

A REVIEW OF HEREDITARY FRUCTOSE INTOLERANCE

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Abstract

Fructose intolerance is a metabolic disorder with hereditary determinism, clinically manifested on terms of fructose intake. Untreated, hereditary fructose intolerance may result in renal and hepatic failure. Unfortunately, there are no formal diagnostic and surveillance guidelines for this disease. If identified and treated before the occurrence of permanent organ damage, patients can improve their symptoms and self-rated health. Implementation and adherence to a strict fructose free diet is often difficult, but not impossible.

key words: *fructose intolerance, diagnosis, diet*

Introduction

Fructose intolerance is an inborn error of carbohydrate metabolism with a wide specter of manifestations, ranging from subtle symptoms to fatal complications (it is a rare cause of hepatic cirrhosis in the young), from infancy to later in life. This autosomal recessive disorder is due to a deficiency of fructose-1-phosphate aldolase activity, that results in the accumulation of fructose-1-phosphate in the liver, small intestine and kidneys [1-3].

The most important problem in treating this disorder is the difficulty of its diagnosis. European prevalence estimates range between 1:18.000 and 1:31.000. Although most cases have been reported in Europe and North America, it is a rare disease, making its precise prevalence estimates in adults challenging [2].

The purpose of our review is to offer updated information regarding fructose

intolerance, its effects and clinical significance, all very useful to the standard clinical practice.

Etiopathogenesis

This disease is explained by the deficiency of fructose 1 phosphate aldolase deficiency, an enzyme which partakes in the metabolism of fructose, immediately after fructokinase. It allows the transformation of fructose 1 phosphate to glyceraldehyd. In its absence, the fructose 1 phosphate cannot be metabolized; it accumulates on cellular level and, in its own turn, inhibits the activity of fructokinase. Consequently, fructose is not metabolized anymore. Its blood concentration and its urinary elimination increase. We also observe the secondary inhibition of fructose 1,6 bisphosphate metabolism. The accumulation of both fructose 1,6 bisphosphate and fructose 1 phosphate inhibits the hepatic phosphorylase, preventing the release of glucose from glycogen. At the

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same time, we observe an inhibition of gluconeogenesis.

Beyond what we have already mentioned before, the inhibition of fructose 1 phosphate metabolism determines the sequestration of phosphorus in the structure of the metabolite, followed by hypophosphatemia. The enhanced phosphorus deficiency is responsible for the lower level of generated ATP.

Both hypophosphatemia and the inhibition of the activity of hepatic phosphorylase and gluconeogenesis are responsible for the occurrence of hypoglycemia.

Whereas fructose 1 phosphate is a metabolite with active osmotic influence, its accumulation over certain limits determines the occurrence of nausea, vomiting and intestinal pain. It also exerts toxic influence over the liver and kidneys [4-6].

Clinical and Laboratory Diagnosis

The clinical manifestations of hereditary fructose intolerance vary both with the age of the patient and the severity of the disease. It becomes symptomatic later than galactosemia (the galactose is found in lactose, a disaccharide present in milk), at the same time with the food diversification and the introduction of nutritive products containing fructose [7].

The clinical picture is dominated by hypoglycemic manifestations (sweating, shakiness, neurologic alteration, from confusion up to delirium, coma and convulsions). Hypoglycemia is not influenced by glucagon administration, as the blockage of gluconeogenesis and glycogenolysis in the presence of hereditary fructose intolerance is significantly stronger than the metabolic effects of glucagon over glycemia.

Hypoglycemia is accompanied by nausea and vomiting, which occur shortly after the ingestion of fructose. If fructose is not

progressively discarded from the diet, hepatic and renal impairment occur. The first one manifests itself by jaundice, hepatomegaly, hyperbilirubinemia and elevated transaminases. The renal impairment is revealed by the lack of urinary acidification, albuminuria and aminoaciduria. The harmful effects of fructose 1 phosphate over the liver and kidneys are apparently reversible with the elimination of fructose from the diet [8].

Beyond the clinical manifestations already mentioned before, we can observe edema, ascites, and cessation of growth and, in advanced stages, even cachexia, which can lead to death in lack of proper therapy. In the long run, we can observe the occurrence of strong aversion to fruits and sweets [9].

We also mention that the symptoms tend to diminish related to aging. The subjects do not have cerebral distress and their IQ level is normal.

In addition to the laboratory findings already mentioned, once the hepatic and renal distress install we can identify hypophosphatemia, hyperlactacidemia and hyperuricemia.

The diagnosis is established based on medical history and clinical data associated to the intravenous test of fructose tolerance. It consists of intravenous administration of fructose in dose of 0.25 grams/kg of body weight in adults and 3 grams/m² of body surface area in children, in a single, rapid push [10]. Blood samples are collected at start point and every 30 minutes, for 2 hours, with measurement of blood glucose and phosphorus levels. The subjects test positive if we observe a lower glycemic level preceded by a reduction in phosphorus level. The confirmation of diagnosis can be obtained through hepatic biopsy and measurement of fructose 1 phosphate aldolase activity level [11]. Nevertheless, we should take into consideration that fructose loading tests as part of the diagnostics can be dangerous.

Genetic analysis can also be used in order to confirm the diagnosis [5,12,13].

Dietary Treatment

The subjects must receive a diet lacking fructose.

As sucrose and sorbitol are sources of fructose, they must also be eliminated from the diet. In general, nutrition is based upon the removal of all infant products which contain fructose or saccharose, all fruits and fruit juices, most of vegetal products and those in which fructose, saccharose and sorbitol were added. Unfortunately, the data regarding the fructose content of different foods are very few and sometimes even self-contradictory. We present a rough guide of main nutritive products allowed and forbidden in hereditary fructose intolerance in [Table 1](#).

Table 1. Dietary recommendations for hereditary fructose intolerance (Adapted after [14,15]).

Allowed foods	Forbidden foods
Milk and milk derived products, dietetic products without any fructose or sucrose content, for children	Dietetic products containing sugar or fructose (Isomil, Pro- Sobee, Nursoy, Nutramigen)
Milk derived products without added sugar	
Fruits :	All other fruits
Avocado, lemon juice, unsweetened with sugar	
Vegetables :	All other
-Groupe A (< 0.2 grams of fructose in 50 grams per portion; we administer 2 portions per day):	
-endive	
-celery	
-lettuce	
-potatoes (mature, from fresh crops)	
-spinach	
-Groupe B (0.2-0.5 grams of fructose in 50 grams per portion; we administer 1-2 portions per week):	
-brussels sprout	

-cauliflower -cucumbers -green pepper -radish -zucchini	
Cereals (we administer maximum 5 portions per day): -Groupe A (< 0.1 grams of fructose per portion): -white wheat flower -white bread (one slice) -white rice -Groupe B (0.1-0.2 grams of per portion; we limit the intake to 1-2 portions per week): -wheat flower -wheat bran (2 spoons) -wheat berries -wheat cream -rice cream -brown rice -biscuits and types of bread baked with wheat flower, without any added sugar	Cereals containing germs or added sugar Wheat germs Carob powder, soya extract, peanuts, seeds, peanut butter
Meat: any type of meat and fish Eggs Fats without added sugar Sugar substitutes: -glucose -galactose -lactose -maltose -aspartame -saccharin Various alimentary products: -jelly -wine vinegar -tea -coffee The limited use (due to lack of information): -mustard -herbs -spices -cocoa	Meats which contain sugar added during the fabrication process -fructose -sugar -maple syrup -molasses -honey -corn syrup -vanilla

The diet must be strictly followed for at least the first stages of childhood. We will pay attention not to use natural sweet products or other ones with added sugar.

Animal products without sugar added during the fabrication process are allowed without any restrictions. Within diversified food, the introduction of solid foods must not be delayed and must be started with ground meats.

The consumption of vegetal products is used only after the age of 2-3 years, periodically measuring weight, height and liver dimensions. The fructose intake brought by these products must be below 1 gram per day, occasionally 1.5 grams per day. Maximum 2 portions of allowed vegetables will be served daily.

Allowed cereal products will be served in maximum 5 daily portions.

The introduction of fructose can be implemented after the first stages of childhood. The allowed quantity and the appropriate age for fructose intake without any signs or symptoms of intolerance could not be fully established. Therefore, the introduction of fructose in the diet must be thoughtfully performed, periodically

monitoring phosphatemia, glycemia and degree of height-weight development of patients [16].

Because of the elimination of fruits and a considerable part of vegetables from the diet, the organism is exposed to a possible vitamin C deficiency. That is why we must provide a daily supplement of ascorbic acid.

The diet will permanently adapt to the actual requirements of development in children, the dietary guidelines being given both to the patients (beyond a certain age) and to the parents [17].

Conclusions

Doctors should be aware of this rare metabolic disease in order to provide the required follow-up, especially important when the patient reaches adulthood. There are a few elements suggestive of the diagnosis, such as hypoglycemia induced by fructose intake, unexplained liver disease and irritable bowel syndrome. With timely diagnosis and adequate dietary treatment, patients have an excellent prognosis and the main clinical manifestations are thus preventable.

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