Clinical Presentation of Hereditary Fructose Intolerance Prior to Complementary Feeding. What Excipients Can Do

Apresentação Clínica da Intolerância Hereditária à Frutose Prévia à Diversificação Alimentar. O Papel dos Excipientes

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Resumo

Os autores descrevem um caso de intolerância hereditária à frutose com apresentação clínica prévia à diversificação alimentar num lactente de dois meses, que apresentou um primeiro episódio de hipoglicemia sintomática (crise convulsiva generalizada), durante uma infeção respiratória febril dispneizante, sob terapêutica com claritromicina e betametasona orais. Aos 9 meses apresentou um segundo episódio de hipoglicemia após ingestão de um iogurte de aromas. A evidência de hepatomegalia e os achados laboratoriais sugeriam o diagnóstico de doença de Von Gierke, não confirmado por estudos moleculares. Posteriormente, a mãe relatou episódios repetidos de vómitos, duas horas após a ingestão de certos alimentos, o que levou à suspeita clínica de intolerância hereditária à frutose, confirmada por análise genética.
Poucos casos estão descritos de descompensação metabólica de intolerância hereditária à frutose prévia à diversificação alimentar, sobretudo em lactentes exclusivamente amamentados.
Conclui-se que algumas formulações pediátricas de utilização comum contêm excipientes que podem estar na origem de descompensação metabólica da intolerância hereditária à frutose.

Palavras-chave: Hipoglicemia; Intolerância à Frutose/genética; Lactente; Frutose-Bifosfato Aldolase; Excipientes

Abstract

We report a case of hereditary fructose intolerance (HFI) with clinical onset prior to complementary feeding: a two-month-old infant who had a first symptomatic hypoglycaemic episode (generalized seizures) during a febrile respiratory infection with dyspnoea, while medicated with clarithromycin and betamethasone oral formulations. At nine months he presented a new hypoglycaemic episode two hours after eating a flavoured yoghurt. Hepatomegaly and laboratory findings suggested a diagnosis of Von Gierke's disease, not confirmed by molecular studies. Subsequently, his mother reported repeated vomiting episodes two hours after the ingestion of certain foods, leading to the clinical suspicion of HFI, subsequently confirmed by genetic analysis.
There are few cases reporting metabolic decompensation of HFI prior to complementary feeding, mainly in exclusively breastfed children. We conclude that some routinely used formulations contain excipients that can precipitate metabolic decompensation in HFI.

Keywords: Hypoglycemia; Fructose Intolerance/genetics; Infant; Fructose-Bisphosphate Aldolase; Excipients;

Introduction

Hypoglycaemia is common to several clinical entities, including poisoning, endocrine disorders and inborn errors of metabolism. It should be rapidly recognized, promptly treated and the aetiology investigated in order to establish a therapeutic plan and minimize the long-term consequences [1, 2].
In a state of metabolic decompensation, laboratory changes are frequently misleading, making the diagnosis difficult. Genetic analysis makes an important contribution[3,4], but careful anamnesis may be still the key to help identify the underlying cause.
Clinical presentation of HFI rarely occurs prior to complementary feeding, and in breastfed infants finding the cause of metabolic decompensation can be almost detective work.

Case report

A male infant, only child of young, healthy and unrelated parents, had an unremarkable birth and neonatal period, with no episodes of hypoglycaemia and a negative metabolic screening. He was exclusively breastfed up to 5.5 months.

At two months, he was treated with clarithromycin paediatric oral suspension (Klacid pediátrico®, Abbot Laboratories), betamethasone oral solution (Celestone® 0.5 mg/ml oral solution, Merck Sharp & Dohme, Lda) and nebulized salbutamol for a febrile respiratory infection with associated dyspnoea. While on this medication he presented symptomatic hypoglycaemia (plasma glucose 0.4 mmol/l [7 mg/dl]) manifested by a generalized motor crisis with clonic movements of all four limbs. He was being exclusively breastfed, had no history of vomiting and the physical examination was normal including absence of abdominal organomegaly.

At nine months, in the course of persistent vomiting two hours after eating a flavoured yoghurt, he had a new episode of symptomatic hypoglycaemia (blood glucose 1.3 mmol/l [23 mg/dl]), manifested as marked prostration and drowsiness. The physical examination showed age-appropriate growth and psychomotor development and hepatomegaly 7 cm below the right costal margin. Blood tests revealed metabolic acidosis with hyperlactacidaemia (lactic acid 4.8 mmol/l), hyperuricaemia (uric acid 369 µmol/l), hyperlipidaemia (LDL cholesterol 3.55 mmol/l and triglycerides 2.17 mmol/l) and hypertransaminasaemia (alanine aminotransferase 147 IU/l and aspartate aminotransferase 438 IU/l), subsequently reverting to normal levels. Clotting times were normal. Urine reducing substances were negative (urine collected one week after the period of symptomatic hypoglycaemia), as was urine sugar chromatography. Abdominal ultrasonography confirmed the hepatomegaly and suggested hepatic steatosis.

Insulin, C-peptide, growth hormone, IGF-1 and IGF-1-BP3 levels were appropriate for the glycaemia.

Molecular assay of the glucose-6-phosphatase gene was normal.

Reviewing the history, it was noticed that the child had refused certain foods, particularly fruit, some soups and flavoured yoghurt, presenting intermittent vomiting episodes (about 2 to 2.5 hours after the meal) after eating small quantities of these foods.

The anamnesis, hepatomegaly and high transaminases suggested a diagnosis of hereditary fructose intolerance (HFI). This hypothesis was tested and confirmed by genetic analysis of the aldolase B gene, which revealed the p.R60X and p.A175D mutations on exons 3 and 5, respectively.

A fructose, sucrose and sorbitol free diet was started and there was complete recovery of the laboratory abnormalities and the hepatic steatosis. No more hypoglycaemic episodes were detected and the child is achieving age-appropriate developmental milestones and growth.

Discussion

HFI is inherited as an autosomal recessive disease with an estimated prevalence of over 1:26 000 live births in Europe.[4] The condition results from a deficit of fructose-1,6-bisphosphate aldolase (aldolase B) which, in the presence of fructose, sucrose (glucose + fructose) or sorbitol leads to the accumulation of fructose 1-phosphate, a toxic metabolite which inhibits the process of gluconeogenesis, resulting in hypoglycaemia.[5] The onset of clinical manifestations prior to complementary feeding is classically linked to formulas containing one of these sugars (such as soy formulas) and there are few descriptions of symptoms during exclusive breastfeeding.[6,7] Nevertheless, many paediatric drugs[8] such as oral suspension of clarithromycin[9] and betamethasone oral solution[10] contain sucrose and sugar alcohols among their excipients. The drugs given to our patient were probably responsible for the metabolic decompensation and the early onset symptoms of HFI.

In this particular case, the onset of symptoms before the initiation of complementary feeding, and the triad of lactic acidosis, hyperuricaemia and hyperlipidaemia (which later was found not to be persistent) concomitant with hypoglycaemia, hepatomegaly and hepatic steatosis, initially suggested a diagnosis of type Ia glycogen storage disease (von Gierke's disease). The clinical onset of symptomatic hypoglycemia long before the complementary feeding, the lack of urinary reducing substances and repeated normal urine sugar chromatography complicated the diagnosis. However, the normal glucose-6-phosphatase gene molecular assay, the refusal of fruit, yoghurt and some sweet vegetables like carrots, the repeated episodes of vomiting and hypoglycaemia occurring about 2 to 2.5 hours after a meal containing these foods made the hypothesis of HFI more likely.

Hepatic steatosis with mild to moderate elevation of aminotransferases is described as part of the clinical picture of HFI, sometimes compensated and silent. Proximal tubular dysfunction (Fanconi syndrome) is also described in both type Ia glycogen storage disease and HFI.

The absence of urinary reducing substances and the normal urine sugar chromatography under regular feeding also hampered the initial diagnostic investigation. These are almost invariably present in HFI during periods of decompensation.[1] However, if urine is collected outside this period or if the patient completely refuses foods containing fructose, they lose diagnostic value.

The anamnesis, which highlighted the child's selective food refusal and the short time between the previous meal and the emerging symptoms of hypoglycaemia,

proved to be pivotal to the diagnosis, which was confirmed by genetic testing.[1]

It should be remembered that sucrose and sorbitol, often used as excipients in paediatric formulations (Fig. 1), are not always harmless[2] and may trigger metabolic decompensation in children not yet diagnosed with inborn errors of metabolism, and we emphasize the need for a careful anamnesis, as laboratory findings can sometimes be treacherous and misleading.

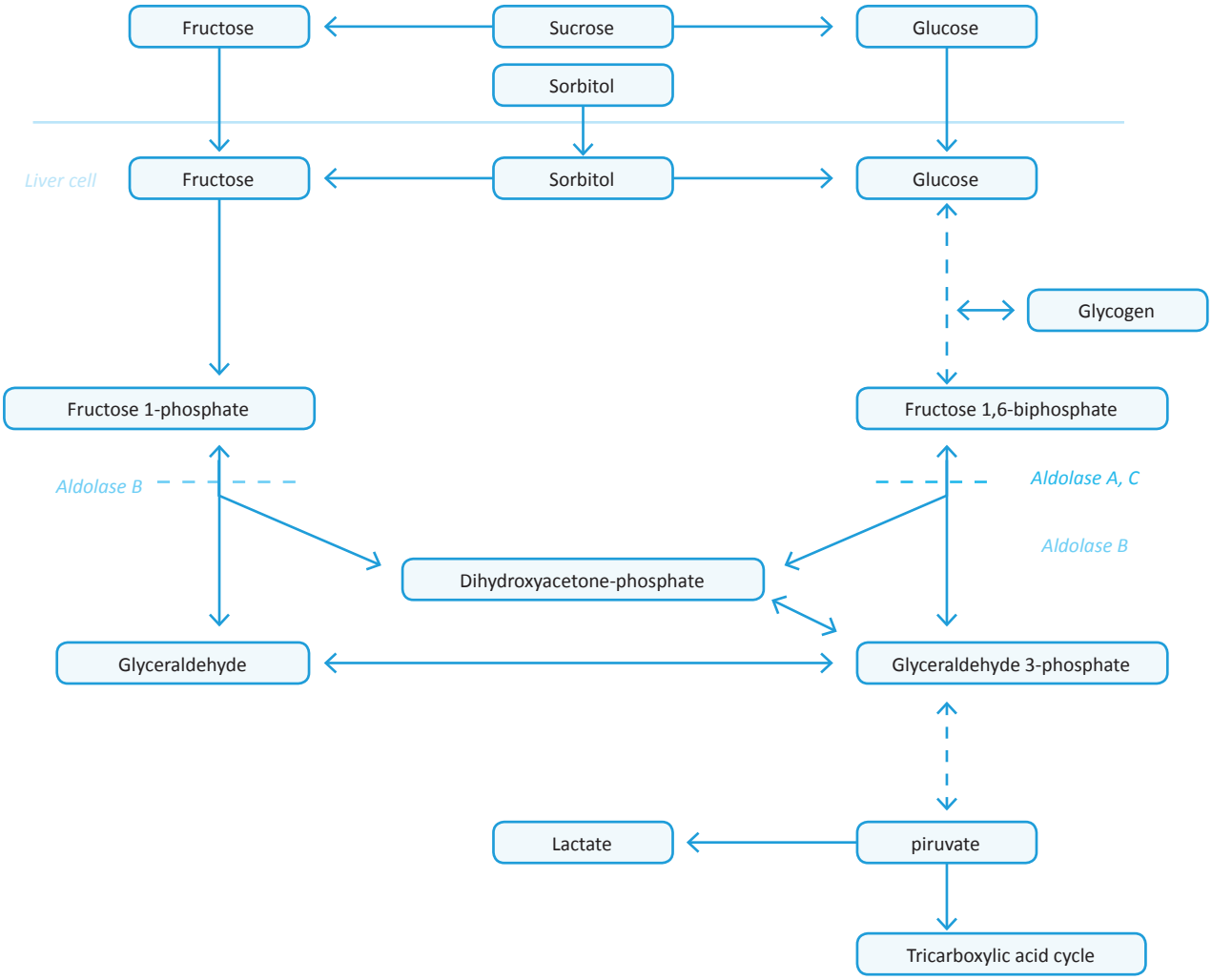

Figure 1. Hepatic fructose metabolism in hereditary fructose intolerance (aldolase B deficiency).

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Protection of human and animal subjects

The authorsdeclare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

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