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Case Report

A Novel Genetic Anomaly in a Case of Hereditary Fructose Intolerance

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Abstract

In the present article, we report the case of a three-year-old female patient who was diagnosed with congenital fructosemia. The distinctive feature of this case lies in the genetic basis of the disease, which consists of two chromosomal deletions, one of which has been entirely unknown until now.

This makes the prognosis difficult to establish, and the patient must be monitored carefully.

Careful clinical and laboratory monitoring is necessary to evaluate the patient's progress.

Keywords: fructose; hypoglycemia; hepatic impairment

Introduction

Fructose is a monosaccharide commonly found in foods consumed daily by humans (fruits, sweet vegetables, honey, syrups, sugar, etc.). [1]

The amount of fructose in each food item is variable. In addition, owing to its sweet taste, fructose is used in pharmacology as an excipient in medicines intended for pediatric use.

The role of fructose in the human body is to produce energy. This is obtained through its breakdown in various tissues (liver, kidney, adipose tissue, etc.), a process known as fructolysis. [1]

The main organ involved in fructose metabolism is the liver. At this level, there is an interplay between the pathways of fructose breakdown and those of endogenous glucose production. [2]

In some patients there is a genetic inability to break down fructose, a condition known as fructosemia or hereditary fructose intolerance. The condition has an autosomal recessive inheritance pattern and is caused by the absence of activity of the enzyme aldolase B, the activity of which is encoded by the ALDOB gene. [3]

The main clinical manifestation is hepatic failure which, if left untreated, may lead to death.

With this article, we aim to raise awareness of this condition as a potential cause of liver disease. This is critically important, given that fructose is widely used as a sweetener in pediatric pharmaceutical practice and the food industry.

Methodology

The diagnosis was established through sequencing of the ALDOB gene by the NGS technique, using PCR and bidirectional sequencing of the coding region and the exon–intron junctions of the ALDOB gene

Two deletions were identified: g.5813delGGTA (IVS2-1Δ4) and g.10699delCAGCTGTTCCTG (Δ12E7).

Whereas the IVS2-1Δ4 deletion in exon 3 has been described in the specialist literature as a variant of pathogenic clinical significance, the Δ12E7 deletion in exon 7 has not been described until now, this being the first reported case.

Case Presentation

The case concerns a three-year-old female patient who presented to medical services for a chronic hepatic condition.

The first episode of hypoglycemia was recorded at the age of four months. In the context of an intestinal rotavirus infection, she was given tea sweetened with sugar for hydration. Following ingestion of the tea, vomiting, hepatic impairment, and hypoglycemia (undetectable blood glucose) accompanied by hyperlactacidemia appeared. Investigations were not pursued further.

At the age of one year, after being given banana, the girl experienced a new episode of hypoglycemia against a background of abruptly occurring hepatic distress. A hepatic ultrasound performed at this time indicated hepatic hyperechogenicity.

After the age of two, episodes of hypoglycemia persist—apparently triggered by the administration of sweet syrups—and hepatomegaly accompanied by hepatic cytolysis is observed. The attending physician suspects congenital fructosemia, noting a cause-and-effect relationship

between the administration of sugar-containing pharmaceutical syrups and the onset of hepatic cytolysis; although this suspicion is recorded in the patient's medical file, further investigations are not pursued.

After the age of three years, since the hepatic impairment persisted, she presented for a consultation for inborn errors of metabolism. From the medical history, several aspects were noted, namely the fact that the girl had hyperketotic hypoglycemia, and also that these episodes appeared abruptly, in a state of apparent health, and shortly after the administration of sucrose or fructose. In these circumstances, we decided to begin the investigations with sequencing of the exons 5 and 9 ALDOB gene.

Nevertheless, the result was negative. Since the clinical picture was nonetheless suggestive of congenital fructosemia, I decided to sequence the entire ALDOB gene by the NGS technique (all eight exons).

Two deletions were identified: g.5813delGGTA (IVS2-1Δ4) and g.10699delCAGCTGTTCCTG (Δ12E7). The IVS2-1Δ4 deletion in exon 3 has been described in the specialist literature as a variant of pathogenic clinical significance; the Δ12E7 deletion in exon 7 has not been described until now, this being the first known case.

The existence of this novel deletion makes the prognosis more difficult to establish and the course of the disease harder to predict. Nevertheless, we decided to manage this case therapeutically in the same manner as other cases of fructosemia.

Treatment and Monitoring

The cornerstone of treatment was the dietary regimen, which aimed at the complete elimination of fructose intake. This could be achieved by excluding fruits and vegetables from the diet. However, a therapeutic challenge arose when the patient experienced the typical respiratory infections of childhood, since the pharmaceutical syrups used in pediatric practice are enriched with sugar in order to improve the taste and increase therapeutic compliance.

The solution adopted was the preparation of special pharmaceutical compounds at a specialized compounding pharmacy.

Liver function tests were monitored monthly, and their normalization was observed under a strict dietary regimen (see table 1)

Before treatment				After treatment		
				Diet but with sugar containing syrups	Diet and no sugar containing syrups	
Parameter	Normal range	Results		Results		
TGO	10-35	162	139.1	91.7	65.2	96.9
TGP	10-35	96	241.8	75.8	50.7	102.5
glycemia	60-100	61	21.8	147.7		

Table 1: The liver ultrasound performed prior to the initiation of treatment indicated liver enlargement and hyperechogenicity.

Discussion

Fructose is a monosaccharide widely distributed in nature, found abundantly in fruits, vegetables, and honey, as well as in sweet syrups and pharmaceutical syrups for pediatric use. [4]

Once it enters the body, it is taken up by several organs without the need for insulin. Its breakdown, known as fructolysis, is closely linked to the process of glucose catabolism. The main site of its breakdown is the liver, and the final products are glycogen and triglycerides. [4]

Another site of fructose breakdown is the small intestine, and the breakdown process is rapid enough that, after only two hours from ingestion, the serum level falls to the fasting value. [5] If the rate of ingestion is very high, the breakdown capacity of the intestine is exceeded, and the catabolic products reach the liver, where they are completely broken down. [5]

Fructose may also enter gluconeogenesis, which ultimately leads to glucose production. [6]

Excessive fructose consumption leads to obesity and dyslipidemia. The mechanism of dyslipidemia is presented schematically in the diagram below. [7]

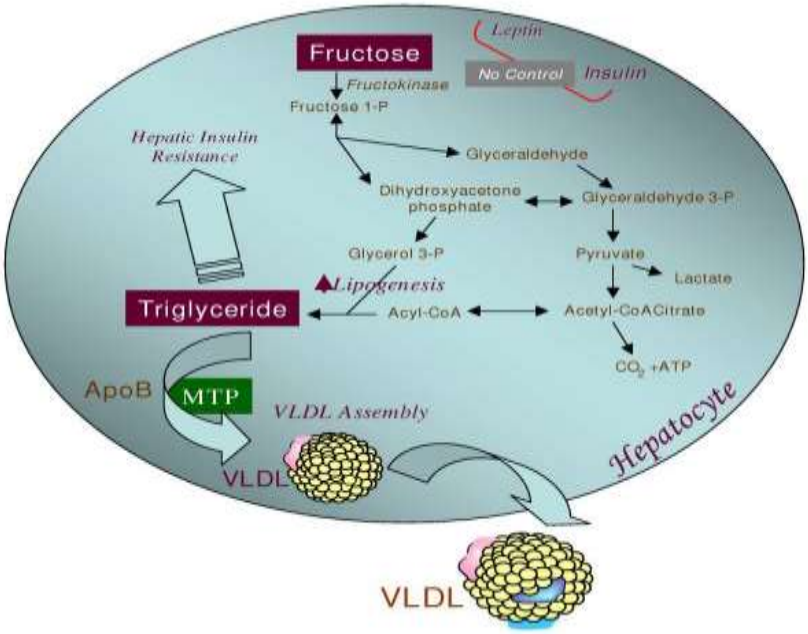


Figure 1: Fructose metabolism in the human body

A very important enzyme in fructose metabolism is aldolase B, which converts fructose-1-phosphate into dihydroxyacetone phosphate and glyceraldehyde. [8]

Fructose-1-phosphate is a molecule with a strong inhibitory effect on phosphomannose isomerase, an enzyme involved in the process of N-glycosylation. [9]

In addition, the accumulation of fructose-1-phosphate is hepatotoxic and also leads to a decrease in the level of intracellular phosphorus. [9]

The production and activity of the enzyme aldolase B are controlled by the ALDOB gene. This gene is located on chromosome 9q22.3. A mutation occurring at this level leads to the production of an enzyme of poor quality, which results in an increase in the serum level of fructose-1-phosphate, a situation known as hereditary fructose intolerance. [10]

To date, several gene mutations are known and reported, the most frequent being p.A150P (64%), p.A175D (16%), and p.N335K (5%). Deletions, insertions, and splice-site mutations have also been reported. [11]

Primary fructose intolerance is an inborn error of metabolism characterized by the inability to break down fructose. This fructose originates from sugar-rich foods, but there is also an endogenous production of fructose that starts from glucose via the polyol pathway. [12]

The central element in this disease is the dysfunction of an enzyme called aldolase B. The role of this enzyme is to catabolize a product called fructose-1-phosphate. Its production requires phosphate, which is drawn from intracellular reserves. The enzymatic dysfunction has two main effects, namely the accumulation of fructose-1-phosphate and the depletion of intracellular phosphate reserves, which lead to the inhibition of phosphorylase A. [3]

The role of phosphorylase A is to inhibit glycogen synthase. [13] Another effect is the decrease in ATP, which leads to increased breakdown of AMP and to secondary hyperuricemia. [3]

The clinical picture of this condition is dominated by hepatic distress. This is due primarily to the accumulation of fructose-1-phosphate and, secondarily, to the depletion of intracellular phosphate. Hepatic impairment is clinically expressed through vomiting, jaundice, bleeding, and lethargy. [14]

A rarer manifestation of this disease is hypoglycemia. Its main mechanism is the inhibition of both gluconeogenesis and glycogenolysis by the excess of fructose-1-phosphate. [14]

An increase in pyruvate kinase activity is also observed, which leads to the accumulation of Krebs cycle precursors, in particular lactate and pyruvate, with secondary metabolic acidosis. [14]

Another element encountered in this pathology is the decrease in the level of intracellular phosphate. Secondary to this process, an increase in the level of uric acid in the blood is observed through the activation of adenosine deaminase, which leads to the stimulation of purine breakdown. In addition to hyperuricemia, hypophosphatemia and hypermagnesemia are also observed. [14]

The renal impairment encountered in hereditary fructose intolerance is due to the same mechanism as the acidosis. The nephropathy has the clinical appearance of Fanconi syndrome, more precisely aminoaciduria, phosphaturia, and renal loss of bicarbonate with secondary tubular acidosis. [14]

Treatment

The cornerstone of the treatment of this condition is the avoidance of fructose-1-phosphate accumulation. This originates from two main sources, namely the dietary intake of fructose and the endogenous production of fructose-1-phosphate.

Reducing the dietary intake of fructose represents the most important therapeutic link. [15] This can be achieved by encouraging breastfeeding during the first six months of life or by using special formulas. Complementary feeding is recommended, but with avoidance of foods with a high fructose content. Special attention must be paid to products that contain alternative sources of fructose to sugar, such as sorbitol. [16]

An increasingly common practice is the addition of fructose as an excipient in pediatric pharmaceutical preparations, which requires heightened vigilance on the part of parents and medical staff.

A therapeutic possibility currently under study is the pharmaceutical inhibition of hexofructokinase, an enzyme essential to fructose catabolism. This can be achieved with the help of two molecules under investigation, pyridine 12 [17] and PF06835919. [18]

A complication of the dietary regimen is vitamin C deficiency. This is clinically manifested by marked asthenia; therefore, monitoring vitamin C levels and supplementation in the event of deficiency are mandatory. [19]

Another source of fructose, and by implication of fructose-1-phosphate, is the endogenous production of fructose from sorbitol via the polyol pathway. [20] This pathway does not ensure a significant production of fructose and, by implication, of fructose-1-phosphate; rather, it is a metabolic pathway that is particularly active under conditions of hyperglycemia and not of normoglycemia or hypoglycemia. [21]

The prognosis in this disease is difficult to establish because of several particularities. First, there are not enough patients who have reached adulthood and been monitored, the incidence of this disease being low (1/100,000 births). [22] The impact of the renal impairment and the incidence of diabetes mellitus associated with this disease are not fully known.

There is also an endogenous production of fructose-1-phosphate which, although not of significant intensity, may influence the long-term prognosis.

The degree of hepatic impairment is variable. In patients who adhere to the dietary regimen, it ranges from simple hepatic cytolysis to hepatic steatosis. [22]

However, the studies conducted so far do not indicate a clear correlation between fructose intake and the degree of hepatic impairment. A correlation is nonetheless observed between the severity of hepatic impairment and the percentage of disialotransferrin and the ratio between tetrasialotransferrin and disialotransferrin. [23] This observation makes the sialotransferrin profile an interesting indicator for establishing the prognosis of fructosemia; however, further clinical studies in this direction are needed.

Conclusion

Primary fructose intolerance, also known as fructosemia, is a rare inborn error of metabolism. Nevertheless, this diagnosis must be considered in any patient with hepatic impairment, especially if the symptomatology is triggered by the administration of medicines or sugar-rich foods.
The prognosis remains good as long as the diagnosis is established early. However, it can be observed that, despite a very strict diet and the complete exclusion of fructose sources—including fructose-enriched pharmaceutical preparations—complete normalization of liver function tests was not achieved after six months.

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