

Infantile Nephropathic Cystinosis Presenting as Bartter-like Syndrome in Infancy: A Case Report with CTNS Gene Variant

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ABSTRACT

Nephropathic cystinosis is a rare autosomal recessive lysosomal storage disorder caused by mutations in the CTNS gene, leading to cystine accumulation and multiorgan involvement. It typically presents with features of proximal tubular dysfunction; however, atypical presentations may pose diagnostic challenges. In the present case, a male infant, aged 11 months, who was born out of a non-consanguineous marriage was brought to the hospital with a history of failure to thrive, polyuria, and polydipsia. Both his height and weight were below the third percentile. Bartter syndrome like tubulopathy was suggested by hypokalaemia, and elevated renin levels. Following initiation of Indomethacin therapy for suspected Bartter's syndrome, there was partial clinical improvement in symptoms. The results of the ocular examination were normal. Whole exome sequencing identified a mutation in the CTNS that causes infantile nephropathic cystinosis. This case highlights that infantile nephropathic cystinosis should be considered in infants presenting with hypokalaemia, persistent polyuria, polydipsia, failure to thrive, and elevated plasma renin, even in the absence of classical Fanconi syndrome or corneal cystine crystals.

Keywords: Cystine accumulation, Hypokalaemia, Kidney tubules, Lysosomal storage diseases, Whole exome sequencing

CASE REPORT

An 11-month-old male infant was brought to the Department of Paediatrics by his parents with complaints of passing excessive amounts of urine, drinking water frequently, and poor weight gain. According to the parents, these symptoms had progressively worsened over the preceding four months. He was born at term by normal vaginal delivery with a birth weight of 3.5 kg following an uncomplicated pregnancy. His developmental milestones were appropriate for age, and there was no history of parental consanguinity or similar illness in the family.

On presentation, he weighed 6.6 kg, measured 69 cm in height, and had a head circumference was 44 cm at 11 months. His developmental milestones were appropriate for the age. The blood pressure was within the normal range for age. General physical examination revealed a fair complexion with sparse, brittle hair. Bilateral wrist widening suggestive of early rickets was noted. There was no oedema, cyanosis, clubbing, lymphadenopathy, or dysmorphic facial features. Systemic examination was otherwise unremarkable. Severe polyuria was noted, with urine output exceeding 5 mL/kg/hour. Venous blood gas analysis revealed a pH of 7.47, PCO₂ of 32 mmHg, and HCO₃⁻ of 23 mEq/L. His serum potassium level was 2.7 mEq/L, his sodium level was 132.9 mEq/L, and his chloride level was 110 mEq/L, indicating hypokalaemia. He had a normal serum creatinine level (0.3 mg/dL). His serum phosphorus and calcium levels were 3.7 and 10.1 mg/dL, respectively, and his alkaline phosphatase level was somewhat elevated (547 IU/L) and his serum renin levels were elevated (221 ng/L). His vitamin D levels were 16.2 ng/mL. Urine osmolality was 69 mosm/kg. Slit-lamp examination did not reveal corneal cystine crystals. White blood cell cystine levels and urine amino acid analysis could not be performed due to resource limitations. Urine analysis showed normal glucose and protein levels. Urine spot electrolytes, including calcium, potassium, and sodium, were within normal limits.

The combination of clinical symptoms such as failure to thrive, polyuria, and polydipsia, along with biochemical abnormalities such as hypokalaemia with no metabolic acidosis, then the differential diagnoses considered included Bartter syndrome, Gitelman syndrome, Nephrogenic diabetes insipidus, and Fanconi syndrome. Bartter syndrome was initially suspected due to hypokalaemia, polyuria, and elevated renin; however, the absence of metabolic alkalosis and subsequent genetic findings argued against it. Gitelman syndrome was unlikely due to early onset and no hypomagnesaemia. Nephrogenic diabetes insipidus was less likely given associated electrolyte abnormalities. Fanconi syndrome was not supported due to lack of documented glycosuria, proteinuria, or aminoaciduria.

Therapy for Bartter syndrome was initiated with indomethacin (3 mg/kg/day in divided doses) and oral potassium supplementation (2-4 meq/kg/day). Whole exome sequencing revealed a homozygous pathogenic missense variant in the CTNS gene (c.473T>C; p.Leu158Pro) in exon 8, consistent with autosomal recessive nephropathic cystinosis. Based on the characteristic clinical presentation together with the identification of a homozygous pathogenic CTNS variant by whole-exome sequencing, the final diagnosis of infantile nephropathic cystinosis was established [Table/ Fig-1]. This variant has been previously reported and is classified as pathogenic in ClinVar. Parental testing was not performed. Following initiation of indomethacin and oral potassium supplementation, the child demonstrated partial clinical improvement, with a reduction in polyuria and improvement in serum potassium levels. After confirmation of the diagnosis, cysteamine therapy was initiated at a tertiary paediatric nephrology centre. At one-month follow-up, polyuria had further decreased, serum electrolytes had normalised, and the child's general condition had improved. At one year of follow-up, he demonstrated satisfactory weight gain and age-appropriate developmental progress.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED						
SNV(s)/INDELS						
Gene* (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification ⁵
CTNS (+) (ENST0000046640.9)	Exon 8	c.473T>C (p.Leu158Pro)	Homozygous	Cystinosis, nephropathic (OMIM#219800)	Autosomal recessive	Pathogenic (P53,P54)

[Table/Fig-1]: Whole-exome sequencing findings showing the homozygous pathogenic CTNS variant (c.473T>C; p.Leu158Pro) identified in the present case.

DISCUSSION

In the present case, patient presented with failure to thrive, persistent polyuria, polydipsia, hypokalaemia, and elevated plasma renin, initially suggesting a Bartter-like salt-losing tubulopathy. However, the absence of classical Fanconi syndrome and corneal cystine crystal deposition prompted further evaluation, and whole-exome sequencing established the diagnosis of infantile nephropathic cystinosis. This unusual presentation highlights the phenotypic variability of early cystinosis and the diagnostic challenges encountered during infancy. Infantile nephropathic cystinosis is a rare lysosomal storage disorder caused by defective transport of the amino acid cystine out of the lysosome [1]. Similar cases have been reported in the literature. For instance, Du J et al., described a child with infantile nephropathic cystinosis who presented with hypothyroidism and significant renal tubular dysfunction, including glycosuria, proteinuria, aminoaciduria, and phosphaturia [2]. In contrast, our patient had a normal thyroid profile and did not demonstrate glucosuria or proteinuria at presentation. Another report by Li XQ et al., documented binocular corneal crystalline deposits along with renal damage associated with tubular dysfunction, which were also absent in our patient [3]. Compared to these previously reported cases, the current study patient manifested only polyuria, polydipsia, failure to thrive, and hypokalaemia without overt Fanconi syndrome or corneal crystal deposition, emphasising the variability in clinical presentation and the importance of considering infantile nephropathic cystinosis even before the appearance of its classical manifestations [1-4]. In numerous cell types, lysosomes crystallise this poorly soluble stored cystine, causing extensive tissue and organ damage. There are three variations: ocular, juvenile late onset, and infantile onset. Children with infantile cystinosis typically exhibit Fanconi syndrome symptoms, metabolic acidosis, hypokalaemia, polyuria, and failure to thrive within their first year of life [4].

This child presented with polyuria, polydipsia, failure to thrive, and hypokalaemia with no evidence of metabolic acidosis. These findings were suggestive of a Bartter-like tubulopathy. However, the absence of metabolic alkalosis and documented urinary salt wasting was atypical for classical Bartter syndrome [5]. Hence, there was a suspicion that this was not so straightforward, and genetic testing was sent, which revealed infantile nephropathic cystinosis with a CTNS gene mutation [6]. As to the reason why this form of presentation occurs, it is not totally understood, however there are theories. One of the theories suggests that before cystine accumulates in sufficient quantities in the lysosomes to cause the typical Fanconi syndrome, the accumulation probably damages the sodium potassium Adenosine Triphosphatase (ATPase) in the tubular cell lining, thereby causing a leak of all these electrolytes, simulating Bartter syndrome [7]. The normal clinical picture eventually appears as the cystine build up worsens [8-10].

Since it has poor prognosis; if left untreated, children will develop End-Stage Renal Disease (ESRD) by adolescence and, even with intensive cysteamine treatment they will eventually reach ESRD by 25 to 30 years of age [11]. It also affects other organs such as the

pancreas, thyroid, etc., causing diabetes mellitus, hypothyroidism, etc. Therefore, even after a renal transplant, cysteamine treatment is usually needed for the rest of one's life; cysteamine drops for the eyes are used to reduce deposits in the cornea.

Infantile nephropathic cystinosis may initially resemble Bartter syndrome because, during the early stage of the disease, intracellular cystine accumulation is insufficient to produce the classical manifestations of Fanconi syndrome [Table/Fig-2] [12,13]. Instead, early lysosomal cystine accumulation is thought to impair Na⁺/K⁺-ATPase activity, disrupting renal tubular electrolyte transport and resulting in renal salt wasting, polyuria, activation of the renin-angiotensin system, and hypokalaemia, thereby producing a Bartter-like phenotype as described in several published case reports [14-16]. As cystine progressively accumulates within the renal tubules, lysosomal injury worsens, eventually leading to the characteristic features of Fanconi syndrome, including metabolic acidosis and generalised proximal tubular dysfunction. Although classical Bartter syndrome is typically associated with metabolic alkalosis, our patient did not demonstrate this feature, emphasising that early nephropathic cystinosis may mimic Bartter syndrome despite the absence of all classical biochemical features. The absence of metabolic alkalosis does not exclude the diagnosis of cystinosis [17-19].

Clinical features	Bartter syndrome	Infantile cystinosis	Present case
Polyuria/polydipsia	Present	Present	Present
Hypokalaemia	Present	Present	Present
Metabolic alkalosis	Present	Usually absent (typically acidosis)	Absent
Metabolic acidosis	Absent	Characteristic (later stages)	Absent
Hypercalciuria	Present	Absent	Absent
Failure to thrive	Variable	Common	Present
Ocular crystal deposits	Absent	Present (after infancy)	Absent (early stage)

[Table/Fig-2]: Comparison of the clinical and biochemical features of Bartter syndrome, classical infantile nephropathic cystinosis, and the present case [12,13].

The absence of metabolic alkalosis does not exclude the diagnosis of infantile cystinosis, as early disease may present with a Bartter-like biochemical profile long before the onset of classic Fanconi syndrome. Infants with unexplained tubulopathies should therefore, undergo genetic evaluation to avoid missed or delayed diagnoses. Early confirmation of cystinosis enables timely initiation of cysteamine therapy, which can significantly slow disease progression and improve long-term outcomes. Overall, atypical or incomplete presentations must always be approached with a comprehensive, high-index-of-suspicion evaluation to ensure accurate diagnosis and appropriate management.

Infantile nephropathic cystinosis carries a guarded long-term prognosis. Without treatment, nephropathic cystinosis commonly progresses to kidney failure during childhood or adolescence. Early and sustained cysteamine therapy delays the progression of kidney disease and reduces extrarenal complications, although long-term renal outcomes vary [18,20]. In addition to renal deterioration, the disease is associated with significant extra-renal complications, including hypothyroidism, diabetes mellitus, pancreatic insufficiency, progressive myopathy, and ocular crystal deposition, all of which contribute to cumulative morbidity over time [4,17,20].

This case is noteworthy because it highlights an uncommon biochemical pattern in which metabolic alkalosis does not exclude the diagnosis of cystinosis, underscoring the need for clinicians to remain vigilant in atypical presentations. It reinforces the central role of genetic testing in evaluating unexplained tubulopathies and

demonstrates how early identification of cystinosis enables timely initiation of cysteamine therapy, thereby improving long-term outcomes and reducing the risk of irreversible organ damage.

CONCLUSION(S)

Infantile nephropathic cystinosis is a severe multisystem disorder that can initially mimic Bartter syndrome. This diagnostic overlap can delay appropriate therapy. Clinicians should maintain a high index of suspicion for cystinosis in infants presenting with failure to thrive, polyuria, and hypokalaemia, even when metabolic alkalosis is absent. Early genetic testing is crucial to avoid misdiagnosis and prevent long-term morbidity.

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