



Atypical manifestations of infantile-onset nephropathic cystinosis: a diagnostic challenge

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Abstract

A 7-month-old male infant was referred to us for evaluation of hypercalcemia and failure to thrive. He was the second-born child to third-degree consanguineous parents with a birth weight of 3.5 kg. The index child was severely underweight. Initial laboratory investigations showed hypercalcemia (13.6 mg/dL), hypophosphatemia, hyponatremia, hypokalemia and hypochloremia. The initial serum bicarbonate level was 20.9 mEq/L. The urine calcium: creatinine ratio (0.05) was normal. He was noted to have polyuria (6 mL/kg/hr) and required intravenous fluids to maintain intravascular volume and manage hypercalcemia, along with potassium chloride supplements. The serum calcium decreased to 9.7 mg/dL after hydration for 48 h. At this juncture, the child was noted to exhibit metabolic acidosis (serum bicarbonate 16 mEq/L) for the first time. Thereafter, fractional excretion of bicarbonate was estimated to be 16.5% while the tubular threshold maximum for phosphorus per glomerular filtration rate was 1.2 mg/dL; indicating bicarbonaturia and phosphaturia, respectively. Glycosuria with aminoaciduria were also noted. Clinical exome sequencing revealed a NM_004937.3:c.809_811del in exon 10 of the *CTNS* gene that resulted in in-frame deletion of amino acids [NP_004928.2:p.Ser270del] at the protein level. The child is now growing well on oral potassium citrate, neutral phosphate and sodium bicarbonate supplements. This case was notable for absence of metabolic acidosis at admission. Instead, severe hypercalcemia was a striking presenting manifestation, that has not been reported previously in literature. Cystinosis has been earlier described in association with metabolic acidosis, hypocalcemia and hypomagnesemia. However, typical features like metabolic acidosis were masked in early stages of the disease in our case posing a diagnostic challenge. This atypical initial presentation adds to the constellation of clinical features in this condition.

Keywords Hypercalcemia · Cystinosis · *CTNS* gene · Metabolic acidosis · Hypophosphatemia · Polyuria

Introduction

Cystinosis is an autosomal-recessive lysosomal storage disorder with an estimated incidence of approximately 0.5–1.0 per 100,000 live births [1]. Variants in the *CTNS* gene encoding the transporter protein cystinosin have been implicated as the origin of the disease. Cystinosin is extensively expressed on lysosomal membranes, and its dysfunction results in intra-lysosomal accumulation and crystallization of cystine in body cells and multiple organs. The most

frequent (~95%) and the earliest clinical phenotype involves the kidneys; presenting as proximal tubular dysfunction during the first year of life, and subsequently as an accelerated loss of glomerular function leading to end stage renal disease in first decade of life, if untreated. We herein report a case of infantile-onset nephropathic cystinosis with an initial presentation as hypercalcemia, a hitherto unreported manifestation in cystinosis.

Case report

A 7-month-old male infant of south Indian Tamil ethnicity presented with poor weight gain for three months. There was no history of respiratory distress, feeding diaphoresis, preceding diarrheal illness, vomiting, constipation, jaundice

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or abdominal distention, seizures, visual or hearing difficulties. At presentation, the child was hemodynamically stable, but lethargic. There was no pallor, icterus, hepatosplenomegaly, cataract, microcephaly or evidence of rickets. He was severely underweight (weight 4.5 kg [− 4.16 Z]) and severely stunted (length 62 cm [− 3.16 Z]) with a normal head circumference (42 cm [− 2.67 Z]). The vital signs (pulse rate 120/min, respiratory rate 36/min, normal saturation (98%) on room air, and blood pressure 80/60 mm Hg and capillary refill time < 3 s) were normal at admission. There were no features of dehydration. Focused neurological examination revealed decreased bulk and tone across all joints in the arms and legs. Head lag was appreciated on pulling the child to sitting position. Power was noted to be more than 3/5 in all four limbs. The cardiovascular, respiratory and abdominal system were unremarkable on clinical examination.

The child was the second-born of 3rd degree consanguineous healthy parents. The perinatal and neonatal periods had been uneventful. There was no history of polyhydramnios or decreased fetal movements in utero. At birth, the child had normal weight (3.5 kg) and length (51 cm). However, at the time of presentation at 7 months of age, the growth parameters had declined considerably to less than 3rd centile as mentioned earlier. There was mild delay in gross motor skills; the child was unable to sit with support at admission. Nevertheless, other developmental domains had been normal. There was no past history of hospitalizations. However, there was a family history of sibling death at 9 months of age. That sibling had a similar clinical presentation of failure to thrive, polyuria, hypokalemia, and metabolic acidosis. He, however, succumbed to illness before complete evaluation.

We initiated investigations for failure to thrive in the current index case. The complete hemogram showed that hemoglobin was 10.6 g/dL, total leucocyte count was $12.4 \times 10^9/L$ (77% polymorphs, 10% lymphocytes, 11% monocytes), with a platelet count of $3.5 \times 10^9/L$. Peripheral smear showed no evidence of hemolysis or schistocytes. Preliminary laboratory parameters revealed hypercalcemia (13.6 mg/dL), hypophosphatemia (1.4 mg/dL), hyponatremia (125 mEq/L), hypokalemia (2.32 mEq/L) and hypochloremia (95 mEq/L). The blood glucose (92 mg/dL), urea (15 mg/dL), serum creatinine (0.33 mg/dL), serum magnesium (2 mg/dL) and serum albumin (3.7 g/dL) were normal. The initial serum bicarbonate level was 20.9 mEq/L. The urine spot urine calcium: creatinine ratio was 0.05. Electrocardiogram (ECG) done for electrolyte disturbances was normal. The child was further evaluated for causes of hypercalcemia. The 25-OH vitamin-D levels were normal (22.18 ng/mL) and serum parathormone (PTH) levels were low (2.6 pg/mL). He was noted to have polyuria (6 ml/kg/hr), and required intravenous fluids to maintain intravascular volume and manage hypercalcemia, along with potassium chloride supplements. The

serum calcium began to improve after hydration for 48 h and reached 9.7 mg/dL. Nutritional status was also assessed and the child was started on age-specific recommended dietary allowance (RDA). Serial investigations showed an improvement in serum potassium, sodium and calcium.

However, at this juncture, the child was noted to exhibit metabolic acidosis (serum bicarbonate 16 mEq/L) and polyuria was persistent. It was a normal anion gap metabolic acidosis in the absence of gastrointestinal losses. The estimated glomerular filtration rate (eGFR) continued to be normal for age. Thereafter, fractional excretion of bicarbonate was estimated and was found to be 16.5% while the tubular threshold maximum for phosphorus per glomerular filtration rate (T_{mp}/GFR) was found to be 1.2 mg/dL; indicating bicarbonaturia and phosphaturia, respectively. He was also noted to have glycosuria with aminoaciduria, confirming Fanconi syndrome. Renal ultrasonogram showed no evidence of nephrocalcinosis. Clinical exome sequencing revealed a nucleotide deletion [NM_004937.3:c.809_811del] in exon 10 of the *CTNS* gene that resulted in in-frame deletion of amino acids [NP_004928.2:p.Ser270del] at the protein level [2]. The slit lamp examination of cornea to look for the cystine crystals was, however, negative. The serum T₃, T₄, thyroid stimulating hormone (TSH) and blood glucose were normal.

The parents were counseled regarding the clinical course of cystinosis and the need for lifelong electrolyte supplementation (oral potassium citrate, neutral phosphate and sodium bicarbonate supplements). Counseling regarding cysteamine therapy was also provided; however, the drug is unavailable in India.

Discussion

Our patient was referred for the evaluation of hypercalcemia and failure to thrive. The absence of metabolic acidosis at presentation posed a diagnostic challenge. The clinical constellation of hypercalcemia and suppressed PTH, with evidence of impaired tubular concentrating ability led us to suspect idiopathic hypercalcemia of infancy type 2 as initial diagnosis. However, renal tubular acidosis was considered as a possible etiology in this case after the detection of metabolic acidosis at a later juncture during hospital stay. The absence of hepatosplenomegaly, hypoglycemia, cholestasis, distinctive body odor, developmental disability, and cataract ruled out metabolic causes of Fanconi syndrome like tyrosinemia, glycogen storage disease and galactosemia. Dent's disease and Lowe syndrome were considered less likely in the absence of nephrocalcinosis, hypercalciuria, developmental disability and ophthalmological complications. The presence of a suspected renal tubular acidosis in sibling, consanguinity and presentation in early infancy favored the

diagnosis of cystinosis in the present child, which was also confirmed by genetics. The absence of metabolic acidosis at presentation in our case was attributed to possibly, secondary hyperaldosteronism consequent upon polyuria. Severe hypercalcemia is a striking initial presentation of cystinosis in our patient. There could be several plausible explanations. The possibility includes increased calcium mobilization from the bone, such as immobility due to failure to thrive. We also postulate that hypercalcemia might have occurred due to low levels of phosphate which can induce 1-alpha hydroxylase activity in the kidney leading to production of active vitamin-D hormone, which is responsible for increasing serum calcium levels [3]. However, we could not perform serum calcitriol levels which could have confirmed this hypothesis, and acknowledge this aspect as a limitation of our report.

Cystinosis is the most common inherited cause of childhood Fanconi syndrome and is caused by pathogenic bi-allelic mutations in the CTNS gene on 17p13.2, encoding the carrier protein cystinosin. Consequently, impaired cystine efflux presents as a systemic disease characterized by accumulation of cystine crystals in multiple organs [4, 5]. Cystinosis is a monogenic disease with over 140 reported pathogenic mutations, presents chiefly as three distinct clinical phenotypes based on their age of presentation and severity of renal manifestations; the infantile-onset nephropathic cystinosis (NC; OMIM #219800), the juvenile nephropathic cystinosis (OMIM # 219900) and the ocular non-nephropathic cystinosis (OMIM# 219750) [4, 6, 7]. Our patient was proven to have infantile-onset nephropathic cystinosis by clinical exome sequencing.

The clinical phenotype of cystinosis is usually associated with the severity of mutations. While bi-allelic truncating or severe mutations present as infantile severe nephropathic form, juvenile form and ocular variant are associated with a mild mutation [8–14]. The infantile-onset nephropathic form is the most common (95%) and the most severe phenotype of cystinosis. The initial presentation is renal Fanconi syndrome in 85% cases, by the age of 6–12 months [5, 10, 15]. The cystine crystals induce widespread cell atrophy and loss of expression of luminal proximal tubular receptors like SGLT-2, NaPi-IIa transporters and megalin/cubilin causing failure of renal tubular resorptive function, and hence glucosuria, phosphaturia and proteinuria, respectively. The clinical characteristics of cystinosis in infants include failure to thrive, polyuria, or polydipsia, and refractory rickets [5, 16]. Hypocalcemic tetany, and hypokalemic paralysis are well described due to urinary losses of calcium and potassium (5,10). Persistent hypercalciuria and phosphaturia along with the calcium, phosphate and vitamin-D supplementation can cause nephrocalcinosis and nephrolithiasis in a subgroup of patients. Refractory rickets is also a well-known feature of cystinosis, and is due to renal phosphate wasting,

heightened urinary losses of vitamin-D binding protein (DBP), altered alpha-1-hydroxylase activity and abnormal cellular resistance to 1,25(OH)₂ [16]. Hypomagnesemia, and metabolic alkalosis with a Bartter-like presentation has also been reported [17]. Hypercalcemia, that was encountered in our patient, however, has not been reported in literature as an initial presenting feature of cystinosis. Also, there was no hypercalciuria or nephrocalcinosis in our patient. Hypercalcemia resolved with maintenance of good hydration and supplementation of neutral phosphate.

While the clinical presentation of cystinosis is known to be dominated by failure to thrive, electrolyte disturbances, polyuria and progression to end stage renal disease by the end of the first decade [18–20], the extrarenal manifestations of cystinosis too are diverse. Corneal cystine crystals accumulation is the earliest extrarenal manifestation and is observed mostly by the age of 12–18 months on slit lamp examination [21]. Primary hypothyroidism manifests in majority (50–70%) by second decade of life, due to progressive cystine accumulation causing cell atrophy [22]. Nearly half of infantile cystinosis children by the age of 18 years have gradual and progressive pancreatic insufficiency, glucose intolerance and diabetes mellitus. Hepatomegaly is reported in 33% of patients by 15 years [23]. Given the young age, these complications (including cystine crystals in the cornea) were not discernible in our case. Other complications of cystinosis including distal vacuolar myopathy, swallowing dysfunction, primary hypogonadism, retinal blindness, central nervous system dysfunction, pulmonary involvement and gastrointestinal (GI) symptoms (e.g., vomiting, diarrhea, reflux, swallowing dysfunction, diminished appetite, and feeding difficulties) may become apparent with increasing age [24].

The management of infantile nephropathic cystinosis is challenging. The treatment of cystinosis includes supportive therapy for renal Fanconi syndrome, extrarenal complications, and adequate nutrition. The mainstay of therapy currently is a specific cystine-depleting therapy with cysteamine. Cysteamine catalyses thiol-disulfide exchange reaction generating cysteine and cysteamine-cysteine molecules from cystine. Subsequently, these molecules exit the lysosomes bypassing the defective cystinosin transporter, instead using other cationic transporter PQLC2, hence depleting cystine effectively [5, 25]. Despite irrefutable benefits, the limited accessibility of cysteamine in India, prevented the initiation of cysteamine therapy in our case.

Cystinosis being the most common cause of inherited Fanconi syndrome, should be suspected in children with failure to thrive and above listed clinical presentation. Our case exemplifies the fact that cystinosis can present with a multitude of atypical manifestations (absence of metabolic acidosis and presence of hypercalcemia) posing diagnostic challenges. Our case adds hypercalcemia to the constellation

of clinical features of cystinosis. Though hypocalcemia and hypomagnesemia have been often described in this condition, hypercalcemia is a notably different manifestation. We postulate that hypercalcemia could have occurred due to associated polyuria leading to intravascular volume depletion, immobility due to failure to thrive or hypophosphatemia leading to secondary hypercalcemia, in our case.

Author contributions BD, PK, GB, and TNR managed the patient reviewed the literature and drafted the manuscript. SK managed the patient, reviewed the literature and critically revised the manuscript. All authors contributed to review of literature, drafting of the manuscript and approved the final version of the manuscript. SK shall act as guarantor of the paper.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent for publication of the child's clinical details was obtained from the concerned parents.

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