Clinical case

Doctor, my son is so tired… about a case of hereditary fructose intolerance

Docteur, mon fils est si fatigué… à propos d’un cas d’intolérance héréditaire au fructose

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Résumé

Nous rapportons le cas d’un jeune homme de 17 ans, souffrant d’une intolérance héréditaire au fructose (HFI) diagnostiquée à la naissance. Il se plaignait d’une asthénie dès le matin et d’une somnolence postprandiale en dépit d’un sommeil satisfaisant. Les examens cliniques et biologiques n’ont mis en évidence qu’un taux effondré de vitamine C (< 10 mol/l ; normale : 26–84). L’asthénie de ce patient a été attribuée à cette carence en vitamine C, effet secondaire fréquent du régime alimentaire pauvre en fructose. Une modification de régime associée à l’adjonction de vitamine C a été conseillée avec accroissement de la consommation de légumes, à l’exception des carottes, oignons, poireaux et maïs doux en boîte. Ce cas clinique offre l’opportunité d’une revue de cette maladie rare. Deux types d’anomalies du métabolisme du fructose (toutes deux autosomiques récessives) sont connues : 1) la fructosurie essentielle induite par un déficit en fructokinase qui s’avère sans gravité et ne nécessite pas de régime particiel ; 2) l’HFI, liée à des mutations du gène de l’aldolase B dont trois sont particulièrement fréquentes, et dont le diagnostic repose sur le test respiratoire après ingestion de fructose, le test de tolérance au fructose intraveineux et les tests génétiques. Dans l’HFI, l’ingestion de fructose provoque généralement des symptômes gastro-intestinaux (nausées, vomissements, douleurs abdominales, méto- risme) et des signes d’hypoglycémies. Le jeûne est bien toléré. Si le diagnostic n’est pas posé, une atteinte hépatique avec hépatomégalie, une dysfonction tubulaire rénale et un retard staturopondéral peuvent apparaître. En conclusion, cette maladie métabolique rare doit être connue des endocrinologues car ils peuvent être amenés à suivre des patients dont le diagnostic a été posé dans l’enfance et qui ont atteint l’âge adulte. De plus, cette affection est parfois diagnostiquée chez l’adulte devant des hypoglycémies, une atteinte hépatique inexpliquée, un syndrome de « l’intestin irritable » ou une goutte familiale.

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Abstract

We present the case of a 17-year-old male who was diagnosed at birth with hereditary fructose intolerance (HFI). The patient complained of morning-time asthenia and post-prandial drowsiness despite a correct sleep pattern. The physical examination and biological check-up only showed severe vitamin C deficiency (< 10mol/l; normal range: 26–84). The patient’s tiredness was attributed to this vitamin C deficiency, which is a frequent side-effect of the fructose-free diet. A change in diet associated with a supplementation in vitamin C was advised, with an increase in vegetable intake, principally avoiding carrots, onions, leaks and tinned sweet-corn. This case offers the opportunity for a review of this rare disease. Two kinds of fructose metabolism disorders (both autosomal recessive) are recognized: 1) essential fructosuria caused by a deficiency of fructokinase, which has no clinical consequence and requires no dietary treatment; 2) HFI, linked to three main mutations identified in aldolase B gene that may be confirmed by fructose breath test, intravenous fructose tolerance test, and genetic testing. In HFI, fructose ingestion generally induces gastro-intestinal (nausea and vomiting, abdominal pain, meteorism) and hypoglycemic symptoms. Fasting is well tolerated. If the condition remains undiagnosed, it leads to liver disease with hepatomegaly, proximal tubular dysfunction, and slow growth.

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and weight gain. In conclusion, endocrinologists should be aware of this rare metabolic disease in order to provide careful follow-up, particularly important when the patient reaches adulthood. Moreover, hypoglycemia induced by fructose absorption, unexplained liver disease, irritable bowel syndrome or familial gout in an adult is suggestive of the diagnosis.

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**Keywords:** Vitamin C; Hypoglycemia; Hereditary fructose intolerance; Irritable bowel; Gout

### 1. Case study

We present the case of a 17 year-old boy who was diagnosed at birth with hereditary fructose intolerance (from now on referred to as HFI), which has been treated all his life by a strict fructose-free diet. He was complaining of morning-time asthenia and post-prandial drowsiness despite a correct sleep pattern. Clinical examination revealed a low Body Mass Index of 17.7 kg/m² (weight 55 kg, height 1.76 m). Cardiovascular examination was normal. As for the digestive system, this teenager complained of occasional diarrhea and vomiting over periods of a few days. No hypertylrophy of liver or spleen was clinically evident. Blood samples showed:

- blood glucose level at 8 am at 0.87 g/l (4.8 mmol/l) with insulin level at 3 mIU/l. Post-prandial blood glucose level at 2 pm at 1.37g/l (7.6 mmol/l) with insulin level measured at 41.8 mIU/l;
- normal lactic acid (0.84 mmol/l) and uric acid (357 μmol/l or 65 mg/l);
- slightly elevated ALAT (61 IU/l) whereas ASAT (33 IU/l) and gamma-GT (20 IU/l) were normal;
- normal renal function (serum creatinine 707 μmol/l or 8 mg/l); Cockroft-estimated glomerular filtration rate: 130 ml/min);
- normal sodium and potassium concentration;
- vitamin C deficiency (<10 mol/l; normal range: 26-84).

Vitamins A and E were normal. Diet evaluation showed that meals were based on meat and carbohydrate, with no fruit or vegetables. The electrencephalogram was normal. The patient’s tiredness was attributed to the vitamin C deficiency, which is a frequent side-effect of the fructose-free diet. Note that there were no clinical signs of scorbuc such as gingival bleeding. A change in diet was advised with an increase in vegetable intake, principally avoiding carrots, onions, leaks and tinned sweet-corn. A supplementation in vitamin C was advocated leading to a clinical improvement.

### 2. Discussion

This case creates an opportunity:

- for a review of this disease, which is a rare cause of hypoglycaemia, not necessarily well known from non pediatrician endocrinologists;
- to report the clinical status of adult patients which has not been extensively described [1].

#### 2.1. Fructose metabolism

Fructose is found:

- in its free form in honey, fruit and many vegetables;
- in the form of the fructose–glucose disaccharide sucrose in many foods;
- in the form of sorbitol (found in fruit and vegetables) converted into fructose in the liver (by sorbitol-dehydrogenase).

Fructose is mainly metabolized by a specialized pathway found in the liver, kidney cortex and small intestine mucosa. The three principle enzymes involved are fructokinase, aldolase B and triose kinase (Fig. 1).

Two kinds of fructose metabolism disorders are recognized:

- Essential Fructosuria (autosomal recessive inheritance) caused by a deficiency of fructokinase, has no clinical consequence and no dietary treatment is required;
- hereditary fructose intolerance (HFI).

HFI prevalence in Central Europe has recently been estimated to 1/26,000 [2].

#### 2.2. Clinical manifestations: of HFI

Symptomatology appears when fructose is introduced. Babies do well during breast-feeding because breast milk does not contain fructose. Symptoms appear upon introduction of cow’s-milk formulas sweetened with sucrose, or in fruit and vegetables. Individual sensitivity to fructose is variable, but in general, fructose ingestion induces:

- gastro-intestinal symptoms (nausea and vomiting, abdominal pain, meteorism or gastrointestinal discomfort);
- signs of hypoglycaemia: pallor, sweating, trembling, lethargy and eventually seizure.

Headaches and depressive mood have also been reported. Fasting is well tolerated. Often, a protective aversion to foods containing fructose develops. Because of this, children with HFI are far less prone to tooth decay and cavities than their contemporaries. At school age, HFI can be recognized when hepatomegaly or delayed growth is found. If the condition remains undiagnosed, it leads to liver disease (with jaundice, hepatomegaly, a tendency to bleeding, and ultimately edema and ascites), proximal tubular dysfunction and delayed growth and weight-gain [3]. Therefore, case reports of hepatomegaly
with increased blood gammaGT levels have been described [4, 5]. HFI, as well as lactose intolerance and alterations of enteric flora have also been implicated in irritable bowel syndrome in teen-agers or adults [6–12].

2.3. Physiopathology

Activity of Aldolase B is diminished, with a reduced ability to split fructose-1-phosphate (F-1-P) into dihydroxyacetone phosphate and glyceraldehyde, which means that in the tissues that possess the specialized fructose pathway, conversion of fructose into glucose and lactate is impossible and F-1-P accumulates. The consequences of F-1-P accumulation are as follows:

- inhibition of glycogenolysis: F-1-P inhibits phosphorylase (which catalyzes transformation of glycogen into glucose-1-phosphate, using one inorganic phosphate molecule);
- inhibition of gluconeogenesis: F-1-P inhibits condensation of glyceraldehyde-3-phosphate with dihydroxyacetone phosphate which produces fructose-1,6-biphosphate; F-1-P also inhibits glucose-6-phosphate isomerase which transforms fructose-6-phosphate into glucose-6-phosphate.

This all leads to an impairment of glucose production, inducing hypoglycaemia. At the same time, sequestration of large amounts of ATP in F-1-P, with simultaneous depletion in inorganic phosphate lead to a depletion in energy for liver, kidney and intestinal cells (with low protein synthesis and ultrastructural lesions, producing gastro-intestinal discomfort and liver and kidney dysfunction) [13].

2.4. Diagnosis

HFI is a hereditary disease, with autosomal-recessive transmission. First the possibility of HFI should be explored by a carefully dietary history, followed by genetic diagnosis. Identification of the two mutated alleles is possible in approximately 80% of cases (by testing for the three most frequent mutations, which are A149P, A174D, and N334K in the aldolase B gene in the European population.) [2,14,15]. Structural and functional investigations of mutated human aldolase B gene have shown that the mutation leads to losses in thermal stability and quaternary structure [16]. Intravenous fructose tolerance test (injection of fructose after several weeks of a fructose-free diet, with regular determination of blood glucose and phosphate levels over 90 minutes) are rarely necessary. It is generally avoided because it can induce severe hypoglycaemia with transient hypophosphatemia, eventually associated with hyper-uricemia, elevation of serum magnesium, and accumulation of lactic acid [17].

Fructose breath test (50 g fructose in 150 ml of water: 33% solution) may be performed, breath samples being collected for hydrogen and methane. A 10% and 20% fructose solution may be used. The test is usually considered positive when an increase of at least 10 ppm hydrogen (sometimes 20) above the fasting level (most commonly observed at 3 h post-administration) is observed [6]. Note that this test, usually considered as easily done and non-invasive may be associated with life-threatening side effects in some cases [18].

Transferrin hypoglycosylation, recently reported, should not only suggest congenital disorders of glycosylation but also FI [19].
Measuring aldolase B activity in liver (or more rarely kidney cortex or intestine) biopsy enables confirmation of diagnosis but is not necessary if two mutated alleles have been identified.

2.5. Treatment

As soon as HFI is suspected (infant with slow weight-gain, digestive symptoms following fructose ingestion and/or distaste for foods containing fructose, hepatomegaly, liver biological anomalies), fructose should be withdrawn from diet [20, 21]. In a fructose-free diet, forbidden foods include sugar made from beet, cane or maple, honey, and all fruits. Glucose and dextrin-maltose are permitted. Permitted vegetables include green beans, courgettes, spinach, celery, cucumber, broccoli, asparagus, lettuce. Vitamin C supplements are recommended (taking care that the excipients contain no fructose). Note that severe cases of hypoglycaemia can be treated with glucose or galactose but not with glucagon or glycerol. (Fructose ingestion does not induce an increase in insulin secretion). Most of the time, diet education must be reinforced by access to a cookbook, and a support group.

2.6. Prognosis and adulthood

The prognosis is generally good. After evocation of fructose, children quickly catch up on weight gain and growth and biological abnormalities disappear. Liver-enlargement often persists for several months or even years. When they are grown up, young patients often escape from medical care. Therefore, it is important to organize a follow-up from pediatric to adult medicine and to provide information to non-pediatrician endocrinologists about this rare disease. Otherwise, a careful follow-up should be provided during pregnancy [22]. In adults, the diagnosis should be evoked in case of unexplained liver disease, irritable bowel syndrome or hypoglycaemia induced by fructose absorption. Heterozygous subjects seem more prone to hyperuricemia, or even gout [23].

3. Conclusion

Hereditary fructose intolerance is a rare condition that induces hypoglycaemia. When a strict fructose-free diet is adhered to, vitamin C supplements should be prescribed (taking care that fructose is not contained in them as an excipient). In adults, diagnosis should be evoked in case of unexplained liver disease, irritable bowel syndrome or hypoglycaemia induced by fructose absorption.

References