Cystinuria in a 13-month-old Girl with Absence of Mutations in the SLC3A1 and SLC7A9 Genes

Sir,

A 13-month-old developmentally normal girl presented with red-colored urine for 2 days. She had been referred to us from another hospital with an ultrasonogram revealing renal stones. There was no history of oliguria, edema, hearing abnormalities, or passage of stones in the urine. She was the first child born of nonconsanguineous Tamil-Muslim parents, and the family history was significant for renal stones in the father that was diagnosed during the evaluation of lumbar pain. On examination, she weighed 8.65 kg (*Z* score of − 1 to − 2), height was 78 cm (*Z* score of − 1 to 0), and head circumference was 44 cm (*Z* score of − 1 to − 2). There was no pallor, rickets, or edema. Vital signs were normal; she was afebrile, and there was no hypertension. There was no organomegaly or renal angle tenderness. Rest of the systemic examination was normal. By the time she arrived at our hospital, the red-colored urine had subsided macroscopically; however, 15–20 red blood cells/high-power field (nondysmorphic, without casts or crystalluria) were detected on urine microscopy. There was no proteinuria. Renal ultrasonogram showed bilateral renal pelvic calculi; 0.5 mm in the right renal pelvis and 0.6 mm in the left renal pelvis, with no hydronephrosis. X-ray abdomen did not reveal any calcifications. Blood investigations were as follows: hemoglobin, 11 g/dl (normal 9–11); urea, 18 mg/dl (range 15–40); creatinine, 0.4 mg/dl (0.3–0.7); pH, 7.38; bicarbonate, 23 mEq/L; sodium, 140 mEq/L; potassium, 3.9 mEq/L; calcium, 9.0 mg/dl; and magnesium 2.1 mg/dl (all within normal reference ranges). Urine investigations were as follows: spot calcium creatinine ratio, 0.06 (normal <0.2); 24-h urine oxalate, 9 mg/1.73 m^2/day (normal <40); 24-h urine uric acid, 213 mg/1.73 m^2/day (normal <815); and 24 h citrate, 303 mg/g creatinine (normal >400). Hence, the investigations showed hypocitraturia, with no hypercalciuria, hyperoxaluria, hyperuricosuria, metabolic acidosis, uremia, hypercalcemia, or hypomagnesemia.

Subsequently, a urine sodium cyanide–nitroprusside test on an early morning specimen was consistently found to be positive on multiple occasions (bright red color) [Figure 1], suggestive of cystinuria. The parents' urine sodium cyanide–nitroprusside test was also found to be consistently positive. Twenty-four hour urine cystine levels were deferred due to logistic constraints. Genetic studies for SLC3A1 and SLC7A9 mutations for the child as well as the parents failed to demonstrate mutations in these two genes by Sanger sequencing and multiplex ligand-dependent probe amplification (MLPA) (SALSA MLPA P426 Cystinuria probemix, MRC Holland). The child was treated with potassium citrate for alkalinization of the urine and was advised plenty of fluids, a low salt diet, and avoidance of red meat.

We diagnosed our patient as having cystinuria based on a consistently positive sodium cyanide–nitroprusside test in the child as well as in the parents in the setting of nephrolithiasis. The sodium cyanide–nitroprusside test is commonly used for rapid qualitative determination of cystine concentration in the urine. Cyanide breaks the disulfide bond of cystine liberating cysteine, which has an SH group. Nitroprusside then binds to the SH group in an alkaline medium (sodium hydroxide), causing a bright red hue in 2–10 min. The test detects cystine levels of higher than 75 mg/g of creatinine. If performed on a concentrated urine sample, this test is very accurate in diagnosing cystinuria (expected error of only 1%).[1] There was no history of an intake of ampicillin, sulfa drugs, or a clinical/biochemical setting of homocystinuria or Fanconi syndrome, which could have led to false positivity. Moreover, the parents were also consistently positive for the test, making false positivity unlikely. Earlier published studies also used the sodium cyanide–nitroprusside test for establishing the diagnosis of cystinuria.[2] We could not perform ion-exchange chromatographic quantitative analysis of a 24-h urine

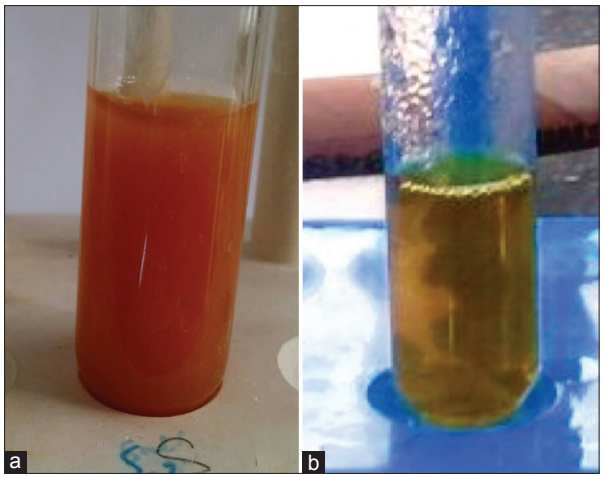

Figure 1: Urine cyanide–sodium nitroprusside test (a) of the child showing bright red color (cystinuria) in comparison with (b) a control sample

sample for cystine and whole exome sequencing (WES) due to logistic constraints.

Cystinuria is an autosomal recessive disorder associated with mutation in SLC3A1 and SLC7A9 genes.[3,4] These mutations lead to defective reabsorption of dibasic amino acids such as cystine, lysine, ornithine, and arginine in the proximal renal tubule. Cystine is insoluble in urine, while the other three are water soluble; hence, cystine precipitates as renal calculi. Currently, cystinuria is classified as:[3] Type A, due to 2 mutations of SLC3A1 on chromosome 2, Type B, due to 2 mutations of SLC7A9 on chromosome 19, and a possible third Type AB with mutation on each of these genes. Interestingly, both types of cystinuria, A and B, have similar outcome. Crystalluria (hexagonal crystals) may not be demonstrable in a significant number of children with cystinuria, as in our case.[3] The condition is usually managed with alkalinization of urine, low salt diet, plenty of fluids, and avoiding purine diet. We managed our patient conservatively and did not administer D-penicillamine due to its toxic potential.

The index case is notable for having undergone genetic studies, with no demonstrable mutations in the SLC3A1 and SLC7A9 genes. Approximately 3% of patients with cystinuria did not demonstrate mutations in both the cystinuria genes in a study by Font-Llitjós *et al*.,[4] implying the need to search for a third cystinuria gene.

There is a paucity of information regarding cystinuria in children from India. In a study on nephrocalcinosis in children from northern India, there was no reported case of cystinuria.[5] In addition, there is no information regarding genetic mutations in cystinuria from India. Information regarding genetic studies in children with cystinuria would help in providing timely prenatal and antenatal counseling for parents of children with cystinuria, help in expansion of the genotypical spectrum of this disorder, and assist in genotype–phenotype correlation in these children for appropriate counseling. In the Indian scenario, these aspects in cystinuria require further delineation due to extreme paucity of information. In this sense, the absence of known cystinuria gene mutations in this case might be a stepping stone rather than a stumbling block.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Smith A. Evaluation of the nitroprusside test for the diagnosis of cystinuria. Med J Aust 1977;2:153-5.
2. Marickar YM. Cystinuria: The South Indian experience. Urol Res 2009;37:341-3.
3. Dello Strologo L, Pras E, Pontesilli C, Beccia E, Ricci-Barbini V, de Sanctis L, *et al.* Comparison between SLC3A1 and SLC7A9 cystinuria patients and carriers: A need for a new classification. J Am Soc Nephrol 2002;13:2547-53.
4. Font-Llitjós M, Jiménez-Vidal M, Bisceglia L, Di Perna M, de Sanctis L, Rousaud F, *et al.* New insights into cystinuria: 40 new mutations, genotype-phenotype correlation, and digenic inheritance causing partial phenotype. J Med Genet 2005;42:58-68.
5. Mantan M, Bagga A, Virdi VS, Menon S, Hari P. Etiology of nephrocalcinosis in Northern Indian children. Pediatr Nephrol 2007;22:829-33.

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