CASE REPORT

A case of fanconi bickel syndrome with atypical presentation: A novel mutation

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ABSTRACT
Fanconi Bickel Syndrome (FBS) is a rare autosomal recessive disorder It is caused by homozygous or compound heterozygous mutations in GLUT2, the gene encoding facilitative glucose transporter in hepatocytes, pancreatic beta-cells, enterocytes, and renal tubular cells. To date, 112 patients have been recorded in the literature. Most patients exhibit the classic symptoms, including hepatomegaly due to glycogen buildup, glucose and galactose intolerance, fasting hypo-glycemia, tubular nephropathy and stunting.[1] Here we report a case of Fanconi Bickel syndrome with rare mutation which presented with hyperphosphatemia and no episode of hypo-glycemia. Diagnosis was made on the basis of clinical suspicion and confirmed by genome sequencing.

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INTRODUCTION

Fanconi-Bickel Syndrome (FBS; OMIM 227,810), a rare autosomal recessive disorder of carbohydrate metabolism was first described by Fanconi and Bickel in 1949 when they identified tubular nephropathy and glycogen storage disease in a Swiss boy. Failure to thrive, hepato-renal glycogen accumulation , fasting hypo-glycemia followed by postprandial hyper-glycemia, proximal tubular nephropathy as evidenced by glycosuria, phosphaturia, aminoaciduria, and hypophosphatemia along with rickets are common features at presentation[2]. Recently rare storage disorders are being increasingly reported.[3] Because the presentation varies, a high level of suspicion is required to diagnose these cases. It is mostly based on clinical symptoms, radiographic and biochemical characteristics of rickets, laboratory data of renal tubular failure, and the resulting metabolic acidosis and glycogen accumulation in the liver or renal biopsy. In india women choose to deliver at home, which further deprives them of proper health care counselling regarding dander signs of childhood illness so further delaying the hospital admission.[4]The existence of a pathogenic mutation in SLC2A2 confirms the diagnosis but 34 distinct GLUT2 mutations have been found through mutation analysis[3]. The treatment of this complex disease is primarily supportive and targeted at managing acid-base imbalances, glucose metabolism, and rickets. As recent studies have shown that breastmilk is protective for children even when applied orally, further relation with this disease need to be studied.[6]

CASE REPORT

A 3 yearold male child born via normal vaginal delivery with uneventful antenatal , natal and postnatal period presented with complaints of fever, difficulty in breathing,photosensitivity ,loose stools, polyuria and vomiting . History of consanguinity was present in the family along with history of sibling death on day 2 of life, details of which are not known. On examination, our patient had facial dysmorphism (saggy cheeks, upward slanting palpebral fissures), microcephaly (head circumference 49cms, less than -3SD), severe stunting (height 97cms , less than -3 SD) , genu valgum, harrison sulcus and sandal gap . Patient had pallor and bitotsspot. Liver was palpable 2cm below coastal margin (left lobe palpable) and no splenomegaly. Ophthalmic examination revealed presence of corneal and conjunctival xerosis along with photosensitivity . Blood pressure was 108/74 mm of Hg which was more than 95th centile. Patient was given symptomatic management along with IV Antibiotics. Serial RBS monitoringdid not revealany hypo-glycemia events.Differential diagnosis of Hepatic GSD, Fanconi Bickle syndrome and oligosaccharidosis was made at this point.Patient had severe anemia , Hb was 4.8 gm%, TLC was raised and

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platelets were adequate in number. Serum creatinine levels were high throughout the hospital stay with the highest reading being 1.6mg / dL. Patient had hyponatremia and hyperkalemia. Urinary protein was within normal range. Serum lactate, phosphate, PTH and vitamin D3 levels were increase. USG whole abdomen was suggestive of B/L echogenickidney.ABG was suggestive of Compensated Respiratory Alkalosis with Metabolic Acidosis. Chest X-ray showed B/L heterogenous infiltrates. Patient responded to treatment and gradually patient condition improved and was thus discharged on oral medications. Patient was also advised to do skeletal survey and clinical exome sequencing . Xray radiograph showed classical changes suggestive of rickets.(fig 1,2 &3)

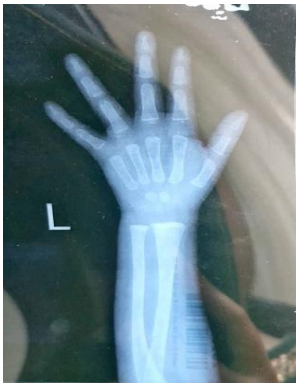

Figure 1: Xray Left hand showing cupping of metaphysis, widening of epiphyseal plate, white line of Frankel

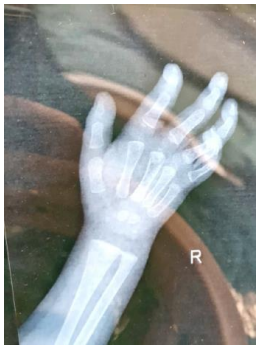

Figure 2: Xray Right hand showing cupping of metaphysis, widening of epiphyseal plate, white line of Frankel

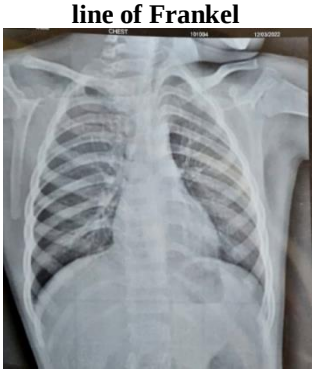

Figure 3: Chest Xray PA view showing B/L infiltrates.

Genome sequencing showed heterozygous missense mutation in exon 11 of the KIF11 gene (chr10g.94388636A-C; Depth: 95x) that results in the amino acid substitution of Alanine for Glutamic acid at codon 430 (p.Glu430Ala: ENST00000260731.3) was detected . It has autosomal dominant inheritance which was different from the inheritance pattern found in majority of population The mutation in this gene is associated with microcephaly (mild to severe) with or without chorioretinopathy, lymphedema or developmental delay along with characteristic facial phenotype with upslanting palperbral fissure, broad nose with rounded tip, prominent chin and prominent ears. Due to partial phenotype match and lack of literature evidence, this KIF-11 variation was classified as variant of uncertain significance. Genetic counselling was advised in parents and other affected members, if any. Now the patient is kept in follow up care for supportive management.

DISCUSSION

Fanconi-Bickel syndrome is a rare type of glycogen storage disease (GSD). The gene GLUT2, which codes for the primary facilitative glucose transporter in hepatocytes, pancreatic beta-cells, enterocytes, and renal tubular cells, is the source of the mutations in most cases.. The majority of patients present with a typical set of clinical signs, including stunting , tubular nephropathy, glucose and galactose intolerance, hypoglycemia during fasting, and hepatomegaly due to glycogen accumulation. In the case that we are reporting patient had no episode of hypoglycemia and the mutation was seen in KIF11 gene which is a rare missense mutationwhich is classified as variant of uncertain significance. The management of this disease consists of supportive measures aimed at treating acid-base disequilibrium and rickets. Patients respond very well to treatment and timely corrections is necessary; nevertheless, long-term follow-up is required to assess their growth and puberty further.

CONCLUSIONS

Fanconi Bickel syndrome is a disguised glycogen storage disorder which usually gets un-noticed due to clinicians chasing the symptoms of rickets rather than focusing on the bigger clinical picture. To confirm this diagnosis genome sequencing is the key but it can only be made possible when a high level of suspicion is made based on classical features including dysmorphic facies, stunting, global developmental delay ,hepatomegaly and hypoglycemia. But while we deal with this complex disease we should always keep an eye for any atypical manifestations and mutations like we report in our case.

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