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Case Report

An Indian girl with Fanconi-Bickel syndrome without *SLC2A2* gene mutation

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Abstract. Fanconi-Bickel syndrome is a rare autosomal-recessive disorder caused by defects in the facilitative glucose transporter 2 (*GLUT2*) gene. It is characterized by hepatorenal glycogen accumulation, tubular nephropathy and impaired utilization of glucose and galactose. In this communication, we present the case of a 5-year-old girl who presented with deforming rickets and massive hepatomegaly. Liver biopsy confirmed the diagnosis of glycogen storage disorder. However, the mutation of the *SLC2A2* (*GLUT2*) gene was not found. Mutation negative patients with characteristic Fanconi-Bickel syndrome phenotype suggest additional underlying mechanisms that need exploration.

Keywords: Fanconi-Bickel syndrome, hypophosphatemic rickets, glycogen storage disease type XI

1. Introduction

Fanconi-Bickel syndrome (FBS) classified as glycogen storage disease type XI is a rare autosomal recessive disorder caused by defects in the facilitative glucose transporter involved in transport of glucose in and out of hepatocytes, pancreatic beta cells and basolateral membranes of intestinal and renal epithelial cells [1]. The defective protein, GLUT2, also known as solute carrier family 2 member 2 (SLC2A2), is a transmembrane carrier protein encoded by the *SLC2A2* gene located at chromosome 3q26.1. FBS is considered to be a single gene disorder resulting from mutations in the *SLC2A2* gene [2]. These mutations are scattered over the whole coding sequence of the *GLUT2* gene and are found in all exons. About half of the newly diagnosed patients have novel mutations [1]. Overall mutations are identified in about 70% of patients. Patients without mutations suggest the possibility of more than one gene or other mechanisms involved in causing the disease manifestations. In this report we discuss a girl who had all the clinical and laboratory features to suggest FBS but was negative for the mutation in the *SLC2A2* gene.

2. Case report

A 5-year-old girl, third child of non-consanguineous parents, born at term with a birth weight of 2.9 kg presented with difficulty in walking due to deformity of both lower limbs. At the age of 2 yr she had been diagnosed as nutritional rickets and received two mega doses (6,00,000 IU each 1 mo apart) of vitamin D along with calcium supplements but there was no further follow

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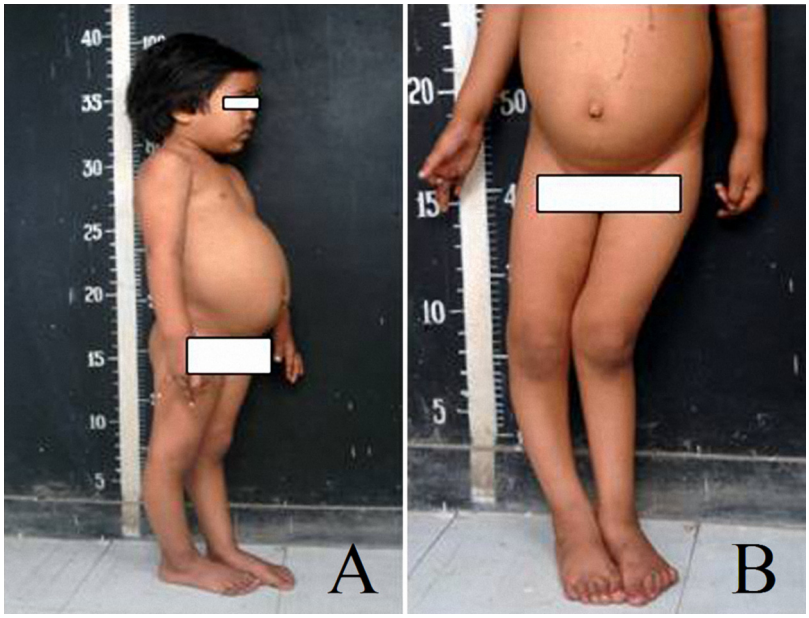
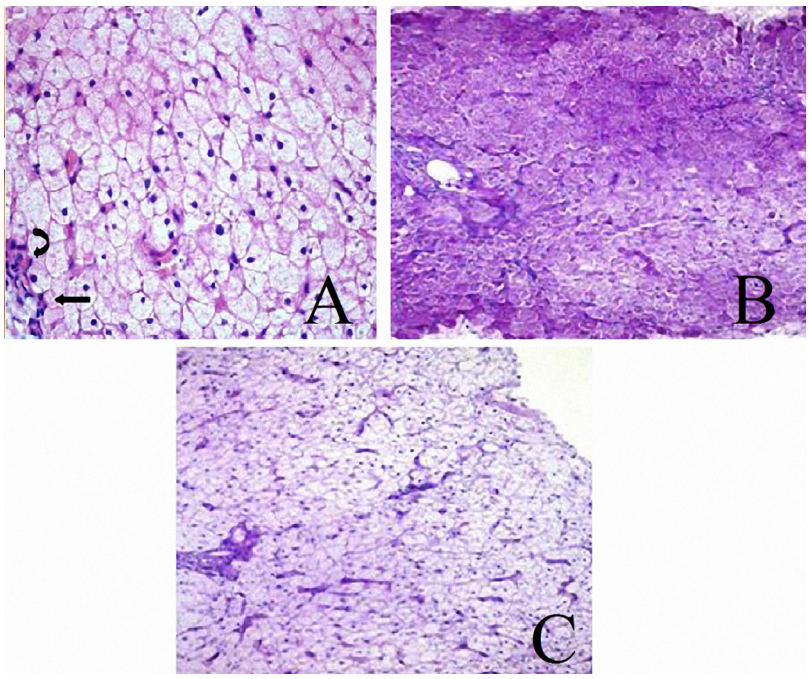
up and healing of rickets was not demonstrated. She had delay in achieving her major motor milestones (sitting 9 mo, standing 1.5 yr, walking 2 yr). There was no history suggestive of any chronic systemic disease, dietary deprivation, fasting hypoglycemia or malabsorption especially galactose intolerance. Her other siblings were asymptomatic. The deformity of lower limbs was first noticed by parents at about 3 yr of age and increased progressively. At 4 yr of age, she had sustained a fracture of right femur after trivial trauma. On examination, she had prominent cheeks, doll like face, protuberant abdomen with lumbar hyperlordosis and a windswept deformity of legs (Figs. 1A and 1B). Her weight was 12 kg, height 98 cm (both less than 3rd centiles on CDC 2000 growth charts) and head circumference was 49.5 cm (between mean and -2SD). Her liver was palpable 8 cm below right costal margin (span of 14 cm) and spleen 2 cm below left costal margin. Rest of her systemic examination was unremarkable.

Investigations showed normal levels of blood urea, serum creatinine, lactate and electrolytes. Hemogram revealed anemia (hemoglobin 8.7 g/dL, normal 11.5–15.5 g/dL) and normal platelet and leucocytes counts. Serum calcium was 9.2 mg/dL, phosphorus 3.2 mg/dL (normal 3.7–5.6 mg/dL) and alkaline phosphatase 604 U/L (normal 145-420 U/L). Serum albumin was 3.6 g/dL (normal 4–5.3 g/dL) and alanine aminotransferase and aspartate aminotransferase levels were 258 and 233 U/L respectively (normal 5–45 U/L). Serum ceruloplasmin was 396 mg/L (normal 270–560 mg/L). Lipid profile showed total cholesterol of 148 mg/dL (normal 109–189 mg/dL), triglycerides 244 mg/dL (normal 32–99 mg/dL), high-density lipoprotein cholesterol (HDL-C) 20 mg/dL (normal 35–84 mg/dL) and low-density lipoprotein cholesterol 79.2 mg/dL (normal 60–150 mg/dL). Blood gas analysis revealed mild metabolic acidosis (pH 7.32, bicarbonate 15.9 mmol/L and base deficit -13). Fasting blood glucose was 3.7 mmol/L (normal 3.3–5.5 mmol/L) and 2-hr post load blood glucose was 9.43 mmol/L (normal <7.8 mmol/L). HbA1c was 5.8% (normal 3.0–6.2%). Thyroid function tests were normal. Plasma level of 25-hydroxycholecalciferol was 62 nmol/L (normal 50–250 nmol/L) and 1,25-hydroxycholecalciferol was 74 nmol/L (normal 60-108 nmol/L). Parathyroid hormone level was 4.5 pmol/L (normal 0.95–6.8 pmol/L). Routine urine examination by dipsticks showed glucose 2+, albumin 1+, pH 5.0 (normal 4.5–8) and specific gravity 1.010. Urinary phosphorus was 20.8 g/day (normal 0.4–1.3 g/day) and calculated tubular reabsorption of phosphorus was 64% (normal >90%). Urine aminoacidogram was suggestive of generalized aminoaciduria. Radiographs of lower limbs showed active rickets. Ultrasonography of abdomen revealed hepatomegaly (liver span 13.3 cm) with normal echo texture and right and left kidneys measuring 6.8 and 7.0 cm respectively.



Figs. 1A and 1B. Clinical photographs of the patient showing moon-like face, protuberant abdomen and windswept deformity of legs.



Figs. 2A–2C. (A) Core biopsy of liver with maintained lobular architecture, portal tract fibrosis (arrow) along with expansion and mild inflammation (curved arrow). Hepatocytes are enlarged and had plant like appearance. (B) Liver histology after periodic acid-Schiff staining showing periodic acid-Schiff positivity. (C) Diastase treatment of the periodic acid-Schiff positive sample showing disappearance of stain.

In view of several laboratory features of renal tubular dysfunction and hepatomegaly a probability of FBS was considered and liver biopsy was done which showed maintained lobular architecture, portal tract fibrosis, expansion and mild inflammation and enlarged hepatocytes having plant like appearance suggestive of glycogen deposition (Fig. 2A). These cells were periodic acid-Schiff positive (Fig. 2B) and diastase sensitive (Fig. 2C) suggestive of a glycogen storage disorder. To confirm the diagnosis, genomic deoxyribonucleic acid was extracted and sent to Prof. Osamu Sakamoto's Laboratory in Tohoku University School of Medicine, Japan, for mutation analysis. All coding sequences including flanking introns in *GLUT2* gene were amplified using polymerase chain reaction. Direct sequencing of the all-coding exons including flanking introns of *SLC2A2* (*GLUT2*) gene was performed using a Big Dye Primer Cycle Sequencing kit and ABI 310 Genetic Analyzer. No substitution (insertion nor deletion) was found in the sequenced regions.

The child was started on vitamin D, calcium and phosphorus supplements and parents were advised to make some dietary modifications like frequent small meals with adequate calories but restricted in glucose and galactose during the day and use of uncooked cornstarch at nighttime. Unfortunately, she was unavailable for follow up assessment due to shifting to another place.

3. Discussion

Our patient presented with all the classical clinical features (short stature, protuberant abdomen, hyperlordosis, facial obesity, rickets, hepatomegaly) seen in FBS; the combination of rickets and hepatomegaly provided us a clue to clinical diagnosis. In addition, she demonstrated almost all the biochemical (tubulopathy, glucose abnormalities) and histopathological evidence typical of hepatorenal glycogenosis. The presence of tubular dysfunction in our patient excluded the possibility of another hepatorenal glycogenosis, Von Gierke disease. Although FBS patients may be identified during neonatal screening due to hypergalactosemia [3], the typical presentation is during infancy with a combination of failure to thrive, rickets and hepatomegaly, hypoglycemia in the fasted state, and glucose and galactose intolerance in the fed state [4]. Delayed presentations with short stature, deforming rickets, massive hepatomegaly and lumbar hyperlordosis as in the index patient,

have generally been reported from developing countries [5]. Impaired glucose tolerance as seen in our patient is related to a defective insulin secretion from pancreas producing a state of relative insulinopenia seen in majority of patients of FBS [6]. Of the lipid abnormalities, hyperlipidemia (increased triglycerides, total cholesterol) is common but the finding of a low HDL-C in our patient was unusual and remains unexplained. Although certain *SLC2A2* gene polymorphisms are observed to influence HDL-C levels in adults without FBS phenotype, this mechanism cannot be proposed to have resulted in lower HDL-C levels in our patient as no gene variant was either detected [7].

Mutations of *SLC2A2* that are found in the majority of patients are considered as the basic defect that results in the characteristic FBS phenotype [2,8]. These mutations are also identified in patients with atypical or a milder manifestations of FBS [2,9]. Few patients detected positive for *SLC2A2* gene mutations in the cohort described by Santer et al. [2] had atypical clinical features like intestinal malabsorption, failure to thrive, no hepatomegaly and renal hyperfiltration. Similarly, two siblings with novel mutations of the *SLC2A2* gene diagnosed during infancy did not develop characteristic features of FBS and remained relatively asymptomatic over long-term follow up [9]. These reports suggest that mutations of the *SLC2A2* gene may not necessarily result in clinical features considered hallmark for FBS. Conversely the mutations may be absent in patients with all the manifestations characteristic of FBS [10]. This may be because of presence of heterozygous long-range deletions, which are not detectable with the usual polymerase chain reaction-based method [2]. In addition, the molecular genetic diagnosis is very labor-intensive since none of the *SLC2A2* gene mutations are particularly frequent [2,8]. The absence of mutations in patients with a characteristic FBS phenotype may also suggest the possibility of involvement of some other gene as well as other mechanisms that need further exploration. The reports on patients documented to have no mutations of *SLC2A2* may prompt researchers in developed setups to explore other mechanisms or gene combinations (in addition to *SLC2A2*) responsible for varied disease manifestations of FBS.

In conclusion, although FBS has long been considered a single gene disorder, patients with characteristic phenotype but no *SLC2A2* mutations suggest the presence of as yet unexplored gene combinations or alternative mechanisms in this disease.

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