Fructose 1,6 bisphosphatase (fbpase) deficiency

Novel Fructose 1, 6 bisphosphatase gene mutation presenting as recurrent vomiting in an Indian child

Abstract:

Fructose 1, 6 bisphosphatase(FBPase) deficiency is an autosomal recessive disorder of gluconeogenesis resulting in severe metabolic attacks of hypoglycaemia and lactic acidosis. It often presents as recurrent life threatening hypoglycaemic episodes in infancy. We here report a sixteen month old girl who presented with recurrent episodes of vomiting, fast breathing, lactic acidosis, hyperuricemia and hypertriglyceridemia. The initial episodes were however not associated with hypoglycaemia, which developed during the later episodes. Genetic analysis revealed a novel compound heterozygous mutation in FBP1 gene confirming the diagnosis of FBPase deficiency. Mutations in FBP1 gene have been previously described from various ethnicities but there is limited data available from Indian population, hence the importance of this case.

Introduction:

Fructose 1, 6 bisphosphatase deficiency is a rare enzymatic defect first described in 1970 by Baker and Winegrad (1). It is characterized by episodic spells of hypoglycemia, ketosis and lactic acidosis and is often lethal during neonatal period and infancy. Fasting and febrile infectious diseases are known to trigger these symptoms [2]. Fructose-1, 6- bisphosphatase, which catalyzes the splitting of fructose-1, 6-bisphosphate (FBP) into fructose 6-phosphate and inorganic phosphate, is a key enzyme in the regulation of gluconeogenesis [2]. The enzyme is most active in the intestine and liver.

Human FBPases are coded in 2 distinct genes, namely FBP1 and FBP2. Since Kikawa et al [2] identified 3 mutations of FBP1 responsible for FBPase deficiency in 10 Japanese patients, other FBP1 mutations have been reported in patients with other ethnic backgrounds. Here we describe a novel compound heterozygous germline mutation in FBP1 gene responsible for FBPase deficiency in a young Indian girl.

Case report:

A sixteen month old girl child, born out of non consanguineous marriage, presented to our hospital with complaints of vomiting and fast breathing for 1 day. There was no associated history of fever, cough, loose motions, abdominal distension, jaundice or lethargy. There was a significant history of recurrent hospital admissions in the past with similar signs and symptoms starting at 6 months of age. Prior to that, her neonatal and early infancy period was uneventful. The physical examination on admittance revealed her weight and height to be at median centiles, with dry mucosa, tachypnea, acidotic breathing, hepatomegaly and lethargy. The laboratory workup showed normoglycemia with high anion gap metabolic acidosis, high serum lactate, slightly raised alanine aminotransferase(ALT) and elevated serum triglycerides. Urine analysis was positive for ketonuria but did not show presence of any organic acids on gas chromatography (GCMS). The patient responded to intravenous glucose infusion and sodium bicarbonate with marked clinical and biochemical improvement within 48 hours. Further work-up for lactic acidosis was planned and patient was discharged. The patient was lost to our follow-up for one year as she had gone back to her hometown. She gave a history of 3 similar episodes during this one year

each of them associated with normoglycemia and lactic acidosis as documented on her discharge papers. In between the episodes she was well and growing normally. There were no features suggestive of hepatic failure, no specific aversion or precipitation of illness by any particular food. At two and a half years of age she presented with one episode of convulsion, not associated with any fever or vomiting. There was a significant history of prolonged fasting for 8-10 hours prior to this episode. During the present episode, she was found to be severely hypoglycaemic along with hyperuricemia in addition to her previous findings. A diagnosis of fructose1, 6 bisphosphatase deficiency was suspected and genetic study for mutation analysis was planned. The molecular analysis of FBP1 gene revealed a novel compound heterozygous mutation IVS4-1G> A in exon 3 and mutation c. 611_614delAAA in exon 6, confirming the diagnosis. The patient was managed with intravenous fluids and sodium bicarbonate infusion. The patient was advised avoidance of fasting and restriction of fructose and glucose in diet. On follow-up, she was found to have normal growth and development for her age with normalization of her metabolic parameters and a decrease in the size of her hepatomegaly.

Discussion:

Fructose 1, 6 bisphosphatase is a focal enzyme in gluconeogenesis which permits endogenous glucose production from gluconeogenic amino acids (eg, alanine and glycine), glycerol, or lactate, via its conversion of fructose 1, 6-diphosphate (FDP) to fructose 6-phosphate (F-6-P). This gluconeogenic pathway is extremely important for maintaining glucose homeostasis in newborn period and during fasting, starvation, low carbohydrate diet and

exercise in more advanced ages. Clinical signs have been reported to manifest within the first week of life in 50 % of affected children and within the first year of life in the remaining patients (3). In the neonatal period, it manifests as life threatening episodes of hypoglycemia, metabolic acidosis, hyperventilation, convulsions and coma. Undiagnosed, the outcome is usually fatal and it has been suggested that a significant high proportion of deficient FBPase have been misdiagnosed as sudden infant death syndrome or Reye’s syndrome.(4)

The classical presentation in older children consists of recurrent attacks of hypoglycemia and metabolic acidosis complicated with hyperventilation, apnea, ketosis and glyceroluria. Though hypoglycemia has been described as a classical finding, rarely these children may present with normoglycemia (as seen in initial episodes of our patient) or even hyperglycemia with acidosis (5). The physical findings include mild transient hepatomegaly during metabolic crisis, which promptly resolves on administration of intravenous dextrose. Patients experience normal health in between attacks which tend to decrease with age. With early diagnosis and preventive therapy, majority of cases exhibit normal somatic and psychomotor development with case report of a successful pregnancy in one of the affected patients (6).

The confirmatory diagnosis is usually based on the low hepatic enzymatic activity assay on liver biopsy specimens. Recently enzymatic activity assay have also been reported from cultured monocytes or leucocytes (2). However it has now been replaced with mutation analysis of FBP1 gene following its recent identification on chromosome 9q22. 2-q22. 3 in 1995(7). FBP1 gene consists of 7 exons, spanning more than 31 kilobases, and

expresses a 362–amino acid protein, mainly in the liver. Homozygous and heterozygous mutations have been determined in various studies, with 1 bp insertion in FBP1 gene defined as the one most commonly encountered (2, 7, 8, 9). In our case the mutation identified is a compound heterozygous mutation not defined previously in any of the studies.

Conclusion:

Long term prognosis of FBPase deficiency is excellent underlining the importance of early recognition of clinical signs, prompt diagnosis and avoidance of fasting in this disease. 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 itthe first reported novel FBP1 gene mutation in our country.