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Case Study

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FANCONI BICKEL SYNDROME – A RARE ENTITY IN A BANGLADESHI CHILD

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ABSTRACT

Fanconi-Bickel syndrome (FBS) is a rare inherited glycogen storage disease (GSD), caused by defects in facilitative Glucose Transporter (GLUT2) gene that codes for the glucose transporter protein 2 expressed in hepatocytes, pancreatic beta cells, enterocytes, and renal tubular cells. The clinical picture is characterized by glycogen accumulation in liver and kidney resulting in hepatomegaly and renomegaly, fasting hypoglycemia and post prandial hyperglycemia, proximal renal tubular acidosis, hypophosphatemic rickets, and short stature. In this article we present a case of Fanconi-Bickel syndrome and its management who initially presented with short stature, hepatomegaly and hypophosphatemic rickets.

KEYWORDS: Fanconi Bickel syndrome, Hypophosphatemic rickets, Renal tubular acidosis.

INTRODUCTION

Fanconi-Bickel syndrome (FBS), a rare autosomal recessive disorder, is classified as glycogen storage disease type XI, 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. Fanconi-Bickel syndrome 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. Cases have been reported from all parts of Europe, Turkey, Israel, Arabian countries of the Near East and North Africa, Japan, and North America.[3,4] In this report we will discuss a girl who had all the clinical and laboratory features suggestive of FBS.

CASE REPORT

A two year 8 months old female child, 3rd issue of consanguineous parents presented to us with gradual abdominal distention since 7 months of her age, which was increasing day by day and repeated history of respiratory tract infection for same duration and for which several times hospital admissions were needed. She was not growing well in comparison to her peers despite having good appetite. On query, mother also told that she had history of polyuria, polydipsia, early morning irritability and craving for food. There was no history of seizures, jaundice, pedal edema, visual disturbance (cataract). Mother also told that her tooth erupted at 6 months of age and at 1½ yrs of age teeth shedding started. She was born at term at home with average birth weight without any perinatal complications. Exclusively breast fed upto 6 months of age, complimentary food started with cereals and banana, now she is on family diet. Mother also told that she had history of developmental regression in the form of not sitting and standing after achieving this domain. She had history of two sib death for the same complains at the age of 2½ years and 1½ years but cause of death could not be ascertained and no record was available. On examination, child was irritable with doll's face and box shaped head (Figure-1). Anterior fontanel was open (1x1.5cm), mildly pale, tachypneic, other vitals were within normal limit. Anthropometrically she was severely underweight (WAZ:-7.7), severely stunted (LAZ: -7.9), mildly wasted (WLZ:-1.35). She had scoliosis (Figure- 2), generalized hypotonia, widening of both wrist and ankle joints (Figure-3) and rachitic rosary were present. On abdominal examination, abdomen was distended and hepatomegaly (5cm) present and other

systemic examinations revealed normal findings. With presence of sib death, consanguinity, early morning irritability we provisionally thought about glycogen storage disease and for rachitic bony change, polyuria and polydipsia, open anterior fontanel and generalized hypotonia we thought about renal tubular acidosis with rickets. These two phenomena can be nomenclatured under a single umbrella of Fanconi Bickel syndrome. For those keeping in mind, patient was extensively evaluated.

Investigations revealed normal level urea, creatinine and electrolytes. Hemogram revealed 11g/dl with normal platelet (2,70,000/mm^3) and leucocyte count (7,800/mm^3). Serum calcium 7.7mg/dl, inorganic phosphate 2.3 mg/dl, parathormone 125pg/ml, alkaline phosphatase 1198 U/L, 25(OH) cholecalciferol increased, albumin, alanine transaminase, prothrombin time, activated partial thromboplastin time, magnesium levels were within normal limit. Fasting lipid profiles were normal except triglyceride 250mg/dl. Alpha fetoprotein 2.21 ng/ml, blood gas analysis showed pH 7.3, base excess -1, HCO3 16.5 mmol/l, anion gap 12.3. Ultrasonogram of whole abdomen showed hepatomegaly (liver span 9.38cm), right and left kidney normal in size and shape and there was no features of obstructive uropathy or nephrolithiasis or pyelonephritis. Plain xray KUB revealed normal. Urine routine examination revealed proteinuria (+), glycosuria (4+), pH 5.4, urine for reducing substance was nil, 24 hour urinary phosphate excretion 15.8mg/dl. Fasting blood sugar 3.6 mmol/l and 2 hours after breakfast 6.8 mmol/l. Spot calcium Creatinine ratio 2.02(excludes distal RTA). (Table-1) Radiograph of wrist and ankles showed features of active rickets (diffuse osteopenia, cupping, fraying and widening of metaphyseal ends) (Figure- 4). Ophthalmological evaluation showed no cataract. Liver biopsy revealed enlarged hepatocytes with abundant amount of granular cytoplasm which was periodic acid Schiff positive and diastase sensitive which is suggestive of glycogen storage disease. (Figure- 5,6). Genetic mutation analysis could not be done due to financial constraint.

She was treated with STOSS therapy 2 months back. After confirmation of the diagnosis we discharged the patient with counseling and treatment. Parents were advised to make some dietary modification like frequent small meals with adequate calories but intake of sugars (particularly glucose and galactose) was restricted from diet and advised to take uncooked cornstarch and high protein diet (2-2.5 g/kg/day). As unlike other ketotic form of glycogen storage disease, gluconeogenesis is impaired in FBS but protein can serve as an alternative energy source for muscles which helps to preserve blood glucose concentration. She was given joulie solution 50 mg/kg/day and calcium and vitamin D supplementation. She was advised to come for follow up after three months, unfortunately she was unavailable for follow up assessment due to shifting to another place.

Table 1: Investigations after admission.

Investiagation	Patient	Normal value
1. CBC: Hb	11.0 g/dl	11.5-16 g/dl
2. Calcium	7.7 mg/dl	8.3-10.6 mg/dl
3. Inorganic phosphate	2.3 mg/dl	2.3-4.7 mg/dl
4. Alkaline phosphatase	1198 U/L	145-420 U/L
5. Parathormone	125 pg/ml	18.6-88 pg/ml
6. 25(OH) cholecalciferol	126.19 ng/ml	20-50ng/ml
7. Tryglyceride	250 mg/dl	< 150 mg/dl
8. Arterial blood gas pH Base Excess HCO3 Anion Gap	 7.3 -1 16.5 mmol/L 12.3	 7.35-7.45 -2 - +3 22-30 mmol/L 12-16
9. Fasting blood sugar	3.6 mmol/L	3.5-5.5 mmol/L
10. 2 hours after breakfast	6.8 mmol/L	< 7.8 mmol/L
11. Urine R/M/E	pH-5.4 Protein (+) Glycosuria (4+)	4.5-8 Nil Nil
12. Urine for reducing substance	Nil	
13. 24 hour urinary phosphate	15.8 mg/dl	4.3-5.4 mg/dl
14. Spot urinary calcium: creatinine	2.02	0.11-0.22
15. Ultrasonogram of abdomen	No significant abnormality found.	
16. Plain X-ray KUB	No nephrocalcinosis	

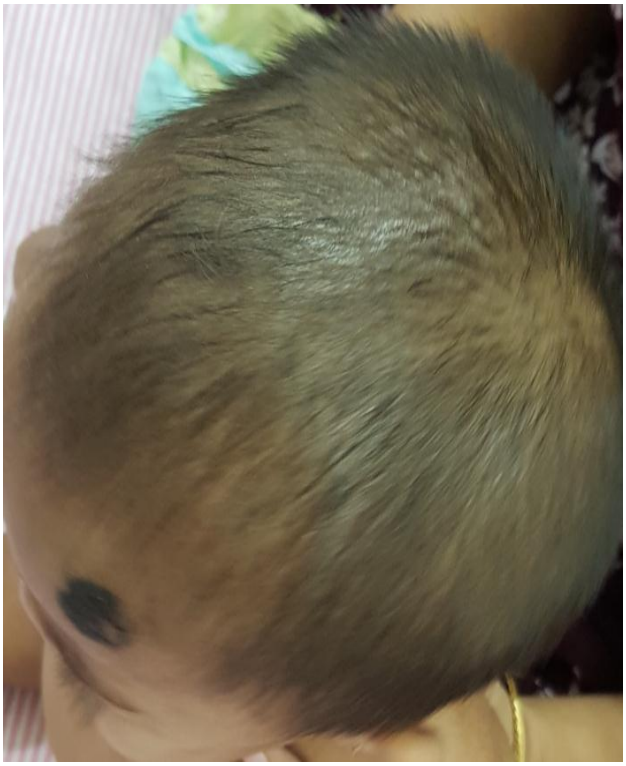

Fig 1: Box shaped head

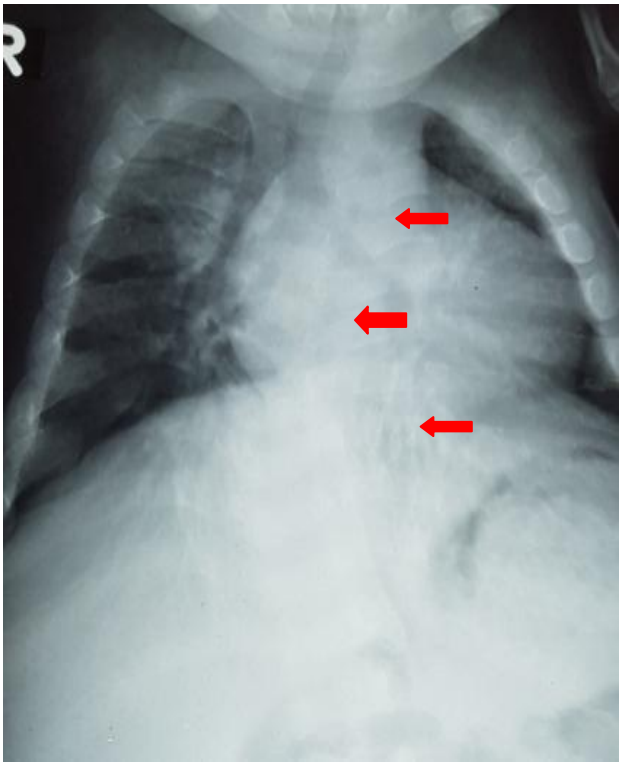

Fig 2: Scoliosis

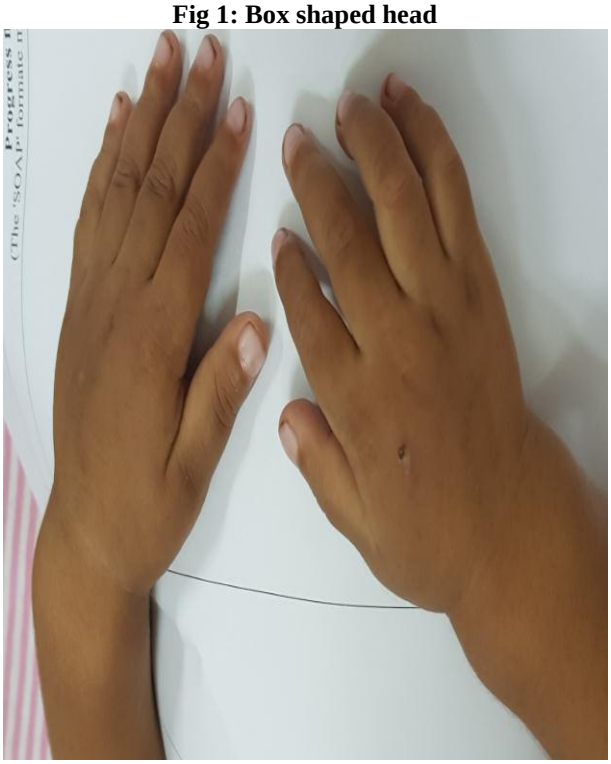

Fig 3: Widening of both wrist

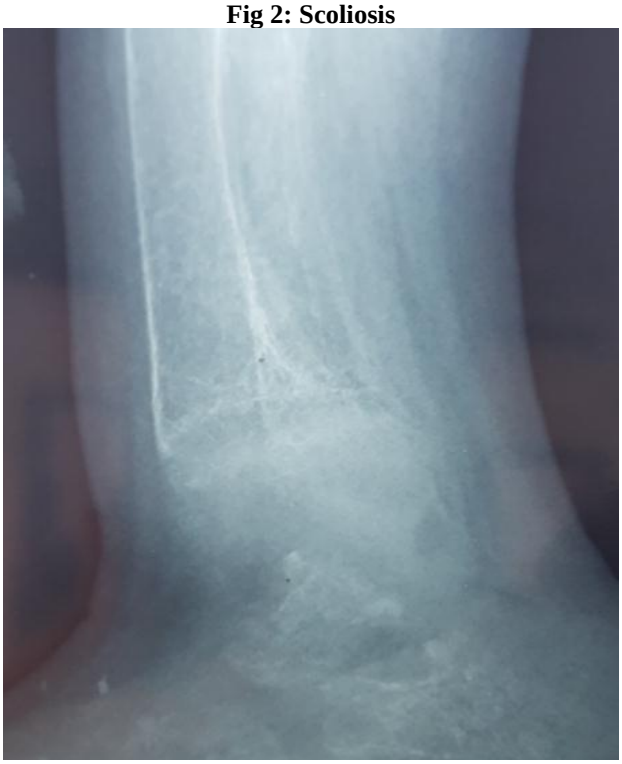

Fig 4: Cupping, fraying and widening of metaphyseal ends

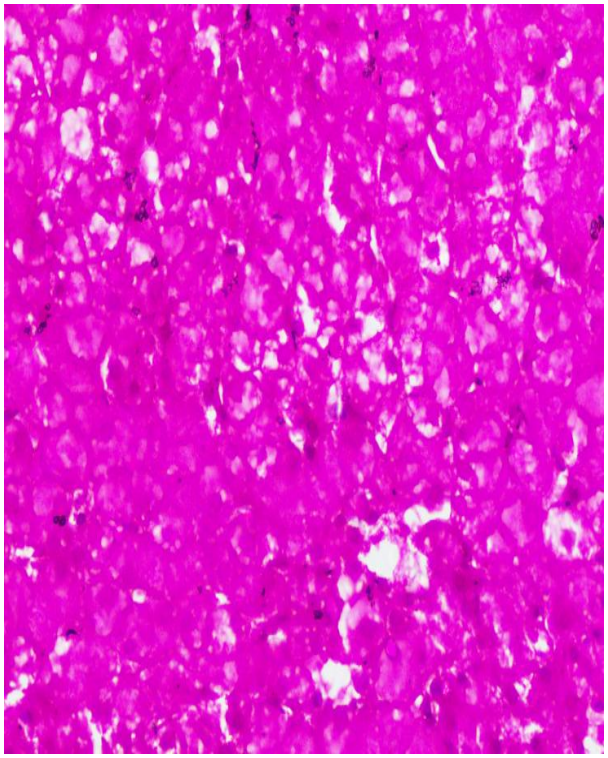

Fig 5: PAS positive liver tissue

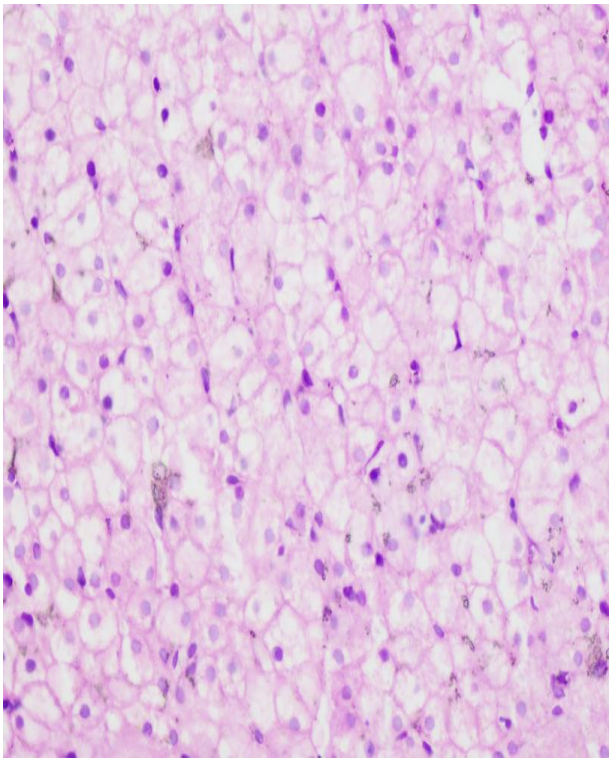

Fig 6: Diastase sensitive liver tissue

DISCUSSION

Fanconi-Bickel syndrome is a rare metabolic disorder of hepato-renal glycogen accumulation, proximal renal tubular dysfunction and impaired utilization of glucose and galactose, first described in 1949 by Guido Fanconi and Horst Bickel.[1,3]

Affected patients usually develop signs and symptoms of FBS during infancy[5] but the diagnosis is often delayed due to the protean nature of the symptoms[6]. Of note, the phenotypic features of FBS are heterogeneous and the sign and symptoms demonstrate an interfamily and intra family variability.[7-10] The initial symptoms may include chronic diarrhea, vomiting, growth failure and hypophosphatemic rickets which typically manifest between 3 and 10 months. The clinical signs and symptoms of FBS result from the impairment of both glucose and galactose utilization. Carbohydrate malabsorption with glucose or dairy products leads to the diarrhea. Impaired glucose transport out of the hepatocyte results in fasting hypoglycemia[11] whereas the decreased glucose uptake by the liver and hypoinsulinemia due to the altered sensitivity of pancreatic-β cells to glucose contribute to postprandial hyperglycemia.[12s] The accumulation of hepatorenal glycogen results in hepatorenomegaly and a protuberant abdomen. Although hypoglycemia is frequently present in patients with FBS, hypoglycemic seizures and mental retardation are rare since the hypoglycemia is associated with prominent ketosis.[5] With glycogen accumulation and failure to export intracellular glucose from the basolateral membrane of the proximal tubule, features of renal Fanconi syndrome manifest (glycosuria, impaired bicarbonate reabsorption, generalized aminoaciduria, phosphaturia, and hypophosphatemia). Ketosis, diarrhea, and proximal renal tubular dysfunction can result in chronic or recurrent acidosis that leads to skeletal buffering and demineralization. Marked phosphaturia will also promote rickets in children with hypophosphatemia.

There is no specific medical treatment. The administration of uncooked cornstarch has been reported to be beneficial on metabolic control and for promoting growth.[13] Puberty is delayed and after onset of puberty the hepatomegaly has been documented to recede.[2,14] Glomerular filtration rate remains normal or is slightly decreased.[1,14,15] Overall prognosis for survival to adulthood seems to be favorable. In recent times FBS has been diagnosed in neonatal screening programs measuring blood galactose in Guthrie test cards.[16] Due to phenotypic variability, FBS may be confused with other metabolic conditions. Features that FBS shares with GSDs include hepatomegaly, renomegaly, fasting ketotic hypoglycemia, postprandial hyperglycemia, and short stature.[17] Fasting hypoglycemia and postprandial hyperglycemia are also characteristics of GSD-0.[18] Myopathy (skeletal or cardiac) and central nervous system symptoms have not been described in patients with FBS, and their presence should suggest an alternate diagnosis. The presence of renal Fanconi syndrome will distinguish FBS from all GSDs except GSD-I. Additional distinguishing features present in GSD-I and absent in FBS include hyperuricemia, hyperlactatemia, and the presence of severe hyperlipidemia. Clinical findings related to proximal tubulopathy may dominate with concomitant growth restriction and hepatic abnormalities. As with the case presented in this report,

FBS can easily be misdiagnosed as renal tubular acidosis. Pathognomonic physical examination or biochemical findings can help distinguish FBS from others.[19]

With early and appropriate treatment, the overall prognosis is very good and survival to adulthood seems to be favorable. In addition to Fanconi and Bickel's original patient at least two more patients have reached adulthood in stable condition.[14] Missed or late diagnosis of FBS has been associated with higher rates of death due to liver failure and respiratory distress.[8,9,20] However, even in cases that are diagnosed late, proper dietary intervention should result in the reduction in the liver size and glycogen content.[14,21] and avoidance of liver transplantation.[22] Importantly, early diagnosis and proper treatment in young children accelerate growth in height and weight and improve cognitive function. The long-term benefits include successful fertility in affected males and females.[23,24] Unlike the other forms of GSD, hepatic adenoma, malignancies or cirrhosis has not been reported.

CONCLUSION

Fanconi-Bickel syndrome should be suspected in children with the supportive history (like consanguinity, abdominal distension due to hepatosplenomegaly, rachitic change in chest wall and distal ends of limbs, polyuria, polydipsia), examination, and laboratory findings, since early diagnosis and treatment can improve the quality of life and reduce end-organ damage. We should do meticulous follow up regarding growth rate, healing of renal and hepatic injury, improved activity level and well-being.

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