Global Pediatric Health
January-December 2014: 1–4

DOI: 10.1177/2333794X14551275
gph.sagepub.com
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Persistent Leukocyturia Was a Clue to Diagnosis of Cystinuria in a Female Patient

Yoshifusa Abe, MD, PhD[1], Shinichi Sakamoto, MD, PhD[2], Eiji Morimoto[3], Yoshitaka Watanabe, MD[1], Keiko Nagahara, MD, PhD[1], Takeshi Mikawa, MD[1], Shuichiro Watanabe, MD, PhD[4], and Kazuo Itabashi, MD, PhD[1]

Introduction

Cystinuria (OMIM 220100) is characterized by the defective reabsorption of cysteine, lysine, ornithine, and arginine in the brush border membrane of proximal renal tubule and in the epithelial cells of the gastrointestinal tract. High cystine concentration causes the formation of recurring renal stones. Two genes, *SLC3A1* (rBAT) and *SLC7A9* (BAT1), are known to be responsible.[1,2] Although leukocyturia is an important sign of urinary tract infection (UTI), we report the case of a female patient with cystinuria that was detected owing to continuous leukocyturia.

Case Report

The patient was a healthy 13-month-old Japanese girl, who was the second child of healthy nonconsanguineous parents. Her brother had asthma. She was referred to our hospital because of leukocyturia, which continued for 1 month without fever. Culture of a urine specimen obtained by catheterization revealed the presence of *Escherichia coli* and *Enterococcus faecalis* (5×10^4 colony-forming units/mL). She was diagnosed as having cystitis and treated with antibiotics. Further tests were performed owing to the persistence of leukocyturia albeit after antibiotic therapy. Renal ultrasonography showed round hyperechoic lesions with sonic shadows, as shown in Figure 1A. Hexagonal crystals were detected in her urine, as shown in Figure 1B. Regarding urinary amino acid excretion in our patient, urinary concentrations of cystine, lysine, ornithine, and arginine were 2005.5, 6617.9, 661.1, and 1756.4 μmol/g·creatinine, respectively. These were extremely high compared with those in her family members, as shown in Figure 1C. Abdominal computed tomography revealed some round-shape high-density lesions at the right pelviureteric junction without hydronephrosis, indicating that she had urolithiasis, as shown in Figure 1D. These findings indicated the diagnosis of cystinura.

At the age of 1 year and 3 months, she was started on tiopronin and citrate. At the age of 1 year and 7 months, she was taken by her mother to our hospital because of fever and vomiting, which were indicative of upper UTI; a urine specimen was obtained by catheterization for culture. She was treated with cefaclor for 2 days without improvement. Then, she was admitted to our hospital for 12 days. Laboratory tests revealed 20 200 leukocytes/μL and a high level of C-reactive protein (10.81 mg/dL). On admission, an abdominal X-ray image showed calculi in the right kidney. She was first treated with cefazolin, which was ineffective and was thus switched to panipenem/betamipron. Although urine culture showed negative results and voiding, cysturethrography revealed she had no vesicoureteral reflux, and renal scintigraphy showed decreased perfusion in the right kidney. These findings did not exclude the possibility that she had acute focal bacterial nephritis or pyelonephritis. At the age of 1 year and 8 months, she passed stones for 2 consecutive days, as shown in Figure 1E. Infrared absorption spectrometry indicated that the stones were composed of cystine (>95%). She was doing well in general, but sterile leukocyturia persisted (see Table 1).

We performed sequence analysis of *SLC7A9* in the patient and her parents. Informed consent was obtained from her parents. The analysis revealed that she had 2 heterozygous mutations (L223M and A354T), whereas her father had a heterogeneous A354T mutation and her mother had a homozygous L223M mutation.

[1]Department of Pediatrics, Showa University School of Medicine, Tokyo, Japan
[2]Department of Urology, Chiba University School of Medicine, Chiba, Japan
[3]Clinical Laboratory, Showa University Hospital, Tokyo, Japan
[4]Watanabe Children's Clinic, Tokyo, Japan

Corresponding Author:
Yoshifusa Abe, Department of Pediatrics, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.
Email: yoshifusa@med.showa-u.ac.jp

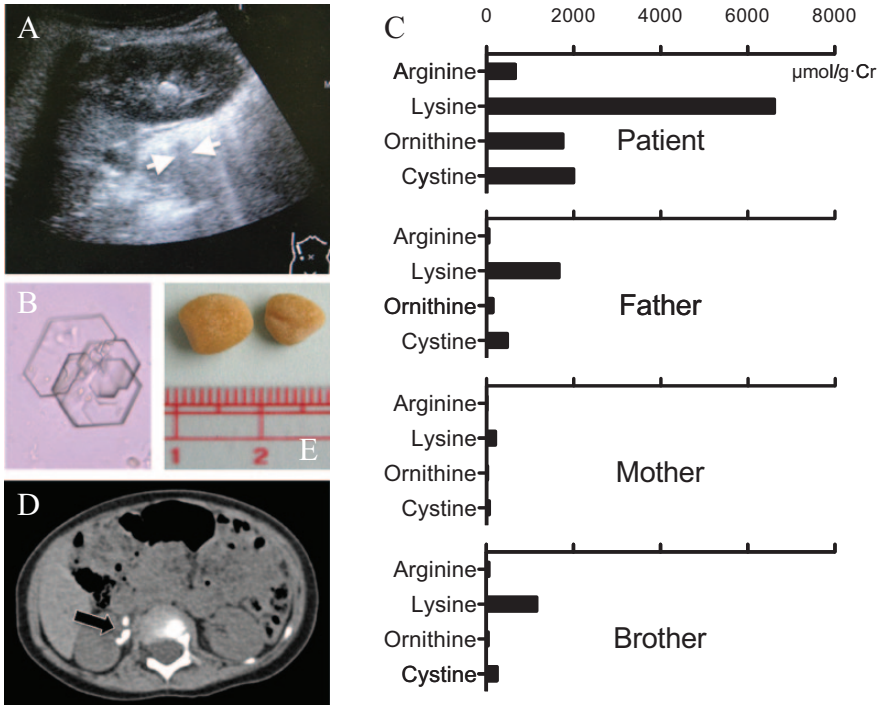

Figure 1. (A) Ultrasonography of right kidney. Ultrasonography was performed at the age of 1 year and 2 months. It revealed approximately 1 cm round hyperechoic lesions with sonic shadows (white arrows), indicating urolithiasis. (B) Cystine crystals. The urinary sediments show hexagonal crystals at the age of 1 year and 4 months, indicating cystine crystals. (C) Urinary amino acid excretion in our patient and her family members. Urinary concentrations of cystine, lysine, ornithine, and arginine were extremely high in our patient compared with those in her family members. (D) Computed tomography of the abdomen. Abdominal computed tomography revealed some round high-density lesions at the right pelviureteric junction without hydronephrosis, indicating urolithiasis. (E) Passing stones. Our patient passed stones at the age of 1 year and 8 months. They were about 7 to 10 mm in length, as indicated by the scale. Infrared absorption spectrometry indicated that stones were composed of cystine (>95%).

Discussion

In our patient, leukocyturia persisting for 1 month was one of the clues to the identification of cystinuria. It was finally diagnosed by gene analysis, which revealed that she had 2 heterozygous mutations in *SLC7A9* (L223M and A354T).

Cystinuria is a global disorder with population-specific prevalence. It varies between different populations. The highest frequency has been observed among Libyan Jews at a rate of 1:2500. The rates are 1:17 000 in the United States, 1:18 000 in Japan, and 1:100000 in Sweden,[1-3] Regarding urolithiasis, it is reported that the mean age of urolithiasis patients, including cystinuria patients, at diagnosis was 5.59 years. Of these patients, 41.4% were younger than 1 year of age and 60.5% were younger than 5 years of age.[4] The commonly presented symptoms are flank pain, restlessness, and hematuria, followed by UTI.[4] However, there are only a few studies showing that persistent leukocyturia is a clue to the diagnosis of cystinuria. Cystine stones account for 6% to 8% of all pediatric nephrolithiasis patients.[1] To prevent the acceleration of cystine stone formation, early diagnosis is important, as in the case of our patient.

Dello Strologo et al proposed the following classification of cystinuria: Type A, cystinuria caused by mutations in both alleles of *SLC3A1* (chromosome 2); Type B, cystinuria caused by mutations in both alleles of *SLC7A9* (chromosome 19); Type AB, cystinuria caused by 1 mutation in *SLC3A1* and 1 mutation in *SLC7A9*.[5] The classification proposed by Eggermann et al is based on the above: Type AA, homozygosity for 1 *SLC3A1* mutation or compound heterozygosity for 2 *SLC3A1* mutations; Type A?, heterozygosity for a *SLC3A1* mutation, a second mutation could not be identified; Type BB, homozygosity for 1 mutation or compound heterozygosity for 2 *SLC7A9* mutations; Type B?, heterozygosity for a *SLC7A9* mutation, a second mutation could

Table 1. Findings of Urinalysis and Urine Culture.

Age	Occult Blood	Leukocyte Esterase	Microscopy: WBC Counts	Urine Culture (cfu/mL)
1 Year	+	500[a]	Not done	*E coli*, 4×10^{4}[b]
	−	75[a]	Not done	
	−	75[a]	Not done	
1 Year and 1 month	−	75[a]	Not done	Negative[b]
	−	500[a]	Not done	
	−	3+	1-4	*E coli* and *Ec faecalis*, 5×10^{4}
1 Year and 2 months	−	3+	10-19	
	−	3+	5-9	
1 Year and 3 months	±	3+	50-99	*E coli*, 10^{5}
	−	3+	1-4	
1 Year and 4 months	2+	3+	30-49	
1 Year and 5 months	−	2+	5-9	
1 Year and 6 months	+	2+	10-19	
	−	3+	20-29	
	−	3+	10-19	
	±	+	5-9	Negative
	−	−	1-4	Negative
	3+	3+	30-49	
	1+	3+	1-4	
1 Year and 7 months	±	2+	1-4	
	−	1+	<1	
	−	2+	5-9	
	−	2+	1-4	Negative
	−	±	1-4	
	−	2+	10-19	
1 Year and 8 months	−	+	20-29	Negative
	±	2+	1-4	
1 Year and 9 months	−	2+	1-4	
1 Year and 10 months	−	2+	1-4	
1 Year and 11 months	−	+	1-4	
2 Years	−	+	20-29	Negative
2 Years and 2 months	−	2+	20-29	
	−	3+	50-99	
	−	+	5-9	
2 Years and 3 months	−	+	20-29	
2 Years and 4 months	−	±	5-9	

Abbreviations: WBC, white blood cell; cfu, colony-forming units; *E coli, Escherichia coli; Ec faecalis, Enterococcus faecalis.*
[a]Semiquantitative studies by dipstick urinalysis.
[b]Analysis of a bag-collected urine specimen.

not be identified; Type AB, mixed heterozygosity of a *SLC3A1* mutation and an *SLC7A9* mutation; Type AAA/AAB/ABB, 3 *SLC3A1*/*SLC7A9* mutations in one patient.[1]

Our patient had 2 heterozygous *SLC7A9* (BAT1) mutations, which were L223M and A354T, whereas her father had the heterogeneous A354T mutation and her mother had the homozygous L223M mutation. Although her father was asymptomatic, his urinary concentrations of cysteine, lysine, ornithine, and arginine were higher than her mother's. Functional analyses using the International Cystinuria Consortium suggest that A354T is a severe cystinuria mutation.[6] Her mother had the homozygous L233M mutation without clinical manifestations. This is consistent with the report that the L233M mutation is apparently a polymorphic change.[7] On the other hand, it is also known that the L233M mutation affects the cystine transport activity.[7] These findings suggest that cystinuria in our patient was mainly induced by A354T, and L223M additionally affected it. Dello

Strologo's classification cannot be adapted to our patient; therefore, type BB is proposed on the basis of Eggermann's classification.

Cystinuria is also observed in cystinuria-hypotonia syndrome, which is characterized by generalized hypotonia at birth, failure to thrive, growth retardation, and nephrolithiasis. This disease is due to microdeletion of part of *SLC3A1* on chromosome 2q21.[8] Our patient showed no developmental disorder or mutation in *SLC3A1*. Hence, we consider that her cystinuria was not associated with cystinuria-hypotonia syndrome.

Leukocyturia is one of the signs of UTI, which itself is also a sign of urolithiasis. About 16% of children with urolithiasis present with UTI.[4] However, there are some reports that sterile leukocyturia is a clue to the diagnosis of cystinuria in a child.[9] Wounding of the urinary tract by cystine stones might be associated with leukocyturia, even when UTI is not induced.

In conclusion, early diagnosis and prophylactic management are important to minimizing cystine stone formation. Therefore, cystinuria should be considered when we come across patients with persistent sterile leukocyturia.

Authors' Note

Yoshifusa Abe and Shinichi Sakamoto contributed equally as first authors.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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