A patient with cystinosis presenting transient features of Bartter syndrome

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A 16-month-old boy was admitted to the clinic because of vomiting and growth failure. His weight and height measurements were under the fifth percentile. He had fair hair and skin, enlarged wrists and rachitic rosaries. The presence of metabolic alkalosis, hypokalemia, hypochloremia, and high renin and aldosterone levels were suggestive of Bartter syndrome. However, in view of the growth failure, fair hair and skin, proteinuria, polyuria and active rickets, cystinosis was considered. Bone marrow smear examination was normal, despite the existence of suspicious crystals in the cornea. Cystine crystals were seen in the conjunctiva biopsy and increased leukocyte cystine level was measured; therefore, definitive cystinosis diagnosis was made. Renal Fanconi syndrome with metabolic acidosis is prominent in cystinosis; however, in rare instances, if sodium-dependent trans-tubular transport defect is present, patients could have Bartter syndrome findings such as hypochloremic metabolic alkalosis. Our case is a good example demonstrating that metabolic alkalosis should not exclude cystinosis and the other signs and symptoms of the patient should be thoroughly evaluated.

Key words: Bartter syndrome, cystinosis, metabolic alkalosis, Fanconi syndrome, glycosuria.

Cystinosis is an autosomal recessively inherited lysosomal storage disease caused by defective transport of the amino acid cystine across the lysosomal membrane. There are two main phenotypes: nephropathic and non-nephropathic. In North America, the estimated incidence of nephropathic cystinosis is 1 case per 100,000 to 200,000 live births. In general, the typical clinical picture is renal Fanconi syndrome in most patients with cystinosis. On the other hand, cystinosis is the most common inherited cause of Fanconi syndrome[1]. Fanconi syndrome is characterized by metabolic acidosis, proteinuria, glucosuria, phosphaturia, bicarbonaturia, aminoaciduria, citraturia and rickets. However, in rare conditions, metabolic alkalosis is found in laboratory studies such that the initial diagnosis of patients may be Bartter syndrome. This report describes an infant who presented with metabolic alkalosis as an uncommon manifestation of cystinosis.

Case Report

A 16-month-old boy was referred to our pediatric clinic for evaluation of failure to thrive and vomiting. The infant was born after a 40-week gestation with birth weight of 3600 g; the pregnancy and delivery were uncomplicated. The parents were unrelated and healthy. His growth was normal for the first six months, after which the infant was unable to gain weight, and had vomiting, polyuria, polydipsia and photophobia. At 16 months of age, his weight was 6.3 kg ($<5^{th}$ percentile) and height 65 cm ($<5^{th}$ percentile). He had blond hair and fair skin. Blood pressure was 80/40 mm Hg, pulse rate 152 beats/min, and temperature 37°C. His wrists were enlarged and he had rachitic rosaries. There was no clinical evidence of dehydration. In the laboratory findings, the venous blood gas analysis showed pH 7.52, pCO_2 25.5 mm Hg and bicarbonate 27.3 mmol/L. Urinalysis

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revealed a specific gravity of 1.007, pH 8, but no blood, leukocyte or glucose. Calcium to creatinine ratio was 0.26 in urine. Protein level measured 1.27 g/m^2/day in urine. Complete blood examination revealed hemoglobin 9 g/dl, hematocrit 24.9%, white blood cells 17,300/mm^3 with a normal differential, and platelets 478,000/mm^3. Blood smear, mean corpuscular volume (MCV), and serum iron and ferritin levels showed iron deficiency anemia. Serum electrolytes were as follows: sodium 125 mEq/L, potassium 2.5 mEq/L, chloride 91 mmol/L, blood urea nitrogen 17 mg/dl, serum creatinine 0.7 mg/dl, glucose 120 mg/dl, calcium 7.5 mg/dl, magnesium 0.87 mg/dl, phosphorus 1.5 mg/dl, alkaline phosphatase 1066 IU/L, total protein 7.8 g/dl, and albumin 4.5 g/dl. Liver function tests were normal. Serum free thyroxine and thyroxine-stimulating hormone levels were 8.1 μg/dl and 1.33 mIU/ml, respectively. Radiologic examination of the wrists showed active rachitic changes. Renal ultrasonographic examination was normal. Further laboratory studies showed no aminoaciduria by paper chromatography and low tubular phosphate re-absorption (63.6%). Blood renin and aldosterone levels were found high (50 mg/ml and 670 ng/dl, respectively). Glomerular filtration rate was 87 ml/min/1.73 m^2. Our first diagnosis was Bartter syndrome because of presence of metabolic alkalosis, hypokalemia, hypochloremia and high renin and aldosterone levels. However, in view of the fair skin and blond hair, rickets, proteinuria, polyuria and low tubular phosphate re-absorption, cystinosis was considered. Slit-lamp examination of the cornea revealed suspicious cystine crystals. Bone marrow smear was normal but cystine crystals were seen in the conjunctiva biopsy, and leukocyte cystine level was measured as 2.19 nmol/mg protein (normal: <0.2 nmol/mg protein); therefore, definitive cystinosis diagnosis was made. Our patient was treated with 1,25-dihydroxycholecalciferol, potassium, Joulie's solution, cysteamine and captopril. Renin and aldosterone levels were normal after one month. When metabolic acidosis occurred one month later, Shohl's solution was added with indomethacin to the treatment.

Discussion

Cystinosis is an autosomal recessive defect which leads to intralysosomal cystine accumulation. In cystinosis, disruption of intracellular organelle function leads to proximal tubular cell dysfunction. Kidney involvement remains the foremost clinical characteristic of the disorder. Proximal renal tubular acidosis in children with cystinosis is usually seen as a part of the renal Fanconi syndrome, consisting of aminoaciduria, proteinuria, glucosuria, bicarbonaturia, phosphaturia and rickets. However, some patients could have Bartter syndrome findings such as hypochloremic metabolic alkalosis, and high renin and aldosterone levels with normal blood pressure[2-4]. Laboratory evaluation of our patient, which revealed metabolic alkalosis, hypokalemia, hypochloremia, and normal blood pressure despite high renin and aldosterone levels, was suggestive of Bartter syndrome.

The cause of transient features of Bartter syndrome in cystinosis is unclear. Tubular cell dysfunctions may be related with this condition, but the pathogenesis of intralysosomal cystine accumulation leading to the dysfunction of the proximal tubule has not been resolved.

There is a relationship between intracellular cystine accumulation and energy metabolism[5]. Cystine-loaded tubules had a 40% reduction in intracellular phosphate[6,7]. Al-Bander et al.[8] found that an increase in glucose uptake and glycolysis generated phosphorylated glycolytic intermediates in a maleic acid model. There is a glucose-dependent decrease in intracellular free phosphate due to the accumulation of phosphorylated glycolytic intermediates with cystine loading[7,9]. As a result of cystine accumulation, decreased free phosphate compromises oxidative phosphorylation and ATP production. Coor et al.[6] showed that tubules incubated with cystine dimethyl ester (CDME) had a dramatic reduction in intracellular ATP. Our patient did not have glycosuria so the free intracellular phosphate and ATP depletion may be more prominent than in glycosuric patients. Reduction of intracellular ATP content was supposed to lead consecutively to an inhibition of Na^+/K^+ -ATPase activity and dissipation of the Na^+ gradient from the extra- to the intracellular space, which drives the Na^+ coupled solute transport[10].

We speculated that sodium-dependent trans-tubular transport defect causes increasing distal tubular delivery of sodium, which results in enhanced exchange of sodium for potassium and hydrogen ion, perpetuating a contraction

alkalosis. As a result, patients may have hyponatremic status. In our patient, sodium level was 125 mEq/L, and suggested this phenomenon. Some investigations showed hyperplasia of juxtaglomerular apparatus and elevated levels of renin and aldosterone in patients with cystinosis[1]. Increase exchange of sodium for hydrogen and potassium ion may be due to aldosterone. At the same time, hyperreninemia and hyperaldosteronism may have contributed to metabolic alkalosis.

Metabolic alkalosis can occur before or after diagnosis of cystinosis. In 1978, Berio[11] reported the case of an Italian boy with cystinosis and Fanconi syndrome where proximal renal tubular acidosis evolved to hypochloremic metabolic alkalosis at five years of age. Subsequently, in 1980, O'Regan et al.[3] briefly reported the case of a normotensive seven-year-old girl who presented with the typical histologic and biochemical features of Bartter syndrome at two years of age and was found to have cystinosis two years later. These two cases were treated with prostaglandin inhibitors and they were reported as cystinosis and Bartter syndrome, the features of which were reversible. Our patient was treated with captopril, fluid and electrolytes. After one month, metabolic alkalosis gradually changed to metabolic acidosis, and Shohl's solution was added to the treatment.

In conclusion, our case is a good example of metabolic alkalosis which could not exclude cystinosis. The other signs and symptoms should be thoroughly evaluated for other causes of renal Fanconi's syndrome, such as cystinosis.

REFERENCES

1. Gahl WA, Thene JG, Schneider JA. Cystinosis: a disorder of lysosomal membrane transport. In: Scriver CR, Beaudet AL, Sly WS, Walle D (eds). The Metabolic & Molecular Bases of Inherited Disease (8th ed) Vol. 3. New York: McGraw-Hill; 2001: 5085-5108.
2. Whyte MP, Shaheb S, Schnaper HW. Cystinosis presenting with features suggesting Bartter syndrome. Case report and literature review. Clin Pediatr (Phila) 1985; 24: 447-451.
3. O'Regan S, Mongeau JG, Robitaille P. A patient with cystinosis presenting with the features of Bartter syndrome. Acta Pediatr Belg 1980; 33: 51-52.
4. Bhandari S. The pathophysiological and molecular basis of Bartter's and Gitelman's syndromes. Postgrad Med J 1999; 75: 391-396.
5. Baum M. The Fanconi syndrome of cystinosis: insights into the pathophysiology. Pediatr Nephrol 1998; 12: 492-497.
6. Coor C, Salmon RF, Quigley R, Marver D, Baum M. Role of adenosine triphosphate (ATP) and NaK ATPase in the inhibition of proximal tubule transport with intracellular cystine loading. J Clin Invest 1991; 87: 955-961.
7. Ben-Nun A, Bashan N, Potashnik R, Moran A. Cystine accumulation impairs glucose transport in LLC-PK1 cells. Cell Physiol Biochem 1991; 1: 294–304.
8. Al-Bander H, Etheredge SB, Paukert T, Humpreys MH, Moris RC Jr. Phosphate loading attenuates renal tubular dysfunction induced by maleic acid in the dog. Am J Physiol 1985; 248: F513-F521.
9. Foreman JW, Benson LL, Wellons M, et al. Metabolic studies of rat renal tubule cells loaded with cystine: the cystine dimethylester model of cystinosis. J Am Soc Nephrol 1995; 6: 269–272.
10. Sakarcan A, Aricheta R, Baum M. Intracellular cystine loading causes proximal tubule respiratory dysfunction: effect of glycine. Pediatr Res 1992; 32: 710-713.
11. Berio A. Considerazioni sulla nefropatia della cistinosi con S. di Bartter secondaria. Minnevra Pediatr 1978; 30: 1825-1831.