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Case Report

A Novel Mutation in Fanconi Bickel Syndrome Diagnosed in the Neonatal Period

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ABSTRACT

Fanconi Bickel Syndrome (FBS), also known as glycogen storage disease Type XI, is a rare autosomal recessive disorder. This syndrome has many different identified mutations and it is rarely diagnosed during the neonatal period. Our patient is a two-week old female newborn who was admitted to our hospital with fever and dehydration. Renal Fanconi Syndrome was diagnosed in the presence of polyuria, proteinuria, glycosuria, hyperchloremic metabolic acidosis with normal anion gap and positive urine anion gap, hyperuricemia, hypophosphatemia and an increased excretion of phosphorus in urine. A novel mutation, IVS8 homozygote g.24401-24406del6 in the *GLUT2* gene was demonstrated by the Sanger method. The same mutation was detected as heterozygote in her parents. Although most of the affected infants have a consanguineous parentage history in the literature, our patient was born to non-consanguineous parents. Also, according to our knowledge, few FBS patients were diagnosed in the newborn period. Our patient was diagnosed with a novel mutation in her first month of life.

Keywords: Fanconi Bickel Syndrome, glycogen storage disease Type XI, mutation, neonatal period

Introduction

Fanconi Bickel Syndrome (FBS), also known as glycogen storage disease Type XI, is a rare autosomal recessive disorder. It is characterized by a mutation in the gene *GLUT2* (SLC2A2) that causes impaired glucose and galactose transportation in the kidney, intestines, liver and pancreas (1,2). Growth retardation, fasting hypoglycemia, postprandial hyperglycemia, generalized tubulopathy and hypophosphatemic rickets are the main symptoms of FBS (3). Treatment of this disorder is generally symptomatic. Here, we report an unusual patient with FBS diagnosed with a novel mutation in the *GLUT2* gene in the neonatal period.

Case Report

A two-week old female newborn was admitted to our hospital with fever and dehydration. On admission, the baby was irritable and dehydrated. Her gestation period was 38 weeks and her birth weight was 2.600 g (10-25 percentile), her height was 47 cm (10-25 percentile) and her head circumference was 35 cm (75-90 percentile) at delivery. She had non-consanguineous parents. Systemic examination was otherwise unremarkable.

Laboratory tests revealed, hyperglycemia (310 mg/dL) (normal: 60-100 mg/dL), hypouricemia (1.1 mg/dL) (normal: 2.6-6.0 mg/dL), hyponatremia (130 mmol/L) (normal:

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135-145 mmol/L), hypokalemia (3.7 mmol/L) (normal: 4.1-5.3mmol/L), hyperchloremia (121 mmol/L) (normal: 98-107 mmol/L), hypophosphatemia (2.6 mg/dL) (normal: 2.5-4.7 mg/dL), metabolic acidosis with normal anion gap (pH: 7.31 HCO3: 17 mEq/L) (normal for pH: 7.35-7.45; normal for HCO3: >15 meq/L) and elevated alkaline phosphatase (1.355 IU/L) (normal: 48-406 U/L).

Urine pH was 6.5 and urine analysis revealed proteinuria and glycosuria. Urine output was 14 cc/kg/hour. Fractional excretion of sodium was 5.8% (normal: 0.3-1.6%), tubular phosphorus reabsorption (TPR) was 65% (normal: >85%), microprotein/creatinine and microalbumin/creatinine ratios were 4.4 mg/mg Cr (normal: <0.7 mg/mg Cr) and 8.5 mg/g Cr (normal: <30 mg/g Cr) respectively. Calcium/creatinine ratio was 0.38 mg/mg Cr (normal: <0.8 mg/mg Cr). Ammonia and lactate were within normal ranges. Insulin, c-peptide and Hemoglobin A1c were 1 uU/mL (normal: 2.6-24.9 uU/mL), 0.458 ng/mL (normal: 0.9-7.1 ng/mL) and 2.5% (normal: <6%) respectively. Ophthalmologic examination was normal in terms of cystine crystals and cataract. Generalized aminoaciduria was found in urine chromatography. There was no finding associated with rickets or pathologic fracture in babygram. 25-hidroksi vitamin D3 (25-OH D3) was 7.95 ng/mL (normal: >21 ng/mL) and parathormone was 42 pg/mL (normal: 11-67 pg/mL). Renal ultrasound revealed kidneys with normal shape, size and renal cortical echogenicity. Measurement of the leukocyte cystine content with high-performance liquid chromatography was normal (0.10 nmol/protein).

Renal Fanconi syndrome was diagnosed in the presence of polyuria, proteinuria, glycosuria, hyperchloremic metabolic acidosis with normal anion gap and positive urine anion gap, hypouricemia, hypophosphatemia and increased excretion of phosphorus in the urine. Genetic analysis was performed to confirm the diagnosis. Informed consent was received from the family. A novel mutation, IVS8 homozygous g.24401-24406del6 in the *GLUT2* gene was demonstrated by the Sanger method. This mutation is seen in the C1065_1068+2delCTCTGT in the *SLC2A2* gene, according to the Human Genome Variation Society. The same mutation was detected as heterozygous in her parents by a segregation study.

Fluid-electrolyte imbalance was corrected and vitamin D, phosphorus and alkali supplementation were initiated. Ibuprofen was used for polyuria. Conservative management was used for proper maintenance of blood glucose levels and short term insulin was used when it was >300 mg/dL. Her weight reached 4.100 g in the sixth month of life, nevertheless polyuria, proteinuria, glycosuria, hyperchloremic metabolic acidosis and hypouricemia continued. She was followed-up in our out-patient clinic without any deterioration until she died in the seven month of life due to aspiration.

Discussion

FBS was first described by Guido Fanconi and Bickel (4) in 1949. It is a rare glycogen storage disease characterized by glycogen accumulation secondary to non-functional glucose transport in the liver and kidney. Severe renal tubular dysfunction and impaired glucose and galactose metabolism are the cardinal symptoms of the disease (5). The mechanism of the disease is a monosaccharide transport defect across the membranes without underlying enzymatic defect in carbohydrate metabolism (1).

FBS is caused by mutations in the *GLUT2* gene, which is located on chromosome 3. GLUT2 expressed on hepatocytes, pancreatic beta cells, basolateral membranes of intestine and renal tubular epithelial cells.

The first patient described by Fanconi and Bickel (4) in 1949 had a homozygous arg301-to-ter (R301X) mutation (5). Sakamoto et al. (6) studied three Japanese patients with FBS and found four novel mutations in the *GLUT2* gene, including a splice site mutation, a nonsense mutation, and two missense mutations. There are 14 reported mutations in Turkish patients with FBS in the literature (7). A novel mutation, IVS8 homozygous g.24401-24406del6 within the gene of the GLUT2 was detected in the genetic analysis of our patient. Although most of the affected infants in the literature have a consanguineous parentage history, our patient was born to non-consanguineous parents (8).

Our patient was diagnosed in her first month of life. According to our knowledge, few cases of FBS have been reported in the neonatal period (3). The first symptoms of this syndrome are usually recognized between 3 and 10 months of age. Diagnosis of FBS normally occurs in late infancy as FBS clinical features develop. In some cases, galactosaemia screening leads to an earlier diagnosis (3,9).

There is no specific therapy available for this syndrome. Symptomatic therapy such as replacement of water, electrolytes, vitamin D3 and phosphate and a diabetes mellitus-like diet with adequate caloric intake as frequent small meals may improve growth (10). Without oral phosphate and vitamin D supplementation, severe hypophosphatemic rickets may occur in the first months of life. After initiation of proper diet and supplements, our patient had showed partial clinical and metabolic improvement. A conservative management of hyperglycemia was carried out as recommended by Taha et al. (11) reported that the use of insulin should be avoided as it may further increase the risk of hypoglycemia, especially, in younger patients.

Our patient did not find a chance to have a longer follow-up period as she died when she was 7 months old because of a reason unrelated to her primary disease.

Our patient had a novel mutation not described in the literature so far. In addition, diagnosis in the neonatal period is a rare condition for FBS in the literature. Although

this disorder is rare, early diagnosis is important to achieve a good clinical condition and to prevent metabolic complications such as rickets by the initiation of a proper diet and supplements.

Ethics

Informed Consent: Informed consent was received from the family.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.K.G., K.Ç., Ş.Ç., Concept: Ş.K.G., Ş.Ç., E.S., Design: Ş.K.G., Ş.Ç., E.S., Data Collection or Processing: Ş.K.G., K.Ç., Analysis or Interpretation: Ş.K.G., E.S., Literature Search: Ş.K.G., K.Ç., Writing: Ş.K.G., E.S.

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