A young patient with unexplained acute hepatorenal dysfunction

Sofie Jamar, Pieter Evenepoel, Dirk Kuypers, Bart Maes and Yves Vanrenterghem

Department of Medicine, Division of Nephrology, University Hospital Leuven, Leuven, Belgium

Keywords: Fanconi syndrome; fructose intolerance; hepatorenal dysfunction

Introduction

Hereditary fructose intolerance (HFI) is a recessively inherited condition, caused by hepatic, renal and intestinal aldolase B deficiency. The characteristic symptoms of nausea, vomiting, abdominal pain and sweating are induced by the ingestion of large quantities of fructose, sucrose or sorbitol. In severe intoxications glucagon-resistant hypoglycaemia, metabolic acidosis and/or hepatorenal failure may occur. More than 20 fatal or near-fatal insults following the administration of fructose or sorbitol containing solutions have been reported [1]. We report a case of a young male in whom suggestive clinical and biochemical manifestations in temporal relationship with infusion of fructose led to the diagnosis of HFI.

Case report

A 23-year-old Caucasian man was admitted in a referring hospital because of headache, nausea and vomiting. His medical history was unremarkable. He took no maintenance medications, did not smoke and denied the use of alcohol or any illicit drugs. On admission (d0), laboratory analysis showed a normal renal function, discretely disturbed liver function tests, negative hepatitis and EBV serology (Table 1). Findings on upper endoscopy and abdominal ultrasound were normal. Metoclopramide, ranitidine and fluids were administered intravenously and he was kept nil by mouth. Two days later, he was transferred to our hospital because of rapidly progressive renal and hepatic dysfunction. On admission he generally looked well. Physical examination revealed no abnormalities. He was afebrile and his blood pressure was 155/85 mmHg.

None of his family members were known with diabetes or renal disease. Biochemistry data obtained on the day of transfer (d2) are shown in Table 1. Chest and abdominal X-ray were normal, as was ECG and echocardiography. Ultrasound showed normal-appearing kidneys, an increased reflectivity of the liver with normal Doppler signal. The evolution of serum creatinine and alanine amino-transferase (ALT) is shown in Figure 1.

Immunological (ANF, ANCA, IgA, IgG, IgM, complement) and microbiological screenings (hepatitis, CMV, EBV, hantaan virus) were negative. Urinary analysis showed haematuria, leucocyturia, glucosuria and significant proteinuria (Table 1). In the afternoon of day 4 he felt much better but his symptoms reappeared in the evening and the following morning. At that point the patient remarked that the abdominal discomfort always worsened after commencing IV fluids. Thorough retrospective analysis revealed that his symptoms were triggered by the administration of Multion™, a fructose-containing fluid (Baxter, Lessines, Belgium). The diagnosis of HFI became even more suspect when the patient explained that his mother and sister were known to have ‘some form of sugar intolerance’. HFI was confirmed by genetic testing demonstrating aldolase B deficiency.

Discussion

HFI, caused by catalytic deficiency of aldolase B (fructose-1,6-biphosphate aldolase), is an autosomal recessively inherited condition in which affected homozygotes develop hypoglycaemia and severe abdominal symptoms after taking foods containing fructose and cognate sugars. The disorder affects approximately 1 in 20,000 individuals. Infants are the most vulnerable to exposure of dietary fructose, especially at weaning. The newborn does not develop any symptoms while taking breast milk since this contains lactose, a disaccharide of glucose and galactose. However, characteristic symptoms are induced after transfer to sweetened milk formulae and solid foods containing added sugar, as well as natural fruit and vegetables. If the undiagnosed infant survives the difficult initial
period of weaning, the child usually develops a self-protective aversion to foods that cause distress. Voluntary dietary exclusion, which is refined by trial and error over a lifetime, includes restriction of most sweet tasting foods. Growth failure often is the presenting feature leading to the diagnosis of HFI in children and youngsters having difficulties to comply to the diet [2]. In those who succeed to adhere to the self-imposed low fructose diet, HFI can remain undiagnosed for a long time [1]. Many authors have noted the extraordinary absence of dental caries in adults with HFI, the consequence of dietary adjustment [1].

A particular hazard for people with undiagnosed HFI is the indiscriminate use of fructose (or cognate sugars) as a source of parenteral feeding.
More than 20 fatal or near-fatal instances resulting from this cause have been and continue to be reported in HFI [1]. The real number is probably higher due to difficulties in establishing a definite diagnosis. These fatal cases already led several countries to eliminate fructose (and cognate sugars) containing solutions for parenteral administration from their pharmacopoeias [3].

In the case under discussion we describe the clinical-pathological consequences of the accidental parenteral administration of 200 g of fructose (fractionated over 48 h) in an adult patient with undiagnosed HFI. Soon after the start of the fructose infusion, gastrointestinal pain occurred and laboratory findings indicating hepatic (both excretory and synthetic) and renal dysfunction (Fanconi syndrome, decreased creatinine clearance) were observed. Disturbances of the intermediary metabolism (hypophosphataemia, mild hypokalaemia, metabolic acidosis) were also noted. These findings are characteristic for fructose intolerance and represent a global functional deterioration of organs, which normally harbour the enzyme aldolase B (i.e. liver, kidneys, intestine) [1,4]. As is evident from Figure 1, hepatic dysfunction occurred with some delay as compared to the renal dysfunction. The often-associated hypoglycaemia was not observed, most probably as a result of the concomitant parenteral administration of glucose.

After discontinuing the fructose infusion, the gastrointestinal symptoms and biochemical abnormalities subsided. The temporal relationship of the gastrointestinal complaints with the fructose containing infusion raised the suspicion of fructose intolerance in our patient. The diagnosis of HFI was definitely confirmed by careful family history and, finally, genetic mapping.

A strict fructose exclusion diet was introduced with assistance of an experienced dietician and the patient was recommended to wear a ‘medical alert bracelet’ advising on prohibited sugars and on the appropriate treatment for hypoglycaemia.

The pathogenetic mechanism of HFI is only partially elucidated. Once exogenous fructose is incorporated into the cell, it is rapidly phosphorylated into fructose-1-phosphate (Figure 2).

Aldolase B catalyses the reversible conversion of fructose-1-phosphate to 3-carbon sugars. When aldolase B is deficient, fructose-1-phosphate accumulates with subsequent inhibition of glycolysis and gluconeogenesis. Depletion of inorganic phosphate and ATP are thought to be responsible for the multiple defects through H+ ATP-ase pump defects [5,6]. Depending on the severity of the fructose ‘intoxication’, the clinical consequences vary from mild and reversible to life-threatening and irreversible. In the most severe cases, patients develop signs of shock and acute hepatorenal failure accompanied by cerebral oedema; death follows within a few days [3,7]. Longstanding, HFI is often complicated by nephrocalcinosis, which may lead to chronic renal insufficiency [8].

### Teaching points

(i) Patients with gastrointestinal symptoms and hepatorenal dysfunction should always be suspected for HFI. Fructose (and cognate sugars) containing infusions should be discontinued immediately in these patients to avoid potential life-threatening complications.

(ii) Fructose (and cognate sugars) containing infusions should not be given routinely, but only with certain indications.

### References


![Fig. 2. Metabolism of fructose.](http://ndt.oxfordjournals.org/Downloadedfrom)