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Case Report

Paediatrics Section

"A Complex Conundrum"- Fanconi-Bickel Syndrome

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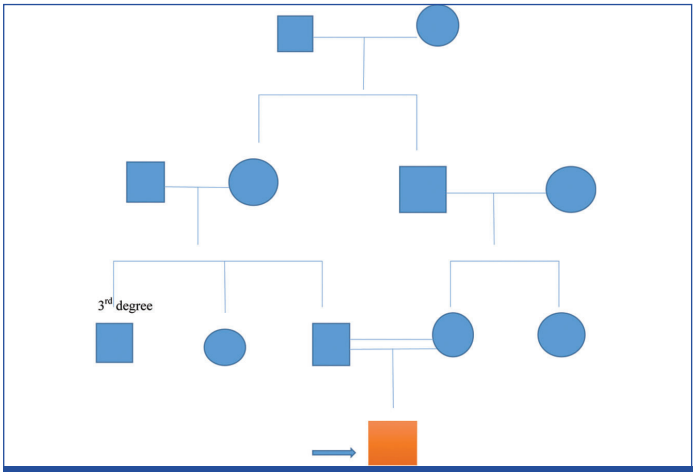
ABSTRACT

Fanconi-Bickel Syndrome (FBS) is a rare form of Glycogen Storage Disease (GSD) type 11 characterised by massive hepatomegaly due to the buildup of glycogen and severe hypophosphatemic rickets due to a proximal renal tubular dysfunction. Since 1940, it has been initially known as hepatorenal glycogenesis with proximal renal tubular dysfunction. It is due to a pathogenic mutation of the GLUT-2 (glucose transporter) gene. Herein, present case report a young toddler who is the firstborn of 3rd-degree consanguinity, presented with rickets, recurrent respiratory tract infections, and hepatomegaly, and was subsequently diagnosed with FBS with the help of genetic studies, showing a mutation in the GLUT-2 gene. With less than 200 cases reported so far, this child represents a unique case with recurrent respiratory infections and developmental delay as presentations along with rachitic features.

Keywords: Glycogen storage disorders, Hepatomegaly, Hypophosphatemia, Rickets

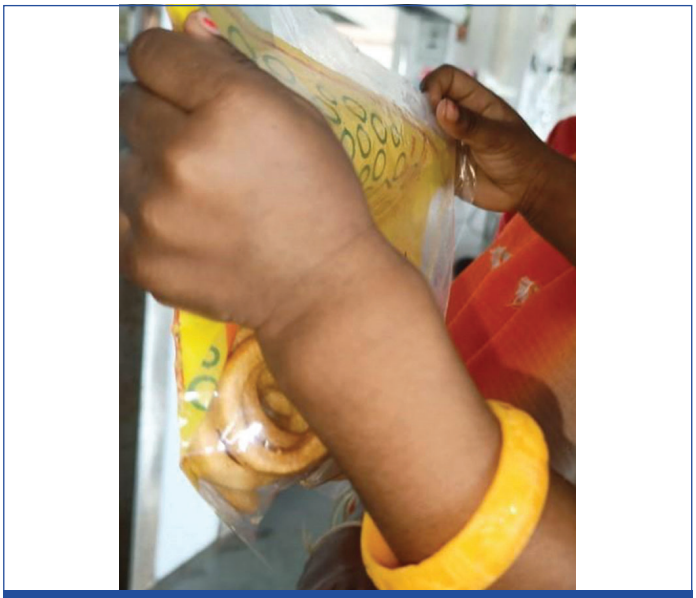
CASE REPORT

A two-year-old male toddler, the firstborn of 3rd-degree consanguinity, as shown in the family tree [Table/Fig-1], presented with fever and respiratory distress in the emergency department. He had three previous admissions, starting from the age of seven months for bronchopneumonia, with the last one being six months ago. During each episode, he presented with complaints of fever and fast breathing for two days, with respiratory distress, thereby requiring hospitalisation and intravenous antibiotics, along with five days. Further work-up revealed nutritional rickets secondary to vitamin D deficiency and predominant gross motor delay. The child is currently able to stand with support but with bowing of the legs, imitates scribbling, can speak in bisyllables, and imitate household tasks. The child's developmental age for motor milestones is nine months, while for fine motor skills, language, and social milestones, it is 1.5 years. He was initiated on daily calcium and vitamin D supplementation but was lost to follow-up.

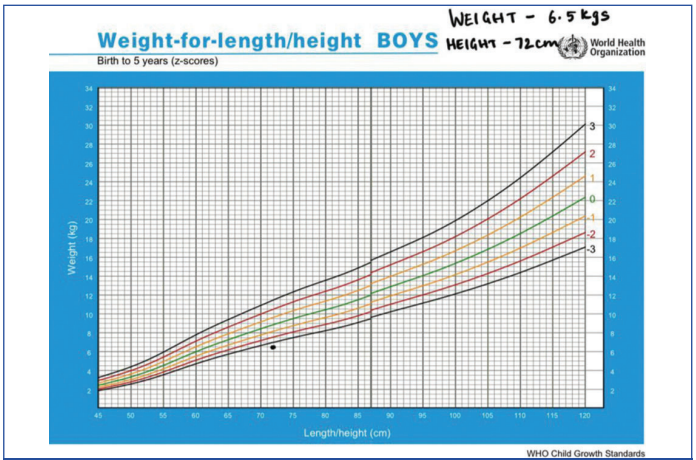


[Table/Fig-1]: Pedigree chart of the child. A 2-year-old male child, 1st born out of third-degree consanguinity, with no family history of similar complaints/illnesses.

Rachitic features like frontal bossing, wide-open anterior fontanelle, doll-like facies, and widening of the wrists [Table/Fig-2] were observed. Harrison sulcus and pectus excavatum were also present, along with tachycardia, tachypnoea, and an SpO_2 of 90% on room air. Capillary blood glucose was 70 mg/dL. The child's weight-for-age, height-for-age, and weight-for-height were all below the 3rd percentile [Table/Fig-3], with a mid-upper arm circumference of 11.5 cm, suggestive of severe acute malnutrition. There was no oedema, but the child exhibited hypotonia and firm hepatomegaly.



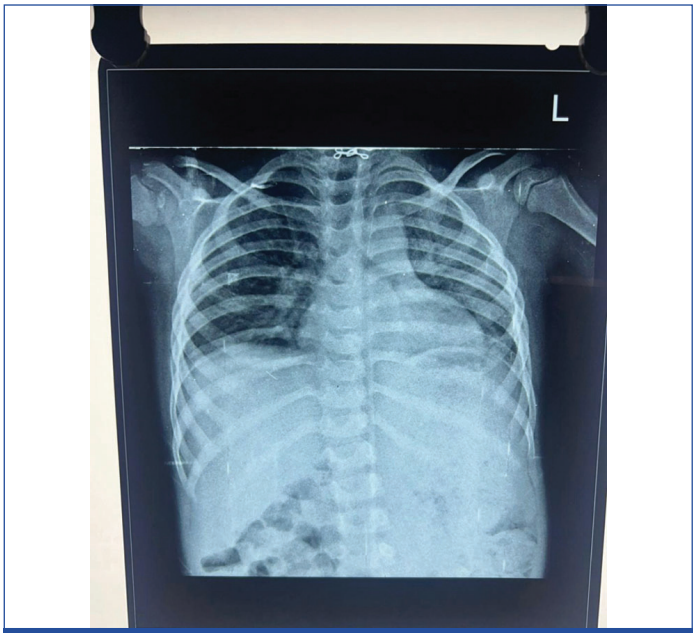
[Table/Fig-2]: Widening of the wrist noted in the child- a feature of rickets.



[Table/Fig-3]: Growth chart of the child showing weight for height <3rd centile- suggestive of severe acute malnutrition.

His laboratory studies showed serum calcium level of 9.8 mg/dL, serum phosphorus level of 1.9 mg/dL, 25-OH vitamin D level of 45.2 ng/mL, Alkaline Phosphatase (ALP) level of 500 IU/L, and intact parathyroid hormone (iPTH) level of 18 pg/mL, with normal renal and liver function tests. Serum albumin was 2.9 g/dL, and blood gas analysis showed a mixed respiratory alkalosis with a normal anion gap metabolic acidosis. Fasting blood glucose was 78 mg/dL, and postprandial blood glucose was 124 mg/dL.

The urine routine showed mild albuminuria and a positive Benedict test. The urine spot PCR result was 1.2. Other urine investigations, such as urine phosphate (51 mg/dL) and creatinine (16.8 mg/dL), were done, with fractional excretion of phosphate at -0.37, tubular reabsorption of phosphate at 63%, and TmP/GFR at 1.2 mg/Dl- all suggestive of renal phosphate wasting [1]. An X-ray showed left lower lobe pneumonia [Table/Fig-4], while the skeletal survey suggested rickets [2]. An ultrasound of the abdomen and Kidney, Ureter, and Bladder (KUB) displayed a liver span of 10 cm, with other solid organs appearing normal. A liver biopsy was not performed as the child's parents were unwilling. Due to financial constraints preventing the assessment of Fibroblast Growth Factor (FGF-23) levels, genetic analysis was preferred, which showed homozygous mutation c.1135T>C of exon 9 of the SLC2A2 gene, which encodes GLUT2 (FBS).



[Table/Fig-4]: Chest X-ray of the child showing left lower lobe consolidation.

Inborn errors of metabolism such as Gaucher's disease and Tay-Sachs disease were initially suspected because of a probable underlying metabolic cause but were ruled out through genetic testing. Glycogen storage diseases such as galactosemia and hereditary fructose intolerance were ruled out since the child did not exhibit gastrointestinal symptoms or feeding difficulties since birth. Biliary atresia was ruled out due to the absence of a prior history of jaundice. Although cystic fibrosis was considered, it was ruled out due to normal serum chloride levels and genetic testing, which could not be further pursued due to financial constraints. Fanconi syndrome (proximal renal tubular acidosis), familial hypophosphatemic rickets, and hereditary hypophosphatemic rickets with hypercalciuria were also contemplated due to similar clinical presentations and laboratory investigations but were ruled out by further evaluation.

The primary treatment involved a strict diet that restricts the intake of glucose and galactose, along with corn-starch, protein supplementation, and carbohydrate restriction, with regular monitoring of blood sugar levels. Symptomatic treatment included oral sodium bicarbonate during the hospital stay. The child was evaluated for hypophosphatemic rickets and started on oral phosphorus supplementation at 2 gm/day, maintaining euglycaemia throughout admission. Genetic Counselling was given to the parents, outlining the risks in future pregnancies and potential episodes of hypoglycaemia in the child. Regular monitoring for appropriate growth and development, with a focus on physiotherapy and occupational therapy, was emphasised.

DISCUSSION

The FBS is a rare form of GSD type 2 inherited in an autosomal recessive mode, characterised by massive hepatomegaly due to build-up of glycogen and impaired utilisation of glucose and galactose [3], and severe hypophosphatemic rickets due to a proximal renal tubular dysfunction [4]. Since 1940, it has been initially known to as hepatorenal glycogenesis with proximal renal tubular dysfunction.

In a case report by Santer R et al., GLUT 2 mutations were the first identified congenital defects within a family of membrane proteins known as facilitative glucose transporters. In 1997, they reported a total of 109 cases from 88 families worldwide diagnosed with FBS [5]. As no underlying enzymatic defect in carbohydrate metabolism had been identified and because the metabolism of both glucose and galactose is impaired, a primary defect in monosaccharide transport across membranes has been suggested. It occurs due to mutations in the SLC2A2 gene on the 3rd chromosome, which encodes the GLUT 2 transporter [6]. This transporter is responsible for glucose transport across cellular membranes in the liver, pancreas, proximal renal tubular cells, and the basolateral side of enterocytes in an insulin-independent fashion. As a result of the defective glucose transport leads to symptoms stemming from proximal renal tubular dysfunction, liver enlargement due to glycogen accumulation, fasting hypoglycaemia, and growth retardation [7].

Roy M et al., presented a case in which they diagnosed FBS based on characteristic clinical features, supported by biochemical, radiological, and histopathologic evidence from a liver biopsy, along with genetic mutation [1]. With less than 200 reported so far, this child represents a unique case with recurrent respiratory infections and developmental delay as initial presentation along with rachitic features.

Typically presenting between two months and two years of age, index patient presented as a toddler with signs of hypophosphatemic rickets and failure to thrive. The doll-like facies, failure to thrive, and low capillary blood glucose levels raised suspicions of a glycogen storage disorder. Diagnosing FBS can be challenging due to its heterogeneous clinical features, and children may be misdiagnosis or treatment for isolated disorders like rickets [8].

The clinical dilemma presented by this child is the recurrence of lower respiratory tract infections, even after correcting Vitamin D deficiency. Vitamin D deficiency is known to predispose individuals to bronchopneumonia [9]. However, the normal levels of Vitamin D in this case raise suspicion that recurrent lower respiratory infections may be an isolated presentation of glucose-deprived epithelial cells in the respiratory tract and subsequent deficiency in clearing.

Early diagnosis and dietary intervention are crucial for optimal outcomes. In cases diagnosed later, appropriate treatment in the form of restricted dietary glucose intake can lead to a reduction in liver size and glycogen content [10]. Early diagnosis has become feasible with the help of whole exome sequencing, which should be considered in children presenting with hypophosphatemic rickets and organomegaly, requiring multiple admissions, in a background of consanguineous marriage with a positive family history. Many individuals diagnosed with FBS exhibit abnormalities in blood sugar regulation, including postprandial hyperglycaemia, fasting hypoglycaemia, glucose intolerance, and occasionally diabetes mellitus [11]. The specific role of human GLUT2 in pancreatic β-cell function remains uncertain, although the occurrence of transient neonatal diabetes in some cases suggests potential involvement during the neonatal period. Additionally, the consistently low

birth weights observed in nearly all reported FBS cases hint at a possible role of GLUT2 in foetal insulin regulation [12].

Currently, there are no pharmaceutical treatments targeting the underlying molecular defects in GLUT2 for patients with FBS, making the management of these individuals clinically complex. Further research focusing on the functional aspects of GLUT2 in various human cell types, including pancreatic β-cells, liver cells, enterocytes, kidney cells, and brain cells, is necessary to gain a deeper understanding of the molecular mechanisms underlying dysglycaemia in FBS [13]. Such insights could pave the way for the development of precision medicine strategies tailored to the specific molecular dysfunctions associated with GLUT2 in FBS. Index patient showed a response to therapy, and the overall prognosis for individuals with FBS is favourable, especially with early and appropriate treatment. The child should be regularly monitored for appropriate growth and development, with an emphasis on physiotherapy and occupational therapy. Regular monitoring of liver and renal function tests will be necessary. With proper monitoring of parameters, individuals with FBS can have a normal life expectancy.

CONCLUSION(S)

This case underscores the importance of considering metabolic disorders in the context of failure to thrive to ensure timely diagnosis and intervention. It is essential to further evaluate other causes of rickets that do not respond to adequate vitamin and calcium supplementation. Diagnosing the type of hypophosphatemic rickets will help us decide on the use of calcitriol along with phosphorus supplementation.

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