ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS

Case Report

Fructose 1, 6 Diphosphatase Enzyme Deficiency, Unrevealed Cause of Hypoglycemia

Saima Asghar* and Ahmad Abdullah

Consultant Pediatrics and Neonatology, Zubaida Memorial Hospital, Pakistan

***Corresponding Author:** Saima Asghar, Consultant Pediatrics and Neonatology, Zubaida Memorial Hospital, Pakistan.

Received: June 06, 2022; **Published:** June 22, 2022

Abstract

Hepatic fructose 1, 6-diphosphatase (FDPase) is one of the four rate limiting enzymes in gluconeogenesis. While investigating a four year old girl with chronic lactic acidosis and fasting hypoglycemia, evidence was accumulated which implicated a defect in hepatic gluconeogenesis by a deficiency of FDPase activity. Rational dietary therapy was instituted which has controlled the recurrence of chronic lactic acidosis and permitted normal mental and physical development. Deficiency of hepatic FDPase was first confirmed in 1970 by Baker and Winegrad. They reported the dramatic clinical picture of acidosis in response to D-fructose challenge [1]. The gene encoding FDPase was reported in 1995 [2,3] and several mutations resulting in loss of function have subsequently been reported in American and Japanese patients [4-6].

Keywords: *Fructose 1, 6 Bisphosphatase (FBSpase); Hypoglycemia; Lactic Acidosis; Molecular Genetics*

Introduction and Case Report

This case report is about four year old Saleha, female, parents consanguineous marriage, delivered vaginally after full term pregnancy, who remained well till 8 month of life. History of 2 siblings death during infancy. Her weaning was started with fruits at this stage and after few days she developed irritability, lethargy, and sweating after ingestion of fruits. Mother noticed that her symptoms, improved with mother feeding. She exhibited normal physical development on dietary regimen of demand breast feeding and gradual introduction of fruits and other canned baby food. In 2 years she exhibited repeated episodes of rapid breathing, lethargy, sweating, loose motions and vomiting which necessitated multiple admissions to local hospitals, patient was given symptomatic treatment every time and was discharged.

After 6 months being well, she presented with similar symptoms. On examination she was dehydrated, tachypneic and lethargic, head circumference of 47 cm (below 5th centile), Height of 80 cm (below 5th centile), weak pulses, dry coated tongue, Liver was palpable 4 cm below costal margins with normal consistency and regular margins.

Lactate level	11 mM
Uric acid	8.8 mg/dl
Triglyceride level	573 mg/dl
Cholesterol	188 mg/dl
Glucose	30 mg/dl
Na^+	143 meq/l
K^+	4.1 meq/l
Cl^-	95 meq/l
Anion gap	27

Hb	10 mg/dl
Hematocrit	30%
WBC's	11,000/mm^3
Platelets	300,000/ mm^3
Differential count	Normal
Total bilirubin	0.6 mg/dl
Serum Alanine transaminase	21 U
Serum gamma glutamyl transaminase	24 U
Coagulation profile	Normal
Total proteins	4.5 g/dl
Blood urea	19 mg/dl
Creatinine	0.67 mg/dl
Urine pH	6.0
Urinary reducing substances	Negative
Urinary ketones	Positive+++
Blood pH	7.1
Blood $C0_2$	24.0 mmHg
Blood bicarbonate level	7.1 mmol/l
Urinary organic acid profile (glycerol 3 phosphate)	High

She was shifted to ICU. She was drowsy, lethargic, developed vomiting and sweating. Blood glucose at bedside was 28 mg/dl and serum lactic acid and ABGs were sent. Serum lactic acid was high up to 11 mmol/l (normal 2 mmol/l) and metabolic acidosis was found. She was rehydrated with saline and given 10% DW, after stabilization she was shifted to ward. Liver biopsy was done after parental consent and it was negative for glycogen storage disease. Liver regressed to normal span and girl became active alert. Lactic acid remained high (5 - 8 mmol/l) after stabilization, arterial blood gases, uric acid, triglyceride and blood glucose levels remained normal. Diagnosis of fructose 1, 6 diphosphatase was made based on clinical and laboratory findings. Direct enzymatic essay of enzyme activity from hepatic specimens remains the most specific diagnostic test for this disorder and showed reduced activity of enzyme that remained less than 25%. Diagnosis was based initially on clinical grounds, hepatic tissue sample was collected and sent to authorized laboratory out of country to establish diagnosis.

She was advised not to give her fruits, cornstarch 2.6 g/kg/day and avoid fasting more than 10 hours.

Discussion

Deficiency of hepatic fructose bisphosphatase (FBSPase) is autosomal recessive disorder with impaired gluconeogenesis leading to hypoglycemia and lactic acidosis. This disorder was first described in 1970 [7]. FBSpase gene is composed of 8 exons located on chromosomes 9q22.2-q23.2 [8]. FBSpase is crucial enzyme to convert FBS to fructose 6 phosphate and inorganic phosphate. Metabolic derangements occurs due to fasting, infections and stress, decreased oral intake and large fructose ingestion. This deficiency of enzymes presents in first year of life. Nearly half present in neonate period due to glucose stores deficiency. In between episodes patients are normal with normal developmental growth and normal psychomotor development [9] patient can develop seizures and comma [10]. Some patients have been found to have impaired catabolism of purine and can develop hyperuricemia [11]. Fructose intolerance is not associated with

any specific clinical manifestations, it is an accidental finding usually made because the asymptomatic patients have urinary reducing substances and due to deficiency of fructokinase. Acute episode usually consists of seizures, irritability, hypotonia, vomiting, lethargy, rapid breathing and comma. Sometimes it is associated with transient hepatic dysfunction which does not require specific treatment [12]. In untreated patients symptoms worsen to develop multi-organ failure especially liver brain and later heart. Sepsis blindness and Reyes like syndrome has been reported [13]. This condition can be differentiated from various other metabolic defects. Aldolase deficiency occurs in infancy, when fructose or sucrose is added, clinical manifestations include jaundice, hepatomegaly, vomiting, lethargy, irritability and convulsions, lab findings include hypoalbuminemia, hyperbilirubinemia and elevated transaminase levels, proximal tubular dysfunction and urinary substances in urine. Glycogen synthetase deficiency represents with hypoglycemia, but no hepatomegaly and hyperlipidemia and occasionally presents with muscle cramps. Glucose storage disease type 1 is due to deficiency of glucose 6 phosphatase and manifests as massive hepatomegaly, enlarged kidneys, failure to thrive, doll like facies, protuberant abdomen, easy bruising and occasional infections, labs indicate hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia.

The diagnosis of FBSpase deficiency is established with clinical and metabolic manifestations along with proband with molecular genetics tests like sequence analysis or either gene targeted deletion/duplication analysis or either by enzyme essay in liver specimen. Internationally accepted guidelines have been developed to treat such cases [14]. Treatment of acute crisis consists of oral glucose or v dextrose, rehydration to restore intravascular volume and symptomatic treatment of seizures and vitals.

Mainstay of daily management is prevention of fasting, illness, stress use of uncooked cornstarch and frequent small meals. Regular immunizations, long term developmental surveillance, monitoring of weight and support to the affected family.

Conclusion

Fructose 1,6 bisphosphatase deficiency is the important cause of hypoglycemia metabolic acidosis and episodic liver enlargement. High index of suspicion should be there to diagnose this uncommon cause to prevent irreversible sequel. Molecular diagnosis should always be undertaken to facilitate the diagnosis.

Conflicts of Interests

Authors have no conflicts of interests.

Financial Support

No financial aid.

Bibliography

1. Baker L and Winegrad AI. "Fasting hypoglycaemia and metabolic acidosis associated with deficiency of hepatic fructose-1,6-diphosphatase activity". *Lancet* 2.7662 (1970): 13-16.

2. Paksu MS., *et al*. "Gluconeogenesis defect presenting with resistant hyperglycemia and acidosis mimicking diabetic ketoacidosis". *Pediatric Emergency Care* 27.12 (2011): 1180-1181.

3. El-Maghrabi MR., *et al*. "Human fructose-1,6-bisphosphatase gene (FBP1): exon-intron organization, localization to chromosome bands 9q22.2-q22.3, and mutation screening in subjects with fructose-1,6-bisphosphatase deficiency". *Genomics* 27.3 (1995): 520-525.

4. Herzog B., *et al*. "Mutation spectrum in patients with fructose-1,6-bisphosphatase deficiency". *Journal of Inherited Metabolic Disease* 24 (2001): 87-88.

5. Kikawa Y., *et al*. "Identification of genetic mutations in Japanese patients with fructose-1,6-bisphosphatase deficiency". *American Journal of Human Genetics* 61 (1997): 852-861.

6. Santamaria R., *et al*. "Functional and molecular modelling studies of two hereditary fructose intolerance-causing mutations at arginine 303 in human liver aldolase". *Biochemical Journal* 350.3 (2000): 823-828.

7. Baker L and Winegrad AI. "Fasting hypoglycemia and metabolic acidosis associated with deficiency of hepatic fructose-1,6-diphosphatase activity". *Lancet* 2 (1970): 13-16.

8. El-Maghrabi MR., *et al*. "Human fructose-1,6-bisphosphatase gene (FBP1):exon-intron organization, localization to chromosome bands 9q22.2q22.3, and mutation screening in subjects with fructose-1,6-bisphosphatase deficiency". *Genomics* 27 (1995): 520-525.

9. Steinmann B and Santer R. "Disorders of fructose metabolism". In: Saudubray JM, edition. Inborn Metabolic Diseases. 6th edition. Springer-Verlag (2016): 165-167.

10. Niu Li., *et al*. "Clinical and Molecular Characterization of Patients with Fructose 1,6Bisphosphatase Deficiency". *International Journal of Molecular Sciences* 18 (2017): 857.

11. Christel Tran. "Inborn errors of fructose metabolism. What can we learn from them?" *Nutrients* 9 (2017): 356.

12. Bhai P., *et al*. "Clinical and molecular characterization of Indian patients with fructose-1, 6-bisphosphatase deficiency: identification of a frequent variant (E281K)". *Annals of Human Genetics* 82 (2018): 309-317.

13. Li N., *et al*. "Clinical and molecular characterization of patients with fructose 1,6-bisphosphatase deficiency". *International Journal of Molecular Sciences* 18 (2017): E857.

14. Pinto A., *et al*. "International practices in the dietary management of fructose 1-6 biphosphatase deficiency". *Orphanet Journal of Rare Diseases* 13 (2018): 21.

Volume 5 Issue 6 June 2022