CASE REPORT

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A Rare Diagnosis in A Pediatric Case Without Metabolic Alkalosis; Bartter Syndrome

Metabolik Alkaloz Olmayan Pediyatrik Olguda Nadir Bir Tanı; Bartter Sendromu

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Abstract

Inherited salt-wasting tubulopathies include antenatal Bartter syndrome (BS), classical (tip 3) BS, and Gitelman syndrome. BS is an autosomal recessive inherited syndrome associated with impaired sodium and chloride reabsorption in the renal tubule. In classical BS cases with mutations in *CLCNKB* gene, dehydration episodes are observed within the first year of life. Polyuria, polydipsia, and dehydration are common symptoms in BS. Hypokalemia, hypochloremia, and metabolic alkalosis are observed in almost all of the cases. In this article, we presented a case of type 3 BS without metabolic alkalosis. In the presence of failure to thrive, polyuria, and low sodium, potassium, and chloride, even in the absence of metabolic alkalosis, type 3 BS should be considered in the differential diagnosis.

Keywords: Bartter syndrome, hypokalemia, metabolic alkalosis

Öz

Tuz kaybettiren herediter tübülopatiler arasında antenatal Bartter sendromu (BS), klasik (tip 3) BS ve Gitelman sendromu yer alır. BS, renal tübülde sodyum ve klorürün geri emiliminde bozukluk ile ilişkili otozomal resesif kalıtsal bir sendromdur. *CLCNKB* geninde mutasyon bulunan klasik BS olgularında yaşamın ilk yılında dehidrasyon atakları görülür. BS'de poliüri, polidipsi ve dehidrasyon sık görülen semptomlardır. Olguların hemen hepsinde hipokalemi, hipokloremi ve metabolik alkaloz görülür. Bu yazıda metabolik alkalozu olmayan tip 3 BS olgusunu sunduk. Gelişme geriliği, poliüri ve düşük sodyum, potasyum ve klorür varlığında, metabolik alkaloz olmasa bile tip 3 BS ayırıcı tanıda düşünülmelidir.

Anahtar kelimeler: Bartter sendromu, hipokalemi, metabolik alkaloz

Introduction

Hypokalemic salt-losing tubulopathies are those in which salt-wasting occurs proximal to the potassium-secreting segments of the distal nephron, resulting is excessive potassium excretion. Inherited salt-wasting tubulopathies include antenatal Bartter syndrome (BS), classical (tip 3) BS, and Gitelman syndrome. BS with autosomal recessive inheritance associated with impaired sodium and chloride reabsorption in the renal tubule. It leads to excessive salt and water loss. It causes hyperaldosteronism secondary to Renin-Angiotensin-Aldosterone system activation due to volume loss.

In classical BS cases with mutations in *CLCNKB* gene, dehydration episodes are observed within the first year of life. Polyuria, polydipsia, and dehydration are common symptoms in BS. Hypokalemia, hypochloremia, and metabolic alkalosis are observed in almost all of the cases (1).

In this article, we presented a case of type 3 BS without metabolic alkalosis.

Case Report

A child at three years and six months age has been admitted to a pediatric outpatient clinic due to nausea and vomiting which accompanied with moderate dehydration. It was

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learned that she ate salt, drank a lot of water, and urinated a lot.

Her perinatal history was unremarkable. There was no polyhydramnios in prenatal history. She was a term baby and her birth weight was 3.2 kg. Her parents were non-consanguineous. There was a sibling death history. Our patient has been hospitalized because of dehydration before.

As the medical history has been elaborated we have learnt that she has been admitted to the pediatric outpatient clinic with the complaint of poor weight gain at 18 months age. Slightly low potassium, sodium, and chloride levels have been detected at that time. Her weight and height were below the 3 percentile. A *CFTR* gene analysis was requested due to the findings of an elevated chloride level (50 mmol/L) in her sweat test, indicating the possibility of cystic fibrosis. Further testing was needed to confirm the diagnosis (Between 30-59 mmol/L = Cystic fibrosis is possible, and additional testing is required) (2). The hypercaloric enteral formula and pancreatin (Creon®) have been started. Pancreatin was discontinued because *CFTR* gene analysis was not compatible with cystic fibrosis.

At our hospital admission; the physical examination revealed the weight 10.1 kg (below 3rd percentile, SDS: -3.9), and the height 91 cm (below 3rd percentile, SDS:-3). She had a dry tongue and dry lips. Arterial blood pressure was 90/50 mmHg. Hypokalemia, hypochloremia, hyponatremia, hypomagnesemia, hypophosphatemia, and hypocalcemia were found in laboratory tests. Nevertheless, serum creatinine level was within the usual range. The patient's urine output rate was 10 mL/kg/h (high). Urinary density was 1005. Urine electrolyte measurement showed the urinary potassium level of 35 mmol/L (high). There were proteinuria, hyperuricosuria, hypercalciuria, hypermagnesuria, and a decrease in tubular reabsorption of phosphorus (TRP). The first laboratory findings of the patient on admission are shown in Table 1.

Parathyroid hormone was 137 pg/mL (high), and 25OHD was 3.8 ng/mL (low). As a result, the patient was diagnosed with nutritional 25OHD deficiency. 25OHD deficiency affected TRP by causing phosphaturia.

Reabsorption of protein, uric acid, sodium and potassium occurs from the proximal tubules. Hypokalemia, hypochloremia, and metabolic alkalosis are observed in almost all of the BS cases. Despite the absence of metabolic alkalosis, the suspected diagnosis was BS due to low sodium, potassium, chloride, and hypercalciuria. Additionally,

Table 1. Laboratory findings (at admission)

		Standard range
Sodium (meq/L)	126	135-145
Potassium (meq/L)	1.59	3.5-5.5
Chloride (meq/L)	83	96-106
Phosphorus (mg/dL)	1.5	3.5-5.5
Magnesium (mg/dL)	1.64	1.8-3.5
Calcium (mg/dL)	8.4	9-11
Albumin (g/dL)	4	3.5-5.5
Urea (mg/dL)	16	7-20
Creatinine (mg/dL)	0.32	0.3-0.6
Uric acid (mg/dL)	2.21	7-8
pH	7.45	7.35-7.45
pCO_2 (mmHg)	32	35-45
HCO_3 (meq/L)	24.7	21-24
Uric acid/creatinine in spot urine (mg/mg)	2.2	<1.5
Calcium/creatinine in spot urine (mg/mg)	0.6	<0.2
TRP (%)	80	>90
Urinary calcium excretion (mg/kg/day)	16	<4
Proteinuria (mg/m²/hr)	31	<4
Magnesium excretion (mg/1.73 m²/day)	100	<30

TRP: Tubular reabsorption of phosphorus

the genetic test result corroborated our diagnosis [whole exome sequencing revealed a homozygous pathogenic mutation in c.371C>T(p.Pro124Leu) *CLCNKB* gene], and she was diagnosed BS type 3.

Cholecalciferol (Devit-3®) 2000 IU/kg, oral potassium chloride (4 mmol/kg per day), indomethacin enteric-coated tablets (0.5 mg/kg per day), and oral magnesium supplement (50 mg/kg per day) treatments were started to the patient. The dosage of indomethacin was increased to 2 mg/kg per day as the treatment continued. Urine output decreased from 10 mL/kg/h to 7 mL/kg/h. Electrolyte disturbance was corrected.

At the time of this writing, she has been 6 years old, 108 cm tall (3rd percentile, SDS:-1.8), and weighed 18.5 kg (15th percentile, SDS:-1).

Discussion

Tubulopathy should be kept in mind in cases of failure to thrive, polyuria, dehydration, and electrolyte imbalance. In the atypical presentation, genetic testing can provide the diagnosis (3,4).

Polyuria, polydipsia, and dehydration are common symptoms in BS. Hypokalemia, hypochloremia, and metabolic alkalosis are observed in almost all of the cases (3). Our patient did not have metabolic alkalosis, clinically, BS was considered possible due to the presence of hypomagnesemia, hypokalemia, hypochloremia, hyponatremia, and hypercalciuria, and genetic testing confirmed the diagnosis.

To our knowledge, this is the first case of type 3 BS in terms of the absence of metabolic alkalosis. Cases with the diagnosis of type 1 and 2 BS without metabolic alkalosis have been described very rarely in the literature (5,6). One of these cases in the literature is a 5-month-old male patient with a history of preterm birth and polyhydramnios. He had hypercalcemia, elevated PTH, hypercalciuria, and nephrocalcinosis. Sodium and potassium levels were within the usual range, and metabolic alkalosis was absent. However, the diagnosis of type 1 BS was made by genetic testing.

Another case in the literature is a 7-year-old female patient with mild hypercalcemia, hypophosphatemia, hypercalciuria, hyperphosphaturia, elevated parathyroid hormone levels, serum creatinine levels within the standard range, and absence of hypokalemic alkalosis, diagnosed with BS type 2 based on the presence of homozygous pathogenic variation in *KCNJ1* gene (7).

The clinical spectrum of type 3 BS is very wide, from classical BS to antenatal BS, to Gitelman syndrome. Sometimes its presentation could seem like antenatal BS or Gitelman syndrome. There should be a history of polyhydramnios and preterm birth in antenatal BS (7). Our patient neither has polyhydramnios nor preterm delivery. Gitelman syndrome is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. Symptoms of Gitelman syndrome usually begin during adolescence (7,8). Our patient was in early childhood and had hypercalciuria.

Urinary calcium excretion in patients with type 3 BS is often within the usual range, yet reports of hyper- or hypocalciuria have been reported (7). The major site of active regulation of magnesium excretion is the loop of Henle. Hypomagnesemia often can be observed in type 3 BS (8).

Conclusion

We present atypical type 3 BS without metabolic alkalosis. In the presence of failure to thrive, polyuria, and low sodium, potassium, and chloride, even in the absence of metabolic alkalosis, type 3 BS should be considered in the differential diagnosis.

Ethics

Informed Consent: The consent form from the family of the case is obtained.

Authorship Contributions

Concept: D.T., S.T., R.Y.Ç., Design: D.T., S.T., R.Y.Ç., Data Collection or Processing: D.T., S.T., Analysis or Interpretation: D.T., S.T., Drafting Manuscript: D.T., S.T., Critical Revision of Manuscript: S.T., R.Y.Ç., Final Approval and Accountability: S.T., R.Y.Ç., Writing: D.T., S.T., R.Y.Ç.

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