CASE REPORT

Fanconi Bickel Syndrome with Hypercalciuria due to *GLUT 2* Mutation

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Background: Fanconi Bickel Syndrome is a rare, autosomal recessive, disorder of carbohydrate metabolism. Presence of hypercalciuria is rare. **Case characteristics**: 4.5-years-old boy presented with growth failure, hepatomegaly, rickets, fasting hypoglycemia with postprandial hyperglycemia, fanconi syndrome and hypercalciuria, **Outcome:** A rare mutation in *GLUT-2* gene suggestive of Fanconi Bickel Syndrome. **Message:** Fanconi Bickel Syndrome may present with hypercalciuria with proximal renal tubulopathy along with fasting hypoglycemia and postprandial hyperglycemia.

Key words: *Diabetes insipidus, Genetics, Glycogen storage disorder type XI.*

Fanconi Bickel Syndrome (FBS, OMIM #227810), previously known as glycogen storage disorder type XI, is a rare autosomal recessive inherited condition presenting with growth failure, rickets, hepatomegaly and proximal renal tubular dysfunction resulting from glycogen accumulation, caused due to mutation in the gene encoding facilitative glucose transporter 2 (GLUT 2) , also known as *SLC2A2* gene [2]. We present a case of Fanconi Bickel Syndrome with associated hypercalciuria due to a rare mutation in *GLUT-2* gene.

CASE-REPORT

A 4.5-year-old boy born of non-consanguineous marriage, presented with gradually progressive abdominal distension since 3 month of age. Polyuria, polydipsia, failure to thrive and progressive lower limb deformity in the form of knock knees was observed since 1.5 years of age. He had undergone deformity correction surgery of genu valgum at 4 years of age and had received 25 lac units of oral cholecalciferol over the past 12 months. There was no history of jaundice, fracture or seizures. He was born at term weighing 2.5 kg, of an uneventful pregnancy. Developmental milestones were normal. Dental eruption started at 20 months. Family history was not significant.

Examination revealed severe retardation of both weight 10.5 kg (Wt SDS: –3.6) and height 80 cm (Ht SDS: –5.8). He had rounded doll-like facies, enamel hypoplasia and features of rickets in form of frontal bossing, wrist widening, rachitic rosary and genu valgum. Systemic examination revealed diffuse, non tender, firm hepatomegaly (liver span 9cm) without splenomegaly. Signs of proximal muscle weakness were present. Quantification of urine output revealed polyuria (urine output 6 mL/kg/hr).

Investigations revealed hyperchloremic (S.Cl-115 mmol/L; normal 96-106) metabolic acidosis (pH-7.38, HCO3-14.1mmol/L, pCO2 24.3), with simultaneous urine pH of 6 and positive urinary anion gap (39). 24-hour urinary calcium was high (17.2 mg/kg/day; normal <4).

Serum creatinine and electrolyte, serum calcium, serum vitamin D (25-OH vitamin D and 25-OH vitamin) were normal. Low serum phosphorus (2.8 mg/dL; normal 4-7) and elevated alkaline phosphatase (673 IU/L; normal 57-180) were found. Other investigations like serum uric acid, SGPT, PT, aPTT, Total serum bilirubin, Total protein, S. Albumin, S. Cholesterol were also normal. Fasting hypoglycemia (blood sugar 28 mg/dL) and post-prandial hyperglycemia (blood sugar 240 mg/dL) was detected on several occasions. Critical sample collected during hypoglycemia (blood sugar 28 mg/dL) revealed normal blood lactate (5 mg/dL; normal 4.5-20), serum ketones (1.2 mg/dL; normal 0.3-2), and serum ammonia (88 U/L; normal 10-90).

Features of Fanconi syndrome in the form of glycosuria (urine sugar 4+), phosphaturia (TmP GFR 0.8; normal 0.8-1.1; TRP (tubular reabsorption of phosphorous) 66%; normal >85%), proteinuria (102 mg/m^2/hour) and generalized aminoaciduria were noted. This was associated with hypercalciuria (24-hour urinary calcium 17.2 mg/kg/day; normal < 4).

Ultrasound abdomen revealed hepatomegaly with bright echotexture. Ophthalmological examination was normal. *X*-ray wrist showed features of rickets. Liver biopsy did not reveal any glycogen-laden cells.

A diagnosis of FBS was considered and genetic analysis by direct sequencing of DNA revealed a rare homozygous splice site mutation c.16-1G>A or IVS 1-1G>A in *GLUT-2* gene. Both parents were carriers.

Child was advised frequent feeds with complex carbohydrate diet, oral sodium bicarbonate (5 mEq/kg/d), potassium (2mEq/kg/day) and phosphate (40 mg/kg/d) supplement. On last follow-up, at 5y 6mo of age, he had gained 2.5 kg in weight (13 kg) and 1.2 cm in height (81.2 cm). Liver span was 9 cm and features of rickets were present. The blood biochemistry was within the normal range, but hypercalciuria was persistent.

DISCUSSION

The gene *GLUT-2* is located on chromosome 3q26.1-q26.3 and encodes glucose transporter protein 2 expressed in hepatocytes, pancreatic beta cells, enterocytes and renal tubular cells. More than 34 different mutations are reported, which provides molecular basis of the disease [2]. Since the first description in 1949, more than 150 cases of FBS have been reported, with three from India [3-5]. Accumulation of glycogen in renal tubular cells causes proximal tubular dysfunction leading to Fanconi nephropathy with variable renal phosphate wasting [6]. Presence of hypercalciuria is rarely reported. Although it is postulated to be due to phosphaturia induced down-regulation of renal tubular 1 alpha-hydroxylase activity, the etiology of hypercalciuria remains uncertain [7].

FBS can present as galactosemia in neonatal screening as the same transporter is required for galactose [8]. FBS presenting as nuclear cataracts and hyperglycemia in the newborn period have also been described [9]. Atypical HNF4A R76W mutations, a close differential in our case, presents with neonatal hyperinsulinism. Diabetes, Fanconi syndrome and nephrocalcinosis may be seen in later childhood, but absence of fasting hypoglycemia helps clinically differentiate this condition [10]. Other atypical presentations like pseudotumor cerebri, intestinal malabsorption and liver failure have also been reported.

No specific treatment has been identified. Small frequent feeds and uncooked corn starch at bedtime should be offered to prevent hypoglycemia. Since glucose wasting is very high, adequate calorie supplementation is very essential for normal growth. Long term replacement therapy for proximal tubular losses is needed.

Overall prognosis is good; many cases have been reported to reach adulthood, with short adult height [6]. Hepatomegaly tends to regress after puberty. Renal phosphate wasting and hypercalciuria contribute to difficult to correct bone features and short adult stature. Mutation studies help not only in diagnosis but also to enable counseling. Genetic counselling and prenatal testing is recommended being an autosomal recessive disorder.

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