

# Nephropathic Cystinosis Mimicking Bartter Syndrome

## A Novel Mutation

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Cystinosis is a rare autosomal recessive disorder resulting from defective lysosomal transport of cystine due to mutations in the cystinosin lysosomal cystine transporter (*CTNS*) gene. The clinical phenotype of nephropathic cystinosis is characterized by renal tubular Fanconi syndrome and development of end-stage renal disease during the first decade. Although metabolic acidosis is the classically prominent finding of the disease, a few cases may present with hypokalemic metabolic alkalosis mimicking Bartter syndrome. Bartter-like presentation may lead to delay in diagnosis and initiation of specific treatment for cystinosis. We report a case of a 6-year-old girl initially presenting with the features of Bartter syndrome that was diagnosed 2 years later with nephropathic cystinosis and a novel *CTNS* mutation.

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### INTRODUCTION

Cystinosis is a rare autosomal recessive disease caused by mutations in the cystinosin lysosomal cystine transporter (*CTNS*) gene on chromosome 17p13, which leads to intralysosomal cystine accumulation in the kidney, liver, eye, thyroid gland, and brain. The disease occurs at an incidence of approximately 1 in 100000 to 200000 live births.<sup>1</sup>

Children generally present between the age of 6 to 12 months with polyuria, polydipsia, and failure to thrive due to generalized proximal tubular damage, called renal Fanconi syndrome. Nephropathic cystinosis presents with infantile-onset renal tubular Fanconi syndrome, and untreated patients progress to end-stage kidney disease within the first decade of life.<sup>2</sup>

The diagnosis of cystinosis can be missed in infants, because not all signs of renal Fanconi syndrome are present during the first months of life. Therefore, the diagnosis and specific treatment of cystinosis are frequently delayed, which has a significant impact on the overall prognosis.<sup>1</sup> We present a 6-year-old girl with nephropathic cystinosis previously misdiagnosed as Bartter syndrome that had a novel mutation in the *CTNS* gene.

### CASE REPORT

The patient was a girl aged 6 years and 3 months, born by spontaneous delivery with a birth weight of 3160 g (25th to 50th percentile) and a height of 49.5 cm (25th percentile) following an uneventful pregnancy. She had been diagnosed and treated as Bartter syndrome at another health center for 3 years. The Bartter syndrome diagnosis was based on a history of failure to thrive, polyuria, polydipsia, hyponatremia, hypochloremia, and persistent hypokalemic metabolic alkalosis (blood pH, 7.49; serum potassium, 2.2 mmol/L; sodium, 130 mmol/L; and chloride, 85 mmol/L) with elevated plasma renin activity (> 230 pg/mL; reference range, 2.4 pg/mL to 21.9 pg/mL), aldosterone secretion (> 1120 pg/mL; reference range, 7.5 pg/mL to 150 pg/mL), and normal blood pressure (95/70 mm Hg). However, the patient's tubulopathy characterized by renal glucosuria, proteinuria (25 mg/m<sup>2</sup>/h), and the presence of kidney failure (serum creatinine, 1.7 mg/dL; creatinine clearance, 30 mL/min/1.73 m<sup>2</sup>) were not consistent with a diagnosis of Bartter syndrome.

On admission to our center, she had malnutrition (weight, 13 kg; height, 100 cm; both < 3rd percentile),

photophobia, hepatomegalia, and splenomegalia on physical examination. Complete blood count revealed a hemoglobin level of 10 g/dL, mean corpuscular volume of 87 fl, leukocyte count of  $6.7 \times 10^9/L$  with a normal differential, and platelet count of  $220 \times 10^9/L$ . Urinalysis revealed a specific gravity of 1004 and pH of 6.5; glucose and protein of 2+; and normal microscopic examination results. Urine amino acids were normal. Blood chemistry analysis showed a sodium level of 130 mmol/L, potassium level of 2.5 mmol/L, chloride level of 86 mmol/L, blood urea nitrogen level of 48 mg/dL, creatinine level of 2.2 mg/dL, creatinine clearance level of 22 mL/min/1.73 m<sup>2</sup>, calcium level of 8.1 mg/dL, phosphorus level of 3.5 mg/dL, alkaline phosphatase level of 885 U/L, and parathyroid hormone level of 455 pg/mL. Liver function tests were normal. Arterial blood gas analysis showed metabolic alkalosis (pH, 7.49; HCO<sub>3</sub>, 26 mmol/L). Thyroid function tests revealed hypothyroidism (free T4, 0.24 ng/mL; thyroid-stimulating hormone, 100 mIU/mL). Renal ultrasonographic examination revealed bilateral grade 1 hydronephrosis and parenchymal hyperechogenicity. Voiding cystoureterography revealed no vesicoureteral reflux.

Having considered a possible diagnosis of cystinosis, slit-lamp examination of the cornea was performed and revealed the punctate needle-shaped crystals. The leukocyte cystine content level was 15.1 mg/mL (reference range, 0 mg/mL to 0.03 mg/mL). Analysis of all the *CTNS* exons in our patient revealed homozygous c.853-1G>A novel splice mutation that confirmed the diagnosis of cystinosis.

The management was started with correction of fluids and electrolytes replacement mainly with potassium chloride, treatment of hypothyroidism with L-thyroxine. The specific treatment with cysteamine bitartrate (65 mg/kg/d in 4 doses), and cysteamine eye drops were initiated. She was also administered phosphate, vitamin D supplements, and levothyroxine. As of the preparation of this article, she was 9 years old. Unfortunately, she had progressed to end-stage kidney disease and was on peritoneal dialysis therapy.

## DISCUSSION

In our report, we describe a rare case of cystinosis where the first presentation begins with the features of Bartter syndrome. Although it is well known that cystinosis may begin with the features of Bartter

syndrome or be associated with it later, only 10 cases have been reported in the literature.<sup>3-12</sup> The cause of this unusual presentation of cystinosis is still unclear. Some authors have speculated that sodium-dependent transtubular transport defect causes increasing distal tubular delivery of sodium, which results in enhanced exchange of sodium for potassium and hydrogen ions.<sup>8</sup> In addition, hyperreninemia and hyperaldosteronemia may contribute to metabolic alkalosis.

Cystinosis with hypochloremic metabolic alkalosis was reported for the first time in a 5-year-old boy by Berio in 1978.<sup>3</sup> Since then, up to 10 cases with nephropathic cystinosis have been reported that initially presented Bartter syndrome findings. Only 1 case report mentions performing genetic mutation analysis. Pennesi and coworkers<sup>8</sup> described 2 siblings with nephropathic cystinosis presenting with features of Bartter syndrome and determined their genetic profile. Both affected siblings were compound heterozygotes showing a 57257-bp deletion and a new nonsense mutation (1044G>A) that produced a stop codon in the transmembrane region of the cystinosin protein. The mother was heterozygous for the 57257-bp deletion, while the father was heterozygous for the new missense mutation (1044G>A). They concluded that further genetic study of other similar cases and correlation between genotype and phenotype might yield more useful evidence.

After identification of the cystinosis gene (*CTNS*), more than 100 *CTNS* mutations have been defined. The most frequent *CTNS* mutation which constitutes 75% of the mutated alleles in patients of Northern European alleles, is a large 57-kb deletion involving the first 9 exons and part of exon 10.<sup>1</sup> However, the spectrum of the mutations varies according to geography. The occurrence of the deletion was limited in the Eastern Mediterranean and Middle East. Topaloglu and colleagues<sup>13</sup> investigated the genetic characteristics of 12 Turkish patients with cystinosis and observed that none carried the 57-kb deletion. Recently, a new study from Turkish Cystinosis Study Group reported that none of the Turkish patients in their nationwide study had the 57-kb deletion, but 7 novel mutations were identified. The most common mutations identified were c.681G.A (p.Glu227Glu; 31%), c.1015G.A (p.Gly339Arg; 22%), and c.18\_21 del (p.Thr7Phefs\*7; 14%).<sup>14</sup> Another study from Iran showed that none

of their patients had the 57-kb deletion and that the most common mutation was c.681G.A (p.E227E; 40%).<sup>15</sup> A study conducted in Egypt performed genetic testing in patients with cystinosis, reporting that 7.7% of the patients had the c.681G.A (p.E227E) mutation.<sup>16</sup> The mutation of c.681G.A (p.E227E) involves the last base pair in exon 9 and the high frequency of this mutation in this region of the world is indicative of a possible founder mutation.

Genetic analysis of our case identified a homozygous c.853-1G>A splice mutation. To the best of our knowledge, this mutation has not been previously described in patients with cystinosis. There was no similar disease among our patient's immediate or extended family members; therefore, genetic analysis was not performed any of her relatives.

Due to the rarity of nephropathic cystinosis, the diagnosis is often delayed; some patients are diagnosed only when they present with end-stage kidney disease.<sup>1,2</sup> Progression of the disease is characterized by severe systemic involvement, but early diagnosis and therapy with cysteamine is effective in slowing down or preventing complications.<sup>17</sup> Our patient's initial diagnosis of Bartter syndrome led to a long delay in the diagnosis and treatment of cystinosis and its eventual progression to end-stage kidney disease.

As a result, hypokalemic metabolic alkalosis, especially in the early infantile period, does not exclude the diagnosis of cystinosis, and these patients should be reevaluated for the diagnosis with repeated investigations when necessary. However, further genetic and clinic studies are necessary to better understand the reasons for transient Bartter syndrome findings in patients with nephropathic cystinosis and the relationship between genotype and phenotypic features.

### CONFLICT OF INTEREST

None declared.

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