects cystine levels higher than 75 mg/g of creatinine.[1] Test results were positive in both 24-hour and random urine sample of patient during present follow-up. However, as cyanide nitroprusside detects amino acids containing free sulfhydryl or disulphide bind, thus resulting false positive results in homocystinuria and acetonuria. Hence, precise quantitative measurement of urinary cystine levels by mass spectrometry is always indicated.[8] We could not perform the later due to lack of facility.

Management of cystinuria requires multi-modal approach and combines lifestyle advice- increased fluid intake, urine alkalization, which increases cysteine solubility, restriction of salt and methionine containing diet, medical therapy with cysteine-binding drugs- penicillamine and tiopronin, which forms soluble heterodimers with cysteine to reduce stone formation. Surgical interventions for renal stones removal are carried when required.[9] Combination of these strategies was followed in our patient. However, there is no curative treatment; patient holds lifelong risk of stone formation, repeated surgery, impaired renal function and quality of life.[10] All health consequences were properly counselled to the patient, with advice to continue urine alkalizer, regular urine pH monitoring and regular follow-up.

Atypical presentation of cystinuria with multiple organ involvement, and huge limitation and challenges faced in diagnosing a simple inherited metabolic disorder like cystinuria was presented. Importance of simple color reactions of amino acids in urine sample with its establishment for future utilization in supporting the diagnosis of suspected cystinuria has been discussed. Many developing countries including Nepal, still struggles in identifying many inborn errors of metabolism in newborns delaying its diagnosis and management.[11]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Biyani CS, Cartledge J. Cystinuria [Internet]. New York (US): Medscape [updated 2019 Dec 12; cited 2021 Dec 21]. [Full Text]

2. Goldfarb DS, Grasso M. Case Study - Case Studies in Cystinuria. Urol Nurs. 2017 Mar-Apr;37(2):90-3. [PubMed | Full Text]

3. John A. Sayer, Fay Hill. Cystinuria: A Review of Inheritance Patterns, Diagnosis, Medical Treatment and Prevention of Stones.; Submitted September 13th 2016, Reviewed June 1st 2017, Published: August 23rd, 2017; [Full Text]

4. Genetic and Rare Diseases Information Center. Cystinuria

[Internet]. Maryland (US): National Institute of Health [updated 2015 Nov 11; cited 2021 Dec 23]. [Full Text]

5. Calonge MJ, Gasparini P, Chillaron J, Chillon M, Gallucci M, Rousaud F, et al. Cystinuria caused by mutations in rBAT, a gene involved in the transport of cystine. Nat Genet. 1994 Apr;6(4):420-5. [PubMed | Full Text | DOI]

6. Bisceglia L, Calonge MJ, Totaro A, Feliubadalo L, Melchionda S, Garcia J, et al. Localization, by linkage analysis, of the cystinuria type III gene to chromosome 19q13.1. Am J Hum Genet. 1997 Mar;60(3):611-6. [PubMed | Full Text]

7. Hoppe B, Leumann E, Millionaire DS. Comprehensive Pediatric Nephrology. 1st ed. Philadelphia: MOSBY ELSEVIER; 2008. Chapter 33, Urolithiasis and Nephrocalcinosis in Childhood; p499-526. [Full Text]

8. Pereira DJ, Schoolwerth AC, Pais VM. Cystinuria: Current concepts and future directions. Clin Nephrol. 2015;83(3):138-146. [PubMed | Full Text]

9. Moe OW, Pearle MS, Sakhaee K. Pharmacotherapy of urolithiasis: evidence from clinical trials. Kidney Int. 2011 Feb;79(4):385-92. [PubMed | Full Text | DOI]

10. Obro LF, Pedersen KV, Lildal SK, Osther SS, Jung HU, Andreassen KH, et al. The challenges of cystinuria in the twenty-first century – a mini review. J Rare Dis Res Treat. 2016;1(3):41-5. [Full Text | DOI]

11. Pandey AS. Metabolic disease in Nepal: A perspective. Kathmandu Univ Med J. 2010; 8(3):333-40 [Full Text | DOI]