Two cases of hereditary fructose intolerance

N Ananth,* G.S. Praveenkumar,* K Aravind Rao,** Vasanthi*** and Srinivas Kakkilaya**

*Department of Biochemistry, Kasturba Medical College, **Nova Diagnostic and Research Centre
***K.S. Hegde Medical Academy, Deralakatte, Mangalore.

ABSTRACT

Hereditary fructose intolerance is a rare cause of hepatic cirrhosis in the young. The disorder has a reported frequency of 1 in 20000 live births and no case has been reported from India so far. We report two cases of hereditary fructose intolerance, both with bilateral cataracts and one with cirrhosis of the liver.

KEY WORDS

Cataract, Cirrhosis, Hereditary fructose intolerance

INTRODUCTION

Hereditary fructose intolerance (HFI) is a rare autosomal recessive disorder of fructose metabolism due to a deficiency of fructose-1-phosphate aldolase activity that results in the accumulation of fructose-1-phosphate in the liver, kidneys and small intestine.(1) In infants and young children, the disorder manifests with intolerance to fruits and vegetables, Reye's like syndrome and hepatic failure.(1,2) In older children and adults, it can present as aversion to fruits, vegetables, sweet-tasting foods, cirrhosis of liver or intolerance to fructose infusion.(1-4) Current diagnostic methods for HFI include the fructose tolerance test that measures clinical symptoms upon intravenous fructose challenge and direct assay of aldolase activity in liver biopsy samples.(1) These tests are relatively invasive and not routinely available.(1) A direct DNA analysis that scans for known and unknown mutations has also been reported.(5)

The underlying problem in treating HFI, as well as for a more complete characterization of the population genetics of the disorder, is the difficulty of its diagnosis.(1) The incidence rate may range from 1 in 10,000 to 1 in 1,000,000 and most cases have been reported in Europe and North America.(1) The prevalence of the disease in adults is not known.(5)

CASE REPORT

We report the cases of two siblings from a consanguineous marriage, the elder male being the index case.

He was 23 years old (Date of birth: March 17th, 1978), third of the eight siblings and had normal developmental milestones. He was repeatedly hospitalized for episodes of vomiting and diarrhea, almost every 2-3 months up to the age of 9 years and less frequently thereafter. In August 1991 he was admitted at a referral hospital with abdominal distention and was diagnosed as cirrhosis of liver with portal hypertension; liver biopsy showed hepatic tissue with loss of architecture, nodules of regenerating hepatocytes surrounded by dense fibroblasts and chronic inflammatory cells with no evidence of necrosis or bile stasis. He had bilateral cataract since the age of 8 years; the right cataract was operated at the age of 10 years and the left cataract at the age 14 years and he developed corneal opacity in right eye after 6 months of surgery. He had been complaining of gradually worsening upper abdominal discomfort since 6 years and swelling of both the lower limbs and distention of abdomen since 2 years.

On examination, he was 165cms tall and weighed 55kgs. His vital signs were normal. He had bilateral pitting pedal oedema with puffiness of face and distention of abdomen. He had lemon yellow discoloration of sclera with conjunctival pallor. His liver was palpable 4cms below the right costal margin, firm and non-tender. He had massive splenomegaly measuring 14cms from left costal margin and it was firm and non-tender. He had
ascites with shifting dullness. His right eye had prephthisis due to cyclitic membrane formation and left eye had evidence of cataract surgery with intraocular lens in situ and amblyopia. Left fundus through constricted pupil showed hypoplastic vertically oval optic disc. There was no evidence of Kayser-Fleischer ring in the cornea on slit lamp examination.

The youngest of the eight siblings, girl aged 11 years, (Date Of Birth: June 6th, 1990) had bilateral cataracts and was operated on the right eye at the age of 10 years. She did not have any other history. On examination, her right eye had irregular pupil with afferent pupillary defect and in situ intraocular lens displaced upwards. Left eye had cataracted lens and normal pupil with brisk light reflex. Right fundus was normal and left was not visualised.

INVESTIGATIONS

The male sibling had hemoglobin of 8.6g/dL, normal total and differential leukocyte count and platelets 1 lakh/cu mm. His total serum bilirubin was 4.7mg/dL (direct 2.9mg/dL), serum AST was 551U/L, serum ALT was 30 IU/L, serum alkaline phosphatase was 200IU/L, serum gamma GT was 65IU/L, total serum protein was 4.1g/dL, serum albumin was 1.8g/dL. His prothrombin time was prolonged with test value of 28 sec and control value of 13 sec. His glycosylated hemoglobin (Hb A1) was 12.3%. His serum creatinine was 1.2mg/dL and serum electrolytes were normal. Urine analysis showed traces of albumin, bile salts and bile pigments and urine sugar was absent. Ultra sound evaluation of abdomen revealed the following: Liver was contracted with nodular margin and non-homogenous texture; portal vein was enlarged (17mm); hepatic veins were normal; gall bladder wall was thickened and there were no gall stones; massive splenomegaly with normal texture, splenic vein was enlarged (16mm); there were multiple tortuous collaterals around the splenic hilum; there was minimal ascites. Common bile duct, pancreas, kidneys and urinary bladder were normal. Gastroscopy showed patchy hyperemia in body and antrum of stomach; oesophagus and duodenum were normal and there were no varices.

In case of the girl, the blood cell counts, liver function tests and ultra sound evaluation of abdomen were normal. Her glycosylated hemoglobin (Hb A1) was 11.4% and urine sugar was negative.

Presence of early onset cataracts, cirrhosis of liver and elevated glycosylated hemoglobin in the absence of glycosuria prompted evaluation for errors of carbohydrate metabolism other than diabetes mellitus. The urine specimen of both the patients were analysed for excretion of sugars. Tests for glucose was negative by glucose oxidase methods (Dip Stix) and resorcinol reaction revealed presence of a ketose. Osazone reaction in the urine revealed characteristic needle shaped crystals of fructose. Partition chromatography in urine confirmed the presence of fructose. The fructose excretion was quantified at 342μmol/day in the male and 355μmol/day in the female (Normal <333μmol/day).

The patients were then subjected to oral fructose loading test (7) with 3g/m² of fructose. While the girl had asymptomatic fasting hypoglycemia (57mg/dL), the fasting blood glucose in the male was 87mg/dL (After the tests he revealed that he had taken food at 1a.m. due to excessive hunger). The one hour post fructose values of blood glucose do not reveal any significant rise and after 75 minutes both patients demanded food due to excessive hunger and that was provided. The rise in blood glucose at 120 minutes is attributed to this.

In the girl, the 3rd hour blood glucose value dropped to 65mg/dL. All the values indicate hypophosphataemia; but both the subjects did not exhibit either hyperuricemia or hypertriglyceridemia, presence of which would have made it a classical presentation. Serum fructose levels reached a maximum at 330μmol/L in the male and 346μmol/L in the female after the load and remained elevated for one and a half hours before gradually declining to near zero concentrations.

RESULTS

The findings were indicative of an error in the metabolism of fructose. The results of the quantitative assays of the two enzymes are shown in Table 2.

It should be noted that the decrease in activity of fructoaldolase is not very significant owing to the fact that it has less affinity to the substrate compared to the other enzyme in vivo. However, the defective enzyme was thus shown to be fructoaldolase and the defect characterised as hereditary fructose intolerance.

DISCUSSION

Hereditary Fructose Tolerance is an inborn error of