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Hereditary fructose intolerance: etiology and main clinical features

Intolerância hereditária à frutose: etiologia e principais características clínicas

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ABSTRACT

Introduction: Fructose is a monosaccharide that makes up sucrose and is found in vegetable sources, honey and fruits. After being consumed, its absorption is facilitated by glucose transporters, metabolized in the liver, small intestine and kidneys. Hereditary fructose intolerance is due to mutations in the ALDOB gene, which encodes the enzyme aldolase B, the main player in fructose catabolism. Therefore, intolerance is the result of a deficiency of this enzyme.

Objective: Review etiological factors of the disease, main symptoms and treatment.

Method: Narrative review of biochemistry and genetics textbooks and electronic databases (PubMed, Orphanet, Google Scholar and Scielo) between July and September 2023.

Result: 18 articles were included.

Conclusion: Being the result of genetic mutations, there is no effective treatment, as is the case with lactose intolerance, due to the fact that aldolase B is not available in capsule, like lactase. Therefore, treatment is dietary restriction of fructose, sucrose, sucralose and sorbitol, with vitamin supplementation. If left untreated, it can most often result in kidney failure, metabolic acidosis, and liver cirrhosis.

KEYWORDS: Hereditary Fructose Intolerance. ALDOB deficiency. Fructose-1-Phosphate aldolase deficiencies.

RESUMO

Introdução: Frutose é um monossacarídeo que compõe a sacarose e é encontrado em fontes vegetais, mel e frutas. Após ser consumida, ela tem sua absorção facilitada pelos transportadores de glicose, metabolizada no fígado, intestino delgado e rins. A intolerância hereditária à frutose é decorrente de mutações no gene ALDOB, que codifica a enzima aldolase B, principal atuante no catabolismo da frutose. Sendo assim, a intolerância é resultado da deficiência dessa enzima.

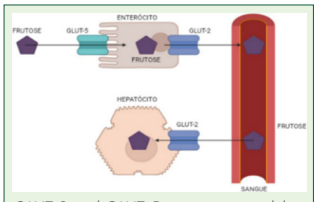
Objetivo: Revisar fatores etiológicos da doença, principais sintomas e tratamento.

Método: Revisão narrativa em livros-texto de bioquímica e genética e em bases de dados eletrônicos (PubMed, Orphanet, Google Acadêmico e Scielo) entre julho e setembro de 2023.

Resultado: Foram incluídos 18 artigos.

Conclusão: Por ser resultado de mutações genéticas, não existe tratamento eficaz como é no caso da intolerância à lactose, pois a aldolase B não está disponível em cápsula, como a lactase. Portanto, o tratamento é restrição alimentar de frutose, sacarose, sucralose e sorbitol, e suplementação vitamínica. Se não tratada, mais frequentemente pode resultar em falha renal, acidose metabólica, e cirrose hepática.

PALAVRAS-CHAVE: Intolerância à frutose. Frutose-bifosfato aldolase, Erros inatos do metabolismo de carboidratos.



GLUT-2 and GLUT-5 transporters and their mechanism of action

Central Message

Fructose is a type of simple sugar found in the human body and in various plant sources, such as honey and fruits. It is also an essential component of sucrose, the predominant sweetener in sweets and syrups. Its intake is a regular part of the diet. Inborn errors of metabolism, which occur in this disease, are relatively rare and with diverse clinical manifestations and associated with enzyme disorders, absent or decreased. This review sought to update the knowledge of this entity, which is uncommon in outpatient clinics and can explain clinical situations that are difficult to diagnose.

Perspective

IHF is a rare and innate error of metabolism, resulting from mutations in ALDOB, located on the long arm of chromosome 9. It has autosomal recessive inheritance, results in undue accumulation of fructose in the bloodstream, and causes gastroenteric symptoms. With its recognition, the prognosis is good, as long as there is total fructose restriction in the diet and multivitamin supplementation, since the dietary diversity of the carrier is more limited.

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INTRODUCTION

Fructose is a type of simple sugar found in the human body and in various plant sources, such as honey and fruits. It is also an essential component of sucrose, the predominant sweetener in sweets and syrups. Its intake is a regular part of the diet.

In the human brain, small amounts of fructose are synthesized through a metabolic pathway called "polyol", and it also plays a key role in regulating the body's redox balance. After being consumed, it is absorbed through glucose transporters (GLUTs) in the intestine GLUT-5 and in the liver GLUT-2. Most of its metabolism occurs in the liver, kidney, and small intestine, where enzymes such as fructokinase, aldolase B, and triokinase play a crucial role.

Fructose is often associated with genetic errors in its processing, which can lead to serious clinical complications, such as hereditary fructose intolerance (IHF). In this disorder, deficiency in the enzyme aldolase B generates accumulation of fructose-1-phosphate in the liver, kidneys, and small intestine, which is harmful to these organs and results in symptoms such as nausea, diarrhea, flatulence, low blood sugar levels, metabolic acidosis, mineral imbalances, and disruption of vital metabolic processes such as gluconeogenesis and glycogenolysis.

It is notable that fructose consumption has increased considerably in recent years, especially in developed nations, due to the increase in the intake of industrialized products that use fructose and sorbitol as sweeteners, since the fructose metabolic pathway is independent of glucose. Therefore, it is crucial to understand the metabolic aspects of fructose and the potential impacts of failures in its metabolic processing.[1]

Due to the relative infrequency, the aim of this study was to review the main etiological factors involved in HFI, the main symptoms found, and the treatment that should be performed.

METHOD

A narrative literature review was performed in pediatric biochemistry and genetics textbooks and in electronic databases (PubMed, Orphanet, Google Scholar, and Scielo), using the descriptors: "hereditary fructose intolerance, ALDOB, and fructose" between July and September 2023.

DISCUSSION

Genetics

Inborn errors of metabolism are relatively rare diseases and usually have a high potential for severity for the health of patients. The clinical manifestations of inborn errors of metabolism are diverse and are associated with enzyme disorders, which may be absent or diminished. Disorders of carbohydrate metabolism include enzymatic deficiencies of galactose, glycogen, and fructose metabolism pathways. Fructose is a 6-carbon monosaccharide that is naturally present in a variety of foods, such as fruits, honey, and vegetables.

Humans have a reduced capacity to absorb fructose, since it has an energy-independent process and has a variable capacity, that is, its metabolism can saturate depending on the concentrations of the media. While glucose is completely absorbed in the small intestine by an active transport mechanism facilitated by the GLUT-2 and GLUT-5 transporters, fructose is primarily absorbed by facilitated diffusion mediated by GLUT-5 and carriers expressed on the brush edges of enterocytes and by GLUT-2 that transports fructose from the enterocyte into the bloodstream and subsequently into the hepatocyte, as shown in Figure 1.[2,3]

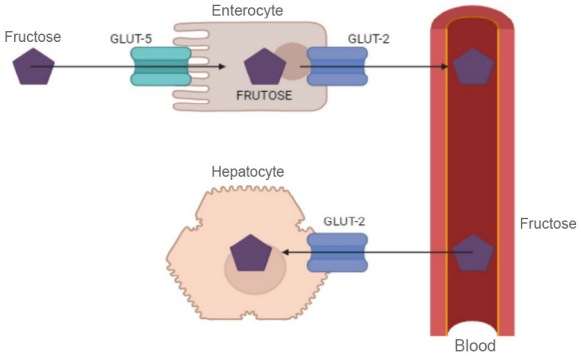


FIGURE 1 — GLUT-2 and GLUT-5 transporters and their mechanism of action

IHF is an autosomal recessive disease, with an estimated prevalence ranging from 1/20,000 to 1/60,000 in Europe, and in the adult population it is unknown because it is poorly diagnosed and often erroneously referred to as irritable bowel syndrome. It can be homozygous or heterozygous compound, caused by mutations in the ALDOB gene (9q22.[3],) which encodes the enzyme aldolase B and results in hepatic fructose-1-phosphate aldolase deficiency. This leads to a variety of gastrointestinal disorders, such as diarrhea, and those affected are unable to fully metabolize fructose in the liver, intestine, and kidneys due to the deficiency of this enzyme.[3]

The frequency of IHF was estimated from carriers of the variants, at 1/70. The p. (Ala150Pro) and p. (Ala175Asp) variants are the most frequent, since they represent approximately 68% of the alleles, and are widely distributed in the world population.[4,5]

Pathogenesis

Being a monosaccharide, fructose is formed by 6 carbon atoms joined by simple covalent bonds, with hydroxyl groups, composed of hydrogen and a carbonyl group, which has a double bond between carbon and oxygen. The difference between glucose and fructose is the position of the carbonyl group, which is critical in determining whether a ketone or aldehyde will be formed after hydrolysis. In the case of fructose, it will provide ketone and glucose, aldehyde.[1]

Currently, fructose, in many cases, replaces glucose in the diet for people with diabetes mellitus, since it does not depend on insulin for its metabolism; however, its excessive use can bring adverse effects, due to the increase in triglycerides and cholesterol in the blood. This monosaccharide is being used more as a sweetener in industrialized beverages and fruits in recent years, making consumers believe it is less harmful to health. In confectioneries, for example, fructose is part of about 1-2% of the weight of food and can be part of up to 11% of the composition if the food has fruit, and up to 42% if it contains honey. In addition to being found in sweets, fructose is also consumed through vegetables, which in turn have 1-2% of this sugar in their composition. With this, it can be ensured that fructose is ingested by the entire current population, whether in the form of sweets, vegetables, beverages, or sweeteners.[1]

The metabolism of this monosaccharide, which can saturate depending on the substrate concentration of the media, depends on some organs, such as the liver, small intestine and kidneys. In turn, these 3 metabolization sites have a different composition, since the liver is lined with connective tissue and has hepatic lobules as its functional part; the small intestine is characterized by mucosa of epithelial tissue with simple columnar lining and lamina propria composed of loose connective tissue itself; and the kidneys are composed of dense connective tissue capsules with a large amount of elastic fibers.

In the intestine, fructose is absorbed initially by the facilitated transport mechanism, which is independent of glucose, and then by a cotransport which, in turn, depends on glucose. Facilitated diffusion occurs due to the presence of membrane proteins called GLUT-5, which are located on the brush border of epithelial enterocytes (absorption cells located in the intestine). After being absorbed, the monosaccharide leaves the enterocyte, with the help of GLUT-2, and goes to the bloodstream, where it will be transported to the liver, to be metabolized mainly by aldolase B.

The liver is the main organ of fructose metabolization, which is initially metabolized by the active enzyme ketohexokinase (KHK), which converts it to fructose-1-phosphate (FP1) and later cleaved by the rate-limiting enzyme aldolase B to glyceraldehyde (GA) and dihydroxyacetone phosphate (DHAP). Glyceraldehyde undergoes a series of metabolic conversions to form pyruvate, which can be transformed into lactate, undergo oxidative breakdown of acetyl and malonyl coenzyme A (CoA), finally generating triacylglycerol (TAG). The formation of malonyl-CoA can alter the balance between oxidation and fatty acid synthesis through an effect on the enzyme acetyl-CoA carboxylase, which results in the inhibition of adenosine monophosphate activated protein kinase (AMPK), which stimulates fatty acid oxidation, and the enzyme carnitine-palmitoyl transferase I (CPT1), which controls the entry of fatty acids into the mitochondria. The enzyme ATP citrate lyase (ACLY), which uses cytosolic citrate to generate acetyl-CoA, also increases in level due to the consumption of fructose. The protein glyceraldehyde-3-phosphate dehydrogenase converts dihydroxyacetone phosphate into glycerol-3-phosphate, which, along with fatty acids, generates triacylglycerol.[6]

Hereditary fructose intolerance, unlike lactose intolerance (which is an intestinal disease), consists of a liver defect caused by the deficiency of the enzyme aldolase B, which is present mainly in the liver, but also in the kidneys and small intestine, causing the accumulation of fructose-1-phosphate (F1P), which damages these organs.[7] In addition to the increase in fructose-1-phosphate levels, there is a decrease in the level of organic phosphorus and a derangement in phosphate potential, which explains symptoms such as nausea, vomiting, renal overload, urinary acidification, and difficulty in tubular reabsorption. Therefore, there is an increase in fructose in the blood, the blockade of phosphorylase and fructose-1,6-diphosphate-aldolase activity, which causes a reduction in glycolysis and glycogenolysis and the interruption of gluconeogenesis, which justifies hypoglycemia in patients. In addition, because the lack of phosphate disrupts the entire cellular process that requires phosphorylation or adenosine triphosphate, including glycogenolysis and gluconeogenesis, the administration of glucagon is not able to correct hypoglycemia. If the case is not treated, it can be accentuated and cause kidney failure, metabolic acidosis, progressive liver cirrhosis, coma and, eventually, death.[1,8-12]

Symptoms

In the clinical case of IHF, described by Lopes et al.[13,] an infant referred to the Pediatric Gastroenterology Unit of Santa Maria Hospital, in Lisbon, at 4 months of age, after vomiting food, is reported. He was exclusively breastfed during the first week of life and continued to use infant formula (Aptamil 1). At 3.[5] months of age, she replaced infant formula with transitional formula, which marked the beginning of a condition of regurgitation and vomiting, frequent, voluminous and, occasionally, in jet. In addition, drowsiness and prostration were associated symptoms. After complementary tests, the hypothesis of gastroesophageal reflux or hypertrophic pylorus stenosis was ruled out. Subsequently, the clinical picture intensified and refusal to eat and weight loss were added to it. Ultrasound evaluations indicated an increase in hepatic dimensions, suggestive of metabolic liver disease, and the hypothesis of hepatitis was discarded. During hospitalization, infant formula was changed, which accompanied the absence of symptoms and improvement in transaminase values. From 4 months of age, food introduction began, including vegetable soup (potato, onion, carrot, turnip) and non-dairy porridge, meat at 5 months, fruit porridge at 6 and natural fruit at 7 (banana, pear, apple). The child maintained the absence of symptoms until 6-7 months, which was consistent with

the introduction to fruits. From this, vomiting, refusal to feed and weight loss reappear, associated with perianal erythema, agitation and night crying. The hypothesis of hereditary intolerance to fructose was now considered, compatible with the measurement of hepatic aldoses and the evaluation of the child's 5-year-old brother, who presented food refusal for fruits and sugary foods. Tests indicated the presence of a mutant allele of aldolase B (A149P) in the mother and brother, which, associated with the nutritional history, confirmed the diagnosis of IHF.[13]

The disease manifests itself through a series of symptoms, including vomiting, nausea, sweating, dysentery, jaundice and abdominal pain, often associated with hypoglycemia and metabolic acidosis. This condition represents exemplarily how genetic and dietary factors, that is, modified by eating behavior, can interact to cause disease. It should be noted that individuals with different levels of tolerance to this monosaccharide have different clinical manifestations.

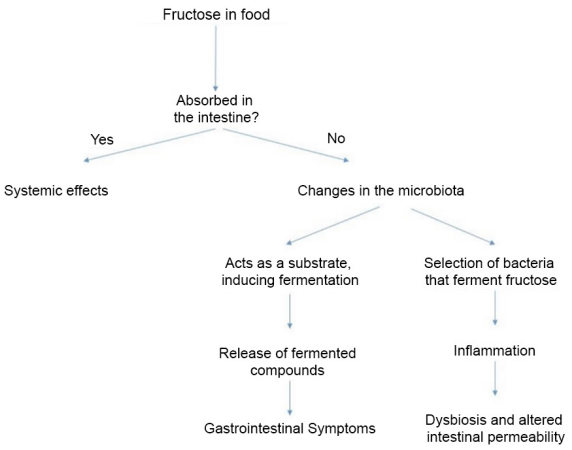
It is observed that in newborns exclusively breastfed there is no manifestation of symptoms, which is due to fact that in milk the main source of carbohydrate is lactose, a disaccharide composed of galactose and glucose. The appearance of signs usually occurs after weaning, during food introduction, in which there is the presence of foods containing fructose, such as fruits, vegetables and honey. In addition, persistent intake of harmful sugars has been found to lead to chronic toxicity syndrome, which can result in growth delays and damage to the liver and kidneys. When the child consumes fructose in large quantities, the acute reaction is more severe; Adults, on the other hand, usually develop an aversion to foods rich in fructose after episodes of abdominal discomfort and nausea.

The intake of fructose, sucrose or sorbitol promotes an increase in fructokinase activity, resulting in the phosphorylation of fructose to fructose 1-phosphate. Fructose-1-phosphate is not cleaved into DHAP and glyceraldehyde and accumulates in excess due to the deficient aldolase B enzyme in IHF carriers. The result of this is the depletion of ATP and the decrease in inorganic phosphate (Pi) levels. This situation has consequences for the kidneys, liver, and intestine, which, in turn, characterize the symptoms of IHF.

In the kidneys, the decrease in inorganic phosphate (Pi) levels promotes derangement in the phosphate potential, generating overload, in addition to vomiting and nausea. The accumulation of phosphate causes the kidneys to lose their capacity, generating urinary acidification and hindering tubular reabsorption, which can lead to kidney failure. The accumulation of fructose (which can even be found in the urine) is also a potent trigger of inflammation and necrosis, and can be considered a facilitator for kidney failure, in addition to the ionic imbalance already presented. In more severe cases, metabolic acidosis may be a present clinical manifestation triggered by hypoglycemia, which is maintained due to the impairment of the hepatic metabolic pathways mentioned above and leads to the formation of ketone bodies as products of an alternative metabolic pathway. The hepatic inability to regulate blood glucose in this disease is the main responsible for the maintenance of hypoglycemia in patients, triggering clinical manifestations such as tremors, sweating, and dizziness, which are commonly reported. The accumulation of fructose-1-phosphate inhibits glycogen phosphorylase and, therefore, prevents glycogenolysis because its intracellular increase indicates cellular anabolic need, despite the hypoglycemia presented by the patient. This effect on glycogen metabolism is exacerbated by low Pi levels and explains the decreased response to glucagon, a possible explanation for the consequent deficiency in glycemic regulation exerted by the liver. In addition, another factor that increases the liver's inability to regulate blood glucose is the inhibition of fructokinase and fructose-1,6-bisphosphate aldolase enzymes by fructose-1-phosphate in excess, since it prevents gluconeogenesis. Together, these factors explain the induction of hypoglycemia after ingestion of fructose, sucrose, or sorbitol. At the hepatic level, a possible prognosis that can manifest clinically is liver cirrhosis. The accumulation of fructose-1-phosphate causes an inflammatory process in the liver, triggering the release of inflammatory mediators and recruitment of defense cells that will destroy the hepatic parenchyma, leading to the process of necrosis and derangement of its entire metabolism, which can evolve to steatonecrosis and liver cirrhosis in more chronic cases. In addition, it is possible to observe in patients with IHP an increase in uric acid levels in the blood and urine, because the depletion of ATP levels and, consequently, the equivalent increase in ADP and AMP stimulates a catabolic pathway, which has uric acid as a product. These complications can lead to late hemodynamic manifestations, coma, and even death.

Finally, in the intestine, studies suggest that the abundance of bacteria of the species Eubacterium eligens, Eubacterium rectale and those belonging to the genus Streptococcus are decreased with the ingestion of fructose; these bacteria are known, respectively, to contain enzymes that degrade polysaccharides, act in the production of butyrate and for being responsible for fermenting lactose and sucrose and for metabolizing fructose.[14] The presence of fructose in the intestine of an intolerant individual quickly triggers its fermentation by intestinal bacteria before it is absorbed, producing hydrogen, carbon dioxide and short-chain fatty acids. This translates into gas production, which causes abdominal distension associated with discomfort, flatulence, nausea, abdominal pain, and bowel dysfunction.[15] Fructose, being incompletely absorbed, contributes to the alteration of the intestinal microbiota, as can be seen in Figure 2.[16] This process occurs primarily in the proximal large intestine and possibly in the distal small intestine. When there is an inability to properly

absorb fructose, it can be used as a substrate by the microbiota for fermentation, or even favor the proliferation of bacteria that ferment fructose, leading to the release of fermented compounds that translate into gastrointestinal symptoms and inflammation that causes dysbiosis and alters intestinal permeability.[16]



Source: Adapted from Payne, Chassard and Lacroix16

FIGURE 2 — Possible mechanism by which fructose promotes changes in the microbiota

Diagnosis

Genetic testing can be used for diagnosis. It is done in a proband with suggestive metabolic disorders and clinical findings after exposure to the fructose, sucrose, or sorbitol diet, demonstrating biallelic pathogenic variants in ALDOB identified in molecular genetic testing or, rarely, in deficient hepatic fructose 1-phosphate aldolase (aldolase B) activity in liver biopsy. Fructose tolerance testing ("fructose challenge") in the diagnosis of HFI should be avoided due to its danger. In addition, it is noteworthy that detailed anamnesis, especially for the patient's eating habits, leads to the diagnosis.

Less invasive diagnostic methods are performed from the sequencing of the entire gene or even allele-specific oligonucleotide hybridization (ASO) analysis, both requiring only a blood sample to be performed. The diagnosis of IHF in adults represents a major challenge. Knowledge of intolerance mutations is required, there are 7 best known that make up approximately 82% of the IHF alleles known worldwide, and more than 10% of the alleles are unknown. The performance of diagnostic tests is of great importance for locating other information that is still unknown, which can contribute positively to better treatment and new diagnostic means.

In addition, the diagnosis of fructose intolerance (fructose malabsorption) can be made by a breath test performed fasting for at least 8 hours. This requires that patients have not smoked, chewed gum or candies, and have not exercised for at least 4 hours prior to the test. Antibiotics, laxatives, or colonoscopy cannot be used in the period of 14 days before the breath test. The day before it, a low-carbohydrate diet should be carried out, avoiding the consumption of foods that contain fructose and lactose, as well as foods rich in fiber and fat. The test is based on fact that unabsorbed fructose is fermented by bacteria, resulting in the production of SCFAs and gases, such as hydrogen. This test measures the amount of hydrogen expired, which was the result of fructose fermentation and partially absorbed into the bloodstream and reached the lungs, where it can be quantified. The breath test first requires disinfection of the mouth and teeth. A sample of expired air is obtained on an empty stomach, and then the patient ingests a fructose solution dissolved in water. Breath samples are taken after ingestion of the fructose solution and from 30-30 min to a maximum of 3 h, quantifying the amount of hydrogen expired. The results take into account the amount of hydrogen released, but also the associated symptomatology. Thus, fructose malabsorption is defined as an increase equal to or greater than 20 ppm of expired hydrogen to the baseline value, obtained at the time before fructose ingestion. A value 2 times higher than the baseline, accompanied by symptoms (abdominal distension, flatulence, nausea, diarrhea, pain and reflux) are indicative of fructose intolerance. The coexistence of symptoms and fructose malabsorption is defined as fructose intolerance.

Treatment

Due to the fact that IHF results from mutations in the ALDOB gene (aldolase B) located on chromosome 9q31 - homo or heterozygous compound - there is no effective treatment as in lactose intolerance. Unlike lactase, the enzyme aldolase B is not available in capsule form. Therefore, the core of IHF treatment is dietary restriction of fructose, sucrose, sucralose, and sorbitol. In hospitalization situations, it is crucial to avoid the use of intravenous fluids containing fructose, as well as infant formulas and medications containing this substance.

Given that reduced intake of fruits and vegetables is an essential part of the diet, it is recommended to supplement daily with sugar-free multivitamins to prevent micronutrient deficiencies, especially water-soluble vitamins.

After the identification of pathogenic variants in the ALDOB gene in an affected family member, carrier testing for at-risk family members, prenatal testing during high-risk pregnancies, and even preimplantation genetic testing can be performed and is advisable. This is because IHF is transmitted in an autosomal recessive manner. When both parents are carriers of a pathogenic variant of the ALDOB gene, each sibling of an affected individual has a 25% probability of being affected, 50% of being a carrier, and 25% of not inheriting any of the pathogenic variants.

Typically, when complete dietary restriction of fructose, sucrose, sorbitol, and/or sucralose is initiated early in life and strictly maintained, the prognosis is positive, including normal neurocognitive development, overall health, and life expectancy. However, failure to adhere to recommended dietary

restrictions can lead to the development of chronic liver and/or kidney disease.[17,18]

CONCLUSION

IHF is a rare and innate error of metabolism, resulting from mutations in ALDOB, located on the long arm of chromosome 9. It has autosomal recessive inheritance, results in undue accumulation of fructose in the bloodstream, and causes gastroenteric symptoms. It can progress to more serious diseases, especially kidney and liver diseases. However, in general, the prognosis is good as long as there is total fructose restriction in the diet and multivitamin supplementation, since the dietary diversity of the carrier is more limited.

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