A Patient with Cystinosis Presenting Like Bartter Syndrome 
and Review of Literature

Pelin Ertan*1, MD; Havva Evrengül2, MD; Serkan Ozen3, MD, and Sinan Emre4, MD

1. Department of Pediatric Nephrology, Celal Bayar University, School of Medicine, Manisa, Turkey
2. Department of Pediatric Nephrology, Celal Bayar University, School of Medicine, Manisa, Turkey
3. Department of Pediatrics, Celal Bayar University, School of Medicine, Manisa, Turkey
4. Department of Ophthalmology, Celal Bayar University, School of Medicine, Manisa, Turkey

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Abstract

Background: Nephropathic cystinosis is an autosomal recessively inherited metabolic disorder presenting with metabolic acidosis, Fanconi syndrome and renal failure.

Case Presentation: We present a 6-year-old girl with severe growth failure, hyponatremia and hypokalemia. Her parents were 4th degree relatives. Two relatives were diagnosed as end stage renal failure. She also had persistent hypokalemic hypochloremic metabolic alkalosis. Her renal function was normal at presentation. She was thought to have Bartter syndrome with supporting findings of elevated levels of renin and aldosterone with normal blood pressure, and hyperplasia of juxtaglomerular apparatus. Her metabolic alkalosis did not resolve despite supportive treatment. At 6th month of follow-up proteinuria, glucosuria and deterioration of renal function developed. Diagnosis of cystinosis was made with slit lamp examination and leukocyte cystine levels. At 12th month of follow-up her metabolic alkalosis has converted to metabolic acidosis.

Conclusion: In children presenting with persistent metabolic alkalosis, with family history of renal failure, and parental consanguinity, cystinosis should always be kept in mind as this disease is an important cause of end stage renal failure which may have features mimicking Bartter syndrome.

Key Words: Nephropathic Cystinosis; Bartter Syndrome; Children; Metabolic Alkalosis

Introduction

Cystinosis is a metabolic disorder due to defective lysosomal transport of cystine characterized by accumulation of cystine crystals in various organs. It is an autosomal recessive disorder associated with mutations of CTNS gene, encoding a lysosomal transport protein named cystinosin[1]. Cystinosin is responsible for transport of cystine out of intracellular lysosomes and into the cytoplasm[2]. There are three variants; nephropathic form is the most commonly seen one which has the worst prognosis[2,3].

Clinical phenotype of nephropathic cystinosis is characterized by renal tubular Fanconi syndrome and development of end stage renal disease (ESRD) during first decade[1]. It was hypothesized that as lysosomes were involved in an important
process of programmed cell death, accumulated cystine crystals may cause increased apoptosis. This in turn may be responsible for retinopathy, early renal tubular dysfunction and other aspects of classic nephropathic cystinosis[3]. Ocular findings involving both cornea and retina are important for early diagnosis[1]. Although, classically, metabolic acidosis is a prominent feature of the disease, rarely patients may present with hypokalemic metabolic alkalosis mimicking Bartter syndrome. Only 11 cases of cystinosis presenting with metabolic alkalosis have been reported in the literature[4-10]. We present a case of nephropathic cystinosis clinically resembling Bartter syndrome.

Case Presentation

A 6-year old girl admitted to our hospital with severe growth failure, was referred to our clinic because hyponatremia (129 mmol/lit) and hypokalemia (2.1 mmol/lit). She had history of polyuria, polydipsia and episodes of dehydration requiring hospitalization. She was born full term. She was a low birth weight newborn. Her parents were 4th degree relatives and healthy. Motor and mental development stages were normal for her age. She had 3 siblings with no health problem. Two cousins of grandfather were being treated with diagnosis of ESRD one of whom died due to ESRD. In physical examination, both weight and height were below 3 percentiles for the age. She had normotensive (50p). She had blonde hair and fair skin. She had a triangular face and protuberant forehead. She was mildly dehydrated with dry mucosal surfaces and decreased skin turgor. Laboratory values: Hb 10.3 g/L, Hct 30.4%, WBC 7.700/mm³, PLT 229.000/mm³. Serum urea was high and creatinine was normal (56 mg/dl, 0.8 mg/dl, respectively). She had hyponatremia, hypokalemia, hypochloremia and hypophosphatemia (126mmol/lt, 2.9 mmol/lt, 88 mmol/lt, and 1.8 mg/dl respectively). Serum Mg (2.3 mg/dl), total protein (6.5 mg/dl), albumin levels (3.5 mg/dl), liver function and thyroid function tests were normal. Urine specific gravity was low (1000), urine pH was 5.5, and urinary glucose was negative. Urine microscopic examination was normal. Urine culture was negative. She had proteinuria (12 mg/m²/hour), and hypercalciuria (5.5 mg/kg/day). Fractional excretion of sodium and potassium was high (1.4% and 34%, respectively), tubular phosphate reabsorption was low (67%). In arterial blood gas analysis there was metabolic alkalosis (pH 7.45, cHCO3 28.3 mmol/L). Urinary aminoacid excretion was normal. Her daily urine volume was 2.5-4 lt/day (10 ml/kg/day) and fluid intake 5-6 lt/day. Glomerular filtration rate was 88 ml/min/1.73 m². Plasma renin activity was 80ng/ml/h (0.5-5.9ng/ml/h), serum aldosterone level was 1400pg/ml (20-240pg/ml). Serum parathyroid hormone level was 1135pg/ml (11-67pg/ml). Urine B₂ microglobulin was 13774µg/ gr creatinin (<300µg/ gr creatinin). On renal ultrasonography (USG) examination there was no finding related to nephrocalcinosis and urinary system anatomy was normal. Renal biopsy has been performed during follow-up due to development of nephrotic range proteinuria, which revealed hyperplasia of juxtaglomerular apparatus.

In view of history of small gestational age birth, polyuria, polydipsia, failure to thrive, history of episodic dehydration, hypercalciuria, hypernatriuria, inability to concentrate urine, persistant hypokalemic hypochloremic metabolic alkalosis, normal blood pressure, elevated renin and aldosterone levels, and renal biopsy finding of hyperplasia at juxtaglomerular apparatus and parental consanguinity patient was thought to have Bartter syndrome. She received indomethacine and potassium chloride. During 6 months of follow-up, metabolic alkalosis and hypokalemia did not resolve, proteinuria increased and also her renal function deteriorated. When reevaluated, we detected increased glucose excretion in urine (24-hour glucose excretion was 5.2 gr/day). Radiologic examination of wrist, performed because of high level of serum alkaline phosphatase (774U/L), was compatible with rickets. As proximal tubulopathy findings were more predominant, rickets was detected, renal failure was settled and rare cases of cystinosis presenting with features of Bartter syndrome like metabolic alkalosis was described. In order to check for cystinosis presenting with metabolic alkalosis, slit lamp examination of the cornea
revealed cystine crystals (Fig 1). Leukocyte cystine levels were high (5.27 nmol 1/2 cystine/mg protein) and was compatible with homozygous cystinosis. We started to treat with oral cysteamine, cysteamine eye drops, 1,25 dihydroxycholecalciferol and oral potassium supplementation. At 12th month of follow-up now her alkalosis was converted to acidosis at last visit.

**Fig. 1:** Corneal cystinosis crystals, documented with slit lamp photography

**Discussion**

Nephropathic cystinosis is the most common inherited cause of renal Fanconi syndrome. Cystinosis classically presents with findings of tubular dysfunction like glucosuria, aminoaciduria, phosphaturia, proximal renal tubular acidosis, and accumulation of cystine crystals in eye. Although renal tubular acidosis is an important feature of nephropathic cystinosis, there are rare reported cases of cystinosis presenting like Bartter syndrome, with metabolic alkalosis[10].

Pathophysiologic mechanisms causing cystinosis presenting with features of Bartter syndrome is not clear[10]. Although tubular dysfunction may be related with it, relationship between cystine accumulation and tubular dysfunction is not known. There were studies reporting association of cystine accumulation with alteration in cellular energy metabolism which results in decreased Na/K-ATPase activity and decreased Na absorption[11]. In a study reported by Yildiz et al, authors speculated that decreased Na reabsorption causes increased distal tubular delivery of sodium and exchange of sodium for potassium and hydrogen ions with resultant hypokalemic alkalosis[9]. Juxtaglomerular apparatus hyperplasia and elevated renin and aldosterone levels were reported in cystinosis patients which may also cause metabolic alkalosis[3].

In a study by Penesi et al, they presented two siblings with a clinical and metabolic picture resembling Bartter syndrome in whom they were able to show a new mutation. As there was close relationship between phenotypic and genotypic features of these patients, this new mutation was possibly thought to be related to a new subtype of cystinosis[8]. Unfortunately we were not able to make genetic evaluation in our patient. It is also important to remember that, in addition to the genetic mutations, other factors like environmental factors and modifying genes may also be important in presentation of a certain phenotype.

Findings of tubular dysfunction in our patient were thought to be compatible with Bartter syndrome. As there was no response to treatment, with appearance of massive proteinuria, rickets and deterioration in renal function, diagnosis of cystinosis was made through demonstration of cystine crystals in cornea. There were 11 reported cases of cystinosis with metabolic alkalosis in literature. In the case reported by Berio et al, proximal renal tubular acidosis converted to metabolic alkalosis at 5 years of age. Average age at first admission was between 1 year and 5 years and average time for diagnosis after first admission were between 1 month and 5 years. Our patient was diagnosed as cystinosis at 8th month of follow-up. Majority of these cases were presented with failure to thrive, polyuria and polydipsia which were also the presenting complaints of our patient[4-10].

During childhood, hypophosphatemic rickets can be thought among the hereditary phosphaturic disorders. However, hypophosphatemic rickets manifest early in childhood with the typical clinical features of rickets particularly bone deformities of lower limbs[13]. Our patient had no signs apart from enlargement of the hand wrist. Additionally, PTH levels in
hypophosphatemic rickets are not as high as in our patient[12].

Early diagnosis is important in nephropathic cystinosis because the patients are candidates for ESRD and renal transplantation; cysteamine treatment given to these patients may delay appearance of this ominous outcome[1]. However, because metabolic alkalosis is rarely a feature of cystinosis, delayed diagnosis is frequent in these patients. So in patients with failure to thrive, metabolic alkalosis and progression to renal failure, cystinosis should always be kept in mind. Slit lamp examination is an easy and generally effective way of diagnosing cystinosis and should be done in patients with this clinical picture.

**Conclusion**

Nephropathic cystinosis is an autosomal recessively inherited metabolic disorder with features of metabolic acidosis, tubulopathy and related Fanconi syndrome, multiple system involvement, and eventual development of ESRD. Clinicians should be careful about atypical presentation of this disease as presented here because it may present with metabolic alkalosis resistant to treatment mimicking Bartter syndrome. With early and appropriate treatment, development of renal failure may be delayed. Slit lamp examination and leukocyte cystine levels, where available, should be performed for diagnosis of this important disease.

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**References**