Novel fructose bisphosphatase 1 gene mutation presenting as recurrent episodes of vomiting in an Indian child

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ABSTRACT
Fructose-1, 6-bisphosphatase 1 (FBP1) deficiency is an autosomal recessive disorder of gluconeogenesis resulting in severe and recurrent life-threatening episodes of hypoglycemia and lactic acidosis in infancy. We report a 16 month-old girl who presented with recurrent episodes of vomiting, rapid breathing, lactic acidosis, hyperuricemia, and hypertriglyceridemia. Genetic analysis revealed a novel compound heterozygous mutation in FBP1 gene confirming the diagnosis of FBP1 deficiency. The patient was managed with treatment of acute episodes and preventive long-term dietary modifications. Long-term prognosis of FBP1 deficiency is excellent underlining the importance of early recognition of clinical signs, prompt diagnosis, and avoidance of fasting in this disease. FBP1 gene mutations have been described from various ethnic backgrounds, but there is limited data available from Indian population, hence the importance of this case.

KEY WORDS: Enzyme defect, fructose 1,6-bisphosphatase deficiency, genetic mutation, gluconeogenesis, recurrent vomiting

Introduction
Fructose 1,6-bisphosphatase (FBPase) deficiency, a rare enzymatic defect of hepatic gluconeogenesis, first described by Baker and Winegrad (1970), is characterized by episodic spells of hypoglycemia, ketosis, and lactic acidosis.[1] Human FBPases are coded in two distinct genes, namely, FBP1 and FBP2. Since Kikawa et al. identified three different FBP1 gene mutations in Japanese patients, more mutations are being reported from other ethnic backgrounds.[2] We describe a case of young girl who presented with recurrent vomiting and lactic acidosis and had novel compound heterozygous FBP1 gene mutation.

Case Report
A 16-month-old girl presented with complaints of vomiting and fast breathing for 1 day. There was no history of fever, cough, diarrhea, abdominal distension, and jaundice. She had history of recurrent admissions with similar complaints for 5 months of age. She was first born of a nonconsanguineous marriage with an uneventful neonatal period and normal developmental milestones.

On examination, she was lethargic with pulse rate 92/min, respiratory rate 56/min, and blood pressure 96/70 mmHg with no signs of dehydration. Her weight (9.3 kg) and height (77 cm) corresponded to the 25th–50th centile on the WHO charts. Per abdomen, nontender, firm hepatomegaly was present 3 cm below right costal margin. Rest of general physical and systemic examination was within normal limits.

Laboratory workup showed hemoglobin 12.5 mg%, total leukocyte count 7800 cell/mm3, blood sugar 84 mg/dl, mildly deranged liver enzymes, normal kidney function tests, and mild ketonuria (1–2+). Venous blood gas revealed high anion
gap (AG) metabolic acidosis (pH = 7.1, HCO$_3^-$ = 15.1 mEq/L, AG = 20 mEq/L (range 8–16 mEq/L)) with high serum lactate levels (53.6 mg/dl, normal 7–14 mg/dl). Ultrasound showed mild hepatomegaly with normal echotexture. Both serum lactate (18.94 mmol/L, normal 0.6–3.2 mmol/L) and cerebrospinal fluid lactate (9.6 mmol/L, normal 1.1–2.8 mmol/L) were elevated with normal blood lactate-to-pyruvate ratio (12.3:1). Blood tandem mass spectrometry and urine metabolic screen was normal with no organic aciduria in urinalysis chromography-mass spectroscopy.

She was managed with intravenous maintenance fluids and sodium bicarbonate with marked clinical improvement within 36 h. She was discharged on parenteral pending further work-up. Two weeks after discharge, she presented again with generalized convulsions and rapid breathing. There was a history of prolonged fasting for 8–10 h before this episode. Mild tachypnea and hepatomegaly were the only findings in otherwise normal clinical examination. On investigation, she had hypoglycemia (21 mg/dl) with high anion gap metabolic acidosis (pH = 7.0, HCO$_3^-$ = 18.1 meq/L, AG = 16 meq/L) and high serum lactate (19.8 mmol/L). Laboratory workup ruled out possibility of infection or meningitis and revealed hyperuricemia (12 mg/dl), hypertriglyceridemia (196 mg/dl), and hypercholesterolemia (176 mg/dl). She improved within 24 h on 25% dextrose, anti-epileptics, intravenous fluids, sodium bicarbonate, and oral allopurinol. A differential diagnosis of FBP1 deficiency or glycogen storage disorder type 1 (GSD1) was considered.

In view of mild hepatomegaly with normal echotexture on ultrasound, a molecular analysis was planned first. The molecular analysis of all the coding exons of FBP1 gene revealed a compound heterozygous mutation IVS4-1G>A (c.426 + 1G>A) in exon 3 and mutation c.611_614delAAAA in exon 6, confirming the diagnosis of FBPase deficiency. The molecular analysis of parents revealed heterozygous mutation in one gene each, making both of them a carrier (Father - heterozygous for c.611_614delAAAA and Mother - heterozygous for IVS4-1G>A [c.426 + 1G>A]), for which they were given appropriate genetic counseling. The patient was given preventive feeding advice including frequent feeding, avoiding fasting, and foods with high fructose:glucose ratio (grapes, apples, cherries, and honey) and to use more uncooked starch such as rice powder in her diet. On follow-up, she was found to have normal growth and development with normalization of metabolic parameters and decrease in her liver size.

### Discussion

Gluconeogenesis is an important pathway for maintaining glucose homeostasis particularly during newborn period, fasting, and low carbohydrate diet intake. FBPase enzyme is rate-limiting enzyme of hepatic gluconeogenesis which converts fructose-1,6-diphosphate to fructose-6-phosphate. Earlier confirmatory diagnosis of FBPase deficiency was based on enzymatic activity assay on liver biopsy specimens or in cultured leukocytes. However, it has now been replaced by molecular analysis of FBP1 gene. FBP1 gene is localized on chromosome 9q22.2-q22.3 and codes for FBP1 enzyme identified as P09467 (NM_000507; transcript id ENST00000375326.8). It consists of seven coding exons spanning >31 kilobases and six introns. The sequence AAC50207.1 in exon 1 is used for erroneous gene model prediction. Homozygous and heterozygous mutations in FBP1 gene were first studied in Japanese population.[3] The homozygous mutation with one G residue insertion at base 961 in exon 7 (c.960/961insG), resulting in a reading frameshift mutation of the 320th amino acid and premature termination at the 333rd amino acid has been reported as the most common FBP1 mutation.[4] Studies describing mutations across various ethnic populations are listed in Table 1. In our case, a compound heterozygous mutation in exon 3 and exon6 was reported as the cause of FBPase deficiency which has not been described previously.

FBP1 deficiency manifests within the first week of life in 50% of affected children or within the first year of life in remaining.[5] In neonatal period, it manifests as life-threatening episodes of hypoglycemia, metabolic acidosis, hyperventilation, convulsions, and coma. FBP1 deficiency beyond neonatal life has been often misdiagnosed as sudden infant death syndrome or Reye’s syndrome.[11] The classical presentation

### Table 1: List of fructose 1,6-bisphosphatase mutations reported till date[2,4-11]

| Authors and study | Population | Mutation |
|------------------|------------|----------|
| Kikawa et al[5] 1997 | Japan (13 patients) | 960-961 G insertion in exon7 |
|                    |            | G→A transition base 490 exon 4 (G164S) |
|                   |            | C→A transition base 530 exon 4 (A177D) |
|                   |            | G→T transition base 88 exon 1 (E30X) |
| Herzog et al[6] 1999 | Germany/ Turkey/ Iran and Pakistan (4 patients) | 35delA in exon 1 |
|                    |            | 778G→A in exon and |
|                   |            | 966delC in exon 7 |
| Herzog et al[7] 2001 | European/North American origin (17 patients) | 881G→T (G294V) |
|                    |            | 704-705insC (frameshift) |
|                    |            | 807delG (frameshift), and |
|                    |            | 639C>G (N213K) |
| Matsuura et al[8] 2002 | Japan (1 patient) | 581T-C transition in exon 5 (F1945S) |
| Faiyaz-ul-Haque M et al[9] 2009 | Saudi Arabia (17 patients) | Six nucleotide repetitive insertion c114_119dupCTGCAC |
|                    |            | c.841G>T |
| Asberg C et al[10] 2010 | Sweden (4 patients) | c.778G>A |
|                    |            | c.881G>A |
| Moon S et al[11] 2011 | Korea (1 patient) | Compound heterozygote for the G164S (exon 4) and 838delT (exon 7) |
| Eren E et al[11] 2013 | Turkey (2 patients) | c.658delT mutation in exon 5 |
| Afroz B et al[11] 2013 | Pakistan (4 patients) | c.841G>A in exon 7 |
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FBP1 deficiency patients experience normal health in between the illness episodes that tend to decrease with age, differentiating it from mitochondrial disorders. In FBP1 deficiency, hepatomegaly is mild and transiently present during the metabolic crisis in contrast to GSD1 where a young infant presents with huge firm hepatomegaly with severe and refractory hypoglycemia, lactic acidosis, and other features. Long-term prognosis of FBP1 deficiency is excellent. With early diagnosis and preventive feeding therapy, majority of cases exhibit normal somatic and psychomotor development with case report of successful pregnancy in one of the affected patients. The only published case report from India also highlight a good long-term outcome with simple dietary interventions.

Conclusion

FBPase deficiency is a rare but important cause of lactic acidosis with hypoglycemia having good prognosis when diagnosed and managed promptly. Our study highlights the natural course of this rare disease along with a compound heterozygous mutation determined by FBP1 analysis, which has not been previously defined making it the first reported novel FBP1 gene mutation from India.

Declaration of patient consent

The authors certify that they have obtained appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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