CASE REPORT

Fructose-1,6-diphosphatase deficiency: a treatable neurometabolic disorder

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SUMMARY

Fructose-1,6-diphosphatase (FDPase) deficiency is usually considered an inborn error of fructose metabolism, however, strictly speaking it is a defect of gluconeogenesis. The disorder is manifested by the appearance of hypoglycaemia, ketosis and lactic acidosis (neonatally or later during fasting or induced by fructose) and may also be life-threatening. FDPase deficiency can be suspected using simple bedside tests such as glucometer random blood sugar, Benedict's test, Rothera's test and Seliwanoff's test. We report our experience with two cases of FDPase deficiency and review the relevant literature. We also describe the fructosuria in these cases during the crises period, which has not been stressed in the literature.

BACKGROUND

With increasing awareness of prevalence of inborn errors of metabolism, widespread availability of neuroimaging facilities such as MRI, and tests such as tandem mass spectrometry (TMS) and urine gas chromatography/mass spectrometry (GC/MS), more cases of various neurometabolic disorders are being diagnosed in India.[1 2] This is resulting in appropriate diagnosis and management of these conditions. But at the same time, it is important to realise that most of these tests are costly and it takes days to a week to get the final results of these biochemical tests (especially for paediatricians practising in small cities) and hence often definitive treatment gets delayed or sometimes is missed. At times, a treatment started unknowingly may be harmful in a given case. Hence there is a need for simple cost-effective tests, especially bedside, easily available, which can help us in diagnosing-specific and/or suspecting-specific neurometabolic disorders. This could help to institute appropriate treatment measures. The confirmatory diagnoses can be performed later, after appropriate tests. We report our experience with two cases of fructose-1,6-diphosphatase (FDPase) deficiency, which is a neurometabolic disorder that can be suspected by simple, widely available tests such as arterial blood gases, blood sugar estimation, urine ketone bodies as well as Benedict's test and Seliwanoff's test.[3] Correct diagnosis can result in institution of appropriate therapeutic measures leading to early recovery and prevention of complications.[4]

CASE PRESENTATION

Case 1

A 17-month-old female baby born to third-degree consanguineous parents was brought to us early one morning with a 1-day history of loose stools (5–6 times watery non-bloody, non-mucoid). The child was irritable and had one episode of vomiting before presentation. Later she started having rapid and shallow breathing without any chest retractions or grunting 2 h prior to presentation. There was no associated fever, seizure or history suggestive of pain in abdomen. On presentation, the child was euthermic, mildly dehydrated, tachycardic, tachypnoeic with acidotic breathing and was drowsy. She had mild hepatomegaly. There was no cyanosis; icterus and other systems were normal. The history revealed that this was the third time she had such symptoms in the past 2 months, with febrile episodes.

On evaluation, she had hypoglycaemia (44 mg/dL on admission) with acidosis (pH of 7.21) and urine ketonuria. Her arterial lactate was 5.6 mmol/L (normal range 0.5–2.0) and ammonia was mildly elevated (45 µg/dL; normal <33). Complete blood count, serum electrolytes, renal function tests and liver function tests were normal. TMS results were within normal limits. Urine GC/MS showed grossly elevated lactic acid, ketones (2-hydroxybutyric acid, 3-hydroxybutyric acid and acetoacetic acid) and glycerol, suggestive of FDPase deficiency. After obtaining the GC/MS report, we performed the urine Benedict's test and Seliwanoff's test, which showed presence of keto-sugar in the urine. Her acidosis and hypoglycaemia responded to intravenous dextrose bolus followed by infusion (8–10 mg/kg/day). Her parents were educated about the disease and she was discharged after 5 days of admission.

Case 2

A 5-year-old boy born to third-degree consanguineous parents had been symptomatic from 1 year of age. He had experienced more than 30 prior episodes of admission for hurried breathing, drowsiness and refusal to feed following either febrile illness or skipping of night feeds. Each time he had recovered with dextrose infusion within 24–48 h. There was no history of seizures. At this presentation he was extensively worked up for possible neurometabolic disorders including TMS, which was normal. His previous hospital records showed hyperlacticacidaemia and ketoacidoses. Urine Seliwanoff's test in one of the episodes and urine GC/MS gave a diagnosis of FDPase. After proper parental counselling and dietary advice, the child has not had any further episodes in the past 12 months.

OUTCOME AND FOLLOW-UP

Follow-up of both cases every 3 months has shown them to be normal for the past 12 months, without any further episodes of metabolic decompensation.

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DISCUSSION

FDPase deficiency, a rare inherited disorder of gluconeogenesis, was first described in 1970.[5] Although the first symptoms tend to appear in early postnatal life,[6] the disease is often not diagnosed at this time. In later infancy, hypoglycaemic attacks are often triggered by refusal of food or vomiting following febrile infections, or by the intake of fructose containing food. Clinical hallmarks of this disorder are hyperventilation, vomiting, irritability, somnolence up to coma, ketoacidosis, muscular hypotonia and hepatomegaly. Attacks are usually precipitated by fasting and intercurrent infections and can often be overcome by administration of sodium bicarbonate and glucose. Such attacks may, however, be life-threatening.

FDPase is a key enzyme for gluconeogenesis and for inducing substrates initiating the hexose monophosphate shunt. Major biochemical features are hypoglycaemia, increased plasma levels of lactate, 3-hydroxybutyrate and acetoacetate, uric acid; as well as alanine, ketonuria and increased urinary glycerol excretion.[7] Enzymatic assay of hepatic FDPase activity is the most specific diagnostic test. However, this assay is performed only by a handful of reference laboratories and hence could not be done in our case. Detection of urinary glycerol during hypoglycaemia and acidosis is an important clue to the diagnosis of FDPase deficiency.[3] This test provides an important and non-invasive method to diagnose FDPase deficiency.[3]

After a fructose loading, such as occurs when a child has fruit juice or a sucrose-rich diet, especially during infections (equivalent to fructose loading test), because of lack of FDPase enzyme, there could be accumulation of fructose-1-phosphate, which in turn can get converted to fructose and eventually get excreted in urine. This results in fructosuria, which can be picked up by Seliwanoff's test thereby prompting further tests such as urine GC/MS.

We wish to emphasise that fructosuria is not a diagnostic test in FDPase but, in a given case, during fasting, if a child receives fruit or fruit juice, fructosuria may be found and this can help in the diagnosis. However, despite a detailed search of the published literature we did not locate any article mentioning fructosuria in FDPase. Nevertheless, it seems logical as this could be the equivalent of a fructose loading test, which should not be performed.

The confirmation of FDPase deficiency is not required for institution of simple therapeutic measures such as restriction of fructose containing foods and correction of blood glucose abnormalities. FDPase deficiency has a less severe course because glycolysis is intact. A 22-year-old patient with FDPase deficiency described in the literature confirms this.[8]

The presence of non-glucose reducing substances in the urine is characteristic of untreated classical galactosaemia, hereditary fructose intolerance (HFI) and FDPase. This is simple to determine at the bedside. Testing a few drops of urine with Benedict's reagent is positive in the presence of glucose, galactose or fructose. However, dipping the urine with glucostix is usually negative in these conditions, indicating that the reducing substance is not glucose. Both diseases are generally associated with other prominent clinical problems. As a rule, patients with galactosaemia and HFI have other evidence of hepatocellular dysfunction (raised liver enzymes), and HFI is associated with marked lactic acidosis. The excretion of non-reducing sugars in the urine in these conditions typically clears rapidly after removal of the toxic sugars from the diet. Therefore, a negative test does not eliminate the possibility of one of these disorders, particularly if the patient has been on intravenous glucose for more than a few hours.[9] We should also be aware that in galactosaemia and HFI, glucosuria may occasionally be seen due to Fanconi syndrome. This should be considered while interpreting the results of reducing sugars in urine.

The combination of hypoglycaemia, marked hepatomegaly and lactic acidosis is also characteristic of HFI, glucose-6-phosphatase deficiency, phosphoenol-pyruvate carboxykinase (PEPCK) deficiency, pyruvate carboxylase (PC) deficiency and amino acid metabolism disorders such as 3-hydroxy-3-methylgtutaryl-CoA lyase (HMG-CoA lyase) deficiency.[9] In patients with HFI, the development of symptoms is clearly related to the ingestion of fructose or sucrose. More prolonged exposure results in failure to thrive, chronic irritability, hepatomegaly, abdominal distension, oedema and jaundice. Sugar intolerance (bloating, abdominal discomfort, diarrhoea) and aversion are characteristic. In comparison to FDPase, patients with HFI have evidence of hepatocellular dysfunction (elevated aminotransferases, increased plasma methionine and tyrosine levels, prolonged prothrombin and partial thromboplastin times, hypoalbuminaemia, hyperbilirubinaemia) and renal tubular dysfunction (hyperchloremic metabolic acidosis, generalised amino aciduria). FDPase deficiency may be difficult to differentiate from glycogen storage disorder 1a (GSDIa). In both diseases, the liver may be greatly enlarged. In FDPase deficiency, however, the response to glucagon is preserved. Mitochondrial PEPCK deficiency is a very rare hereditary defect in gluconeogenesis associated with severe hypoglycaemia, lactic acidosis, hepatomegaly, renal tubular dysfunction, hypotonia and deteriorating liver function. But there is no positive urine reducing sugar or fructosuria in PEPCK and PC deficiencies. In HMG-CoA lyase deficiency, there is no ketonuria.

Thus in a clinical scenario, when there is hypoglycaemia with positive urine reducing sugar by tests such as Benedict's test, we should suspect FDPase as a differential diagnosis and perform urine tests, such as Seliwanoff's test, for fructosuria. If positive this should strongly suggest FDPase and therapeutic measures such as avoidance of sucrose and sorbitol in the diet, and correction of hypoglycaemia and acidosis should be instituted pending the results of urine GC/MS and other confirmatory tests. Sorbitol and sucrose should be avoided by patients with FDPase deficiency (chewing gums, high-fructose corn syrup, iced tea, sports drinks, etc). Fruits, especially apples, pears, grapes and cherry contain a higher ratio of fructose to glucose. Glycerol solution that contains 5% fructose, often used for management of brain oedema, should be avoided in FDPase deficiency. Finally, the use of fructose-free food and avoidance of prolonged fasting with administration of uncooked corn starch (2 g/kg) mixed with water at midnight were of benefit to our patients, preventing nocturnal hypoglycaemia and improving their clinical response to illness.[10] These children need to be regularly followed up to look for behavioural problems and cognitive impairment as they grow.

Treatment mainly consists of parental education, which needs strong emphasis on the importance of avoidance of fasting especially during infections along with avoiding fructose containing foods and glycerol.

Our report emphasises the fact that urinary organic acid analysis should be performed in patients with hypoglycaemia and lactic acidosis not only to exclude amino acid defects, but also to identify disorders of gluconeogenesis, because glycerol excretion on fasting or during acidosis is of diagnostic importance in FDPase deficiency.

Patient's perspective

The parents of both patients reported that diagnoses was only determined almost a year after symptoms' onset. This was due to the lack of awareness of this condition among the treating doctors. The parents were glad when the correct diagnosis was made and simple dietary counselling was provided.

Learning points

- When a child presents with hypoglycaemia along with testing for ketone bodies in urine, testing for urine reducing sugars, such as Benedict's test and Seliwanoff's test, should be performed.
- Urinary organic acid analysis should be performed in patients with hypoglycaemia and lactic acidosis, not only to exclude amino acid defects but also to identify disorders of gluconeogenesis.
- Simple interventional measures such as avoidance of sucrose in the diet and fruits, and care of the child during infections will immensely help a given case.
- Confirmation is not required for treatment purpose.

Competing interests None.

Patient consent Obtained.

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