CASE REPORT

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Bartter Type 4a Syndrome Diagnosed in a 30-week-old Preterm Neonate

Otuz Haftalık Prematüre Yenidoğanda Bartter Tip 4a Sendromu

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Abstract

Bartter syndrome is an uncommon autosomal recessive, salt-losing renal tubular disease. Its defining features are numerous electrolyte abnormalities, including low potassium and chloride levels, metabolic alkalosis, and low or normal blood pressure. We reported a case of neonatal Bartter syndrome presenting with severe hypokalemia, hypochloremic metabolic alkalosis, polyuria, and renal failure in a 28-week premature born to consanguineous parents. She was successfully treated with oral indomethacin and potassium supplements. Genetic tests were resulted in Bartter syndrome Type 4a with mutations in the *BSND* gene.

Keywords: Bartter syndrome, *BSND* gene, neonate, preterm

Öz

Bartter sendromu, otozomal resesif geçişli, tuz kaybettiren nadir bir renal tübüler hastalıktır. Düşük potasyum ve klorür seviyeleri, metabolik alkaloz ve düşük/normal kan basıncı gibi çeşitli elektrolit anormallikleri ile tanımlanır. Akraba anne-babadan 28 haftalık prematüre bir bebekte şiddetli hipokalemi, hipokloremik metabolik alkaloz, poliüri ve böbrek yetmezliği ile başvuran bir neonatal Bartter sendromu olgusunu bildirdik. Oral indometasin ve potasyum takviyeleri ile başarılı bir şekilde tedavi edildi. Genetik testler, *BSND* genindeki mutasyonlarla birlikte Bartter sendromu Tip 4a ile sonuçlandı.

Anahtar kelimeler: Bartter sendromu, *BSND* geni, preterm, yenidoğan

Introduction

One in a million people have Bartter syndrome, a rare autosomal recessive renal tubular disease of the thick ascending loop of Henle that causes salt loss. Five different types have been identified based on genetics. The neonatal form is characterized by polyhydramnios, preterm rupture of membranes, and preterm labor leading to prematurity. In the newborn period, patients often present with polyuria, dehydration, failure to thrive, growth retardation, and dysmorphic facies. Hypercalciuria and nephrocalcinosis are also typical in some forms. Bartter syndrome type IV is a neonatal Bartter syndrome with sensorineural deafness and dysmorphic facies including a triangular face, large eyes, and protruding ears. The *BSND* gene, which encodes the Barttin protein, is associated with this type. Barttin is a basic beta subunit of the ClC-Ka and ClC-Kb chloride channels localized in the renal tubules and inner ear (1).

We report a case of Bartter syndrome Type IVa with pathogenic change in the *BSND* gene, which was diagnosed early due to prenatal and postnatal complications.

Case Report

A 28-week-old female newborn born to a 21-year-old mother was admitted to our emergency delivery service. The infant was born via section because of massive polyhydramnios and breech presentation. On physical examination, the weight of the preterm neonate was 965 g, height 39 cm,

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body temperature 36 °C, heart rate 144/min, respiratory rate 44/min, and arterial blood pressure 60/35 mmHg. In physical appearance; triangular faces, protruding ears, and drooping mouths were visible. Her pH of 7.55, pCO_2 22 mmHg, and HCO_3 20.9 was found in cord blood gases. Complete blood count, biochemical parameters, and bleeding profile were normal. The patient was intubated because of respiratory distress. Her urine output was 4 cc/kg/hr on the first day of her life. Hyponatremia, hypokalaemia, hypochloremia, and hypocalcemia were found in blood tests along with renal failure. Hyponatremia, hypokalaemia, hypochloremia, and hypocalcemia were found in blood tests along with renal failure on the fourth day of the neonate's fourth day of life (Na: 129 mmol/L, K: 2,6 mmol/L, Cl: 87 mmol/L, serum urea 136 and serum creatinine 1.4 mg/dL). In total parenteral nutrition, the amount of intravenous fluid, sodium, and potassium was high. The urinary ultrasound was normal. Although urea and creatinine values decreased following sepsis, polyuria and potassium loss continued due to tubulopathy, and insufficient weight gain was observed, indomethacin was prescribed. As the weight loss of the patient whose polyuria continued, the amount of intravenous fluid increased. Despite this, the patient reached birth weight on the day of the 30th. The glomerular filtration rate was calculated as 13 mL/kg/1.73 m^2. Since the decrease in sodium and potassium continued (Na 123; K: 2.31 mmol/L), oral sodium saline and oral potassium were added to the diet of the patient who tolerated enteral nutrition. A 35 mg/kg dose of $MgSO_4$ was started on the 54th day of her life when hypomagnesemia became evident (magnesium: 1.04 mg/dL). Sodium excretion fraction was 12% and urine output was up to 7.7 cc/kg/hr. Urine density was 1007, protein creatinine ratio was 1.07, and calcium creatinine ratio was 0.92. Despite 11 meq/kg sodium administration, the simultaneously measured sodium level was only increased to 139 mmol/L, while the potassium level was only 2.69 mmol/L even though 40 meq/L potassium replacement was given. Gene analysis was sent from the patient who was suspected of having Bartter's syndrome due to polyuria and excessive loss of sodium and potassium in the urine. We obtained blood samples, pedigree, and informed consent from the parents. DNA was isolated according to the manufacturer's recommendations (QIAamp DNA blood Maxi kit, Qiagen, Hilden, Germany). The coding exon regions and +/-20 exon-intron junction regions of the genes included in the panel test (*BSND, CASR, CLCNKA, CLCNKB KCNJ1, SLC12A1, SLC12A3*) were investigated. We used the GRCh37/hg19 genome as a reference. We used databases [HGMD®, ClinVar, OMMM®, dbSNP (v151), gnomAD (v2.1.1)] and in silico prediction tools (MutatonTaster, SIFT, PolyPhen-2...) to filter and evaluate variants. Variants with minor allele frequencies below 1% (gnomAD) were evaluated and classified according to the ACMG Variant Classification Manual1.

We detected a homozygous c.1A>T (p.M1?) variant due to loss of function in the *BSND* gene (NM_057176.3, BARTTIN CLCNK-TYPE ACCESSORY SUBUNIT BETA, * 606412) (Figure 1). Heterozygosity for the same mutation was found in the parents (Figure 2). Her polyuria decreased

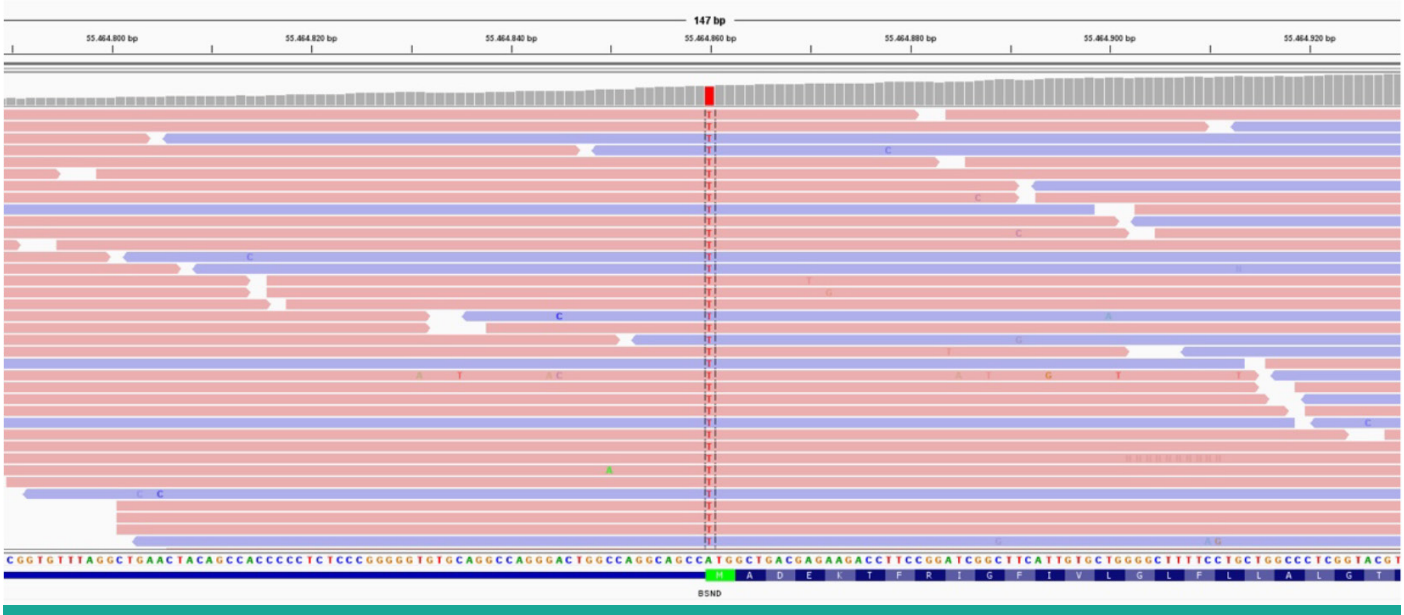

Figure 1. IGV illustration of the NGS result of patient genome

with indomethacin treatment after sepsis, she started to gain weight and was in the fourth stage of chronic kidney disease.

Discussion

Bartter syndrome is a group of diseases characterized by metabolic alkalosis, hypercalciuria, and salt wasting. As antenatal Bartter syndrome (Type 1, 2, and 4) maternal polyhydramnios neonatal salt loss and recurrent episodes of severe dehydration are more severe than classical Bartter syndrome (Type 3) Type 4 Bartter syndrome, which was seen in the patient we presented as a case report, is a prenatal or postnatal manifestation of autosomal recessive inherited sensorineural hearing loss with a mutation in *BSND* gene, but not with nephrocalcinosis. The thick ascending limb of the loop of Henle and the descending convoluted tubule are affected, resulting in sodium chloride and potassium loss. The five different types of Bartter syndrome can be broken down into different disease genes (2). The *BSND* gene is localized in the 1p32.3 region, weighing 35197 Da. BSND codes for Barttin protein, which functions as an accessory subunit of the chloride channels of the kidney and inner ear and modulates the stability of channels (3). The homozygous loss-of-function mutation identified in this study is located in exon 1 encoding the transmembrane domain. The position is strongly maintained (phyloP100way =8.12 greater than 7.2). The variant is not found in gnomAD genomes. This variant has been previously described in the literature with Bartter syndrome patients (4). Our variant is the same, mutations of 5 patients of Turkish origin in this publication (F314, F591, F730, F786, F791). *BSND* gene mutation was originally described as a severe form of antenatal BS4. Renal failure has been found mainly in patients with mutations that lead to complete protein loss (5-7). Polyhydramnios and preterm delivery are typical features of *BSND* gene mutations in patients (8,9). However, variants caused by mild and late-onset phenotypes have also been reported in later studies.

This variability in renal outcome may be explained by the residual function of some mutated proteins or other factors. Despite the highly variable renal clinic, hearing loss is usually present at the time of diagnosis. The auditory brainstem response test performed on the patient was normal, but our patient should be followed up for hearing loss (7). *BSND* gene mutations or deletions involving the *ClCNKB* and *ClCNKA* genes have been reported to be associated with chronic renal failure, a rare complication for other types of Bartter syndrome (4,10,11). Calcium reabsorption occurs mostly by passive paracellular transport in the proximal tubules and loop of the thick ascending limb of Henle. The loss of the transepithelial voltage gradient, which permits calcium reabsorption in the loop of Henle, leads to hypercalciuria in Bartter syndrome. The TRPV5 channel, which is triggered by parathormone, is used by transcellular transport to reabsorb a minimal amount of filtered calcium in the distal tubule (12). In some studies, it has been shown that prostaglandins decrease calcium reabsorption in the distal tubule and increase calcium reabsorption directly by inhibition of prostaglandin E2 (13,14). Management of Bartter syndrome

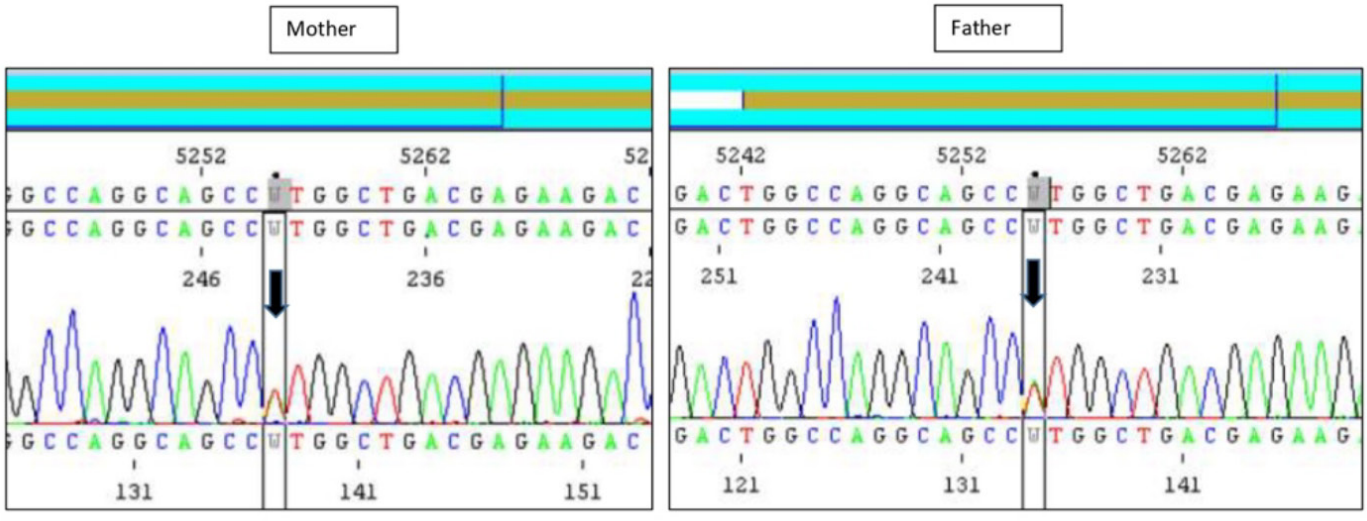

Figure 2. Representative chromatogram sequencing of the mutation is shown fort the unaffected parents. Arrows indicate the nucleotide change in the sequence

is to prevent dehydration and maintain nutritional status to treat electrolyte disorders. Despite electrolyte and fluid replacement therapy, polyuria and electrolyte imbalance persisted and we started indomethacin.

As a result, in newborns with polyhydramnios, alkalosis, hyponatremia, hypokalemia, and tubulopathies involving the ascending loop of the loop Henle such as Bartter's syndrome should be considered in the differential diagnosis. In patients with renal insufficiency, type 4 Bartter syndrome should be considered genetically and diagnosed and supported in treatment.

Ethics

Informed Consent: Written informed consent received from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.C.G., Ö.K., L.Ş., E.C., Ş.H., Concept: Ç.C.G., Ö.K., Design: Ç.C.G., Ö.K., Data Collection or Processing: Ç.C.G., Ö.K., Analysis or Interpretation: Ç.C.G., Ö.K., L.Ş., E.C., Ş.H., Drafting Manuscript: Ç.C.G., Ö.K., Final Approval and Accountability: Ç.C.G., Ö.K., L.Ş., E.C., Ş.H., Supervision: E.C., Ş.H., Writing: Ç.C.G., Ö.K., L.Ş., E.C., Ş.H.

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