TWO CASES WITH NEONATAL BARTTER SYNDROME

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ABSTRACT *: Neonatal Bartter syndrome is characterized by premature delivery, polyhydramnios, nephrocalcinosis and hypokalemic, hypochloremic metabolic alkalosis associated with normal blood pressure despite hyperaldosteronism. In some patients indomethacin therapy failed to resolve or prevent nephrocalcinosis. We report our experience in two patients with neonatal Bartter syndrome who responded well to indomethacin and appropriate electrolyte therapy.*

Key Words: *Neonatal Bartter Syndrome, Nephrocalcinosis, Indomethacin.*

INTRODUCTION

In 1962, Bartter et al. reported two patients with a new syndrome characterized by hypokalemia, metabolic alkalosis, hyperaldosteronism with normal blood pressure, decreased pressor responsiveness to infused angiotensin II, and hyperplasia of the juxtaglomerular complex. Since then, many reports have appeared in the literature under the heading of "Bartter syndrome" (1). Data from numerous clinical studies indicate that Bartter syndrome involves an overlapping set of closely related renal tubular disorders that share common features (2). At present, these patients can be subdivided into at least three clinical phenotypes (a) classic Bartter syndrome (b) neonatal Bartter syndrome associated with severe systemic manifestations and (c) the hypocalciuric - hypomagnesemic variant described by Gitelman et al. (1, 3). In contrast to classic Bartter syndrome and Gitelman syndrome, the neonatal variant of Bartter syndrome typically presents as a life-threatening disorder that is characterized by polyhydramnios, premature delivery, growth retardation, hypercalciuria and nephrocalcinosis. The clinical hallmarks of this rare variant of Bartter syndrome are hypokalemia, metabolic alkalosis, hyper-reninemic hyperaldosteronism with normal blood pressure, hyperprostaglandinuria, vomiting and diarrhea (1, 2, 4). Seyberth et al. (5, 6) have suggested that these patients represent a different pathological entity related to a systemic overproduction of prostaglandins and have proposed the term hyperprostaglandin E syndrome.

We report two patients with the neonatal variant of Bartter syndrome who responded well to indomethacin and appropriate electrolyte treatment.

CASE 1

The male infant was born at 32 weeks gestation to a 40-year-old mother at a rural hospital. Pregnancy was complicated by polyhydramnios. Birth weight was 1500 gr (10th percentile). He was hospitalized in the intensive care unit for one month. After discharge he was hospitalized in another hospital for recurrent vomiting and diarrhea. Two of his brothers had died at 3-year-old and the other at 2.5-years-old. Unfortunately, we did not know the cause of death of the older brother, but from the family history, the youngest died to a renal disease at the age of 10 months. The patient was referred to our hospital because of severe growth failure, recurrent vomiting and diarrhea. Body weight was 2700 gr (below 3rd percentile) and length was 53 cm (below 3rd percentile). He second degree dehydration and had a normal blood pressure. Laboratory investigations revealed metabolic alkalosis (pH of 7.66, bicarbonate 62.1 mmol/L, base excess of +34.5mmol/L) and hyponatremia (126 mEq/L), hypokalemia (2.1 mEq/L) and hypochloremia (69 mEq/L). The plasma calcium concentration was normal (10 mg/dl). His urine pH was 8 and specific gravity was 1010. No glucose, protein, blood or ketones were present. Urinary Cl was 70 mEq/L, and K was 32 mEq/L. Urinary calcium excretion was 4.9 mg/kg/day. Plasma renin and aldosterone levels were elevated at 3.2 pg/ml and 210 pg/ml respectively (normal, 0.15-2.33 pg/ml, and 29.4-161.5 pg/ml respectively). Urine amino acids, stool electrolytes and sweat test were normal. Renal ultrasonography showed hyperechoic renal pyramids. During his stay in the hospital he had intermittent parenteral potassium supplementation due to recurrent vomiting and diarrhea. Because of his recurrent vomiting, continuous enteral feeding was performed. Indomethacin therapy was started at a dose of 0.5 mg/kg/day. During the treatment his serum potassium and chloride levels rose to a stable value of approximately 3.5 mEq/L and 112 mEq/L, respectively. The patient is currently 15 months old and his growth parameters have improved. He continues on 2 mg/kg indomethacin treatment with 4 mEq/kg potassium chloride supplementation.

CASE 2

A male infant was born at 34 weeks gestation to a 20 year old mother by urgent cesarean section because of early rupture of membranes. Pregnancy was complicated by polyhydramnios starting at 20 weeks of gestation. His birth weight was 1700 gr (25th percentile), his height 43 cm (25th percentile). He was hospitalized because of sepsis and necrotizing enterocolitis in neonatal intensive care unit for two months. He was referred to our hospital at the age of seven months with severe growth failure, recurrent vomiting and diarrhea. His weight was 2450 gr (below 3rd percentile) and his height was 53 cm (below 3rd percentile). He appeared morphologically normal but showed severe developmental delay. He was dehydrated and normotensive. Laboratory investigations revealed metabolic alkalosis (pH of 7.64, bicarbonate 46.9 mmol/L, base excess +24 mmol/L) and hyponatremia (122 mEq/L), hypokalemia (1.8 mEq/L) and hypochloremia (68 mEq/L). His blood magnesium was 2.40 mg/dl (1.20-2.5 mg/dl). His urine pH was 8.5 and specific gravity 1010. No glucose, protein, blood or ketones were present. Urinary Na was 51 mEq/L, Cl was 76 mEq/L, and K was 45.5 mEq/L. Urinary calcium excretion was 5.1 mg/kg/day. His blood penin was 4.8 (0.15-2.31ng/ml), aldosterone was 370 (29.4-161.5g /ml). Renal ultrasonography revealed normal findings. Blood and urine amino acids, stool electrolytes and sweat test were normal. The biochemical abnormalities were corrected with appropriate fluid and electrolyte management. During his stay in the hospital, continuos transpyloric enteral feeding was performed for his recurrent vomiting. Treatment with the prostaglandin synthesis inhibitor indomethacin was started at a dose of 1 mg/kg/day and increased slowly up to 4 mg/kg /per day. During the treatment, serum potassium and chloride levels varied from 3.4 to 3.7 mEq/L and 112 to116 mEq/L, respectively and remained stable during the follow-up. The patient was discharged on a dose of 4 mg/kg/per day indomethacin and 2 mEq/Kg per day oral potassium supplementation The patient is currently 2.5 years-old and clinically well while receiving oral supplementation of potassium and chloride with indomethacin at a dosage of 3 mg/kg/day. He displayed catch-up growth and motor development was appropriate for his age.

DISCUSSION

Bartter syndrome is an isolated tubular disease characterized by hypokalemic alkalosis, hyperkaluria, normotension despite marked hyperactivity of the renin-angiotensin-aldosterone system. The diagnosis is frequently made in early adulthood (1). It has been proposed that neonatal Bartter syndrome is a clinical and pathophysiologic entity different from Bartter syndrome (3,4). In 1971, Fanconi et al. (7) reported the neonatal variant of Bartter syndrome in two patients with hypercalciuria and nephrocalcinosis. These two patients were born prematurely and the pregnancies were associated with hydramnios, like our patients. More than 40 cases have been reported since Fanconi's original description. Until recently, the cause of the neonatal variant has been controversial. A defect in chloride transport in the medullary diluting segment of the ascending limb of Henle's loop has been the most plausible hypothesis (3). Recent findings have established the genetic heterogeneity of neonatal Bartter syndrome. Molecular biology studies have clearly established that Bartter-like syndromes constitute an ensemble of inherited renal tubular disorders of NaCl transport. At present four different genes controlling solute transport in the distal nephron have been implicated (1). Most patients with neonatal Bartter syndrome type 1 have defects in transporters in the thick ascending limb of the loop of Henle, such as the Na-K-2Cl cotransporter, where as patients with neonatal Bartter syndrome type II usually have missense mutations of the ROMK gene (3,4). Large deletions or nonsense, missense, and splice mutations at a renal Cl channel gene (CIC-KB) have been found in type III Bartter Syndrome (1). Gitelman syndrome usually has mutations in the thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule (8). Unfortunately, we had no to show these means mutations in our patients.

The presence of developmental delay, hypokalemia, metabolic alkalosis, normal blood pressure despite elevated renin and aldosterone levels, as well as high urinary levels of potassium and chloride in our cases suggest Bartter syndrome. The diagnosis of neonatal Bartter syndrome was supported in these patients by the presence of a history of polyhydramnios, premature delivery and hypercalciuria.

Prostaglandin synthesis inhibitors, such as indomethacin, have been the most effective treatment, resulting in significant improvement of most clinical and biochemical abnormalities of Bartter syndrome (1,3). Also in our patients, indomethacin treatment resulted in a decrease in the formerly elevated levels of plasma renin and aldosterone and urinary calcium as well as good clinical improvement. We have demonstrated good catch-up growth in both of our patients. Renal ultrasonography performed at the follow-up revealed medullar renal hyperecogenity in both patients, but there was no evidence of nephrocalcinosis. Probably the absence of nephrocalcinosis in these patients is due to the good response to the indomethacin treatment. Also Mackie et al. (9) reported absence of nephrocalcinosis in an infant aged 19 months with neonatal Bartter syndrome, whereas Mourani et al. (10) reported a premature girl who developed nephrocalcinosis by the end of first month despite early treatment with indomethacin. Also Mastumuto et al. (11) reported three infants with neonatal Bartter syndrome. Two of them showed significant resolution of nephrocalcinosis with indomethacin therapy. This difference in response to the indomethacin therapy may be due to the genotypic heterogeneity seen in these patients.

In conclusion, the neonatal variant of Bartter syndrome is a rare entity with a life-threatening postnatal course and should be suspected in every premature infant born with a history of polyhydramnios. Although there are conflicting reports about the preventive effects of indomethacin for development of nephrocalcinosis, we believe that early treatment with indomethacin not only prevents life-threatening complications of neonatal Bartter syndrome, but also reduces the development of nephrocalcinosis. We believe that future researches will shed light on the prognosis and the genetic heteogeneity of the disease.

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