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HEREDITARY FRUCTOSE INTOLERANCE IN ADULTS: FROM DIFFERENTIAL DIAGNOSIS TO LONG-TERM MANAGEMENT. A REPORT FROM THE FLORENCE COHORT

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***ABSTRACT* – Objective:** Hereditary fructose intolerance (HFI; OMIM 229600) is an autosomal recessive inborn error of metabolism with an estimated prevalence of 1 in 10,000 worldwide. Patients exhibit metabolic disturbances and experience typical symptoms once fructose-containing foods are first introduced into the diet. Affected children may develop an aversion to fructose-containing foods, and these feeding habits can partially protect them, often resulting in HFI remaining undiagnosed until adulthood.

Patients and Methods: We conducted a retrospective observational analysis of a cohort of 14 adult patients with HFI referred to the Adult Metabolic Disease Clinic at Careggi University Hospital (Florence, Italy).

Results: Eight patients were diagnosed in adulthood. The most frequent mutations in the *ALDOB* gene were p.Ala150Pro and p.Ala175Asp, consistent with previous literature. Gastrointestinal symptoms and symptomatic hypoglycemia were the most common clinical manifestations. All patients had an aversion to sweet foods and fruit since early childhood, and their nutritional history was a key to the diagnosis. Hepatomegaly was the most important clinical feature, present both at diagnosis and at last follow-up. In six cases, other diagnoses were initially made, including eating disorders, epilepsy, chronic intestinal diseases, and glucose intolerance. At the last clinical evaluation, patients had a normal weight, and liver enzymes, creatinine, fasting plasma glucose, and lipid profiles were within the normal ranges. Two patients had osteoporosis/osteopenia, and only one developed a vitamin B12 deficiency.

Conclusions: HFI is an inborn error of metabolism with varying severity of clinical manifestations. The diagnosis requires careful history-taking, particularly focusing on nutritional habits, and is confirmed by molecular analysis of the ALDOB gene. A lifelong fructose-free diet prevents complications, but chronic morbidity can still develop. Patients require periodic clinical and metabolic monitoring to assess dietary adherence, general health, and possible diet-related nutritional deficiencies.

Keywords: Hereditary fructose intolerance, HFI, fructose, fructosemia, ALDOB.

INTRODUCTION

Hereditary fructose intolerance (HFI; OMIM 229600), also known as hereditary fructosemia, is an autosomal recessive inborn error of metabolism (IEM) caused by pathogenetic variants in the *aldolase B* gene (*ALDOB*, NM_000035.3), which result in a deficiency of the enzyme fructose 1-phosphate (F-1P) aldolase, primarily expressed in the liver, small intestine, and kidney[1]. HFI is a rare disease with an estimated prevalence of 1 in 10,000 worldwide, although many cases remain undiagnosed[2,3].

HFI is characterized by metabolic disturbances and symptoms that typically appear when fructose-containing foods (mainly fruits and vegetables) are first introduced into the diet[4].

Under physiological conditions, fructose is initially converted to F-1P by the enzyme fructokinase and subsequently transformed by F-1P aldolase into trioses D-glyceraldehyde and dihydroxyacetone phosphate. These trioses then enter the glycolytic or gluconeogenic pathways to form lactate and pyruvate, or glucose and glycogen, respectively[5].

If untreated, aldolase B deficiency leads to an accumulation of F-1P, causing liver and kidney toxicity. Moreover, the excess of F-1P directly inhibits both glycogenolysis and gluconeogenesis, causing post-prandial hypoglycemia, and activates pyruvate kinase, leading to the accumulation of Krebs cycle precursors (alanine, lactate, and pyruvate) that contribute to the observed metabolic acidosis[5,6].

The accumulation of F1P is a central pathophysiological element as it reduces the pool of inorganic phosphate causing ATP depletion and, in turn, leading to a lack of substrate for hepatic glycogen phosphorylase. This results in impaired glycogenolysis and account for the hypoglycemia observed following fructose ingestion. This complex scenario can be further exacerbated by the development of proximal renal tubular acidosis, causing aminoaciduria, phosphaturia, and bicarbonate wasting, which amplifies the metabolic derangement[6].

Clinical manifestations include gastrointestinal symptoms (nausea, vomiting, abdominal pain, hepatomegaly, and liver steatosis), hypoglycemia, sweating, and kidney failure. Seizures, lethargy, coma, and death can occur in severe, untreated cases due to severe hypoglycemia[7,8].

The diagnosis should initially be suspected based on nutritional history. During infancy, parents may exclude certain foods because of intolerance, while older children may develop an aversion to fructose-containing foods, especially fruits and vegetables[9]. The clinical suspicion of HFI is confirmed by sequencing analysis of the *ALDOB* gene and detection of bi-allelic pathogenetic variants[10]. Elevated urinary fructose excretion, assessed by thin-layer chromatography (TLC), serves as a method to monitor dietary adherence[11].

Thanks to self-imposed nutritional habits, clinical manifestations often become chronic and milder, with acute severe complications occurring only rarely[8]. As a result, HFI can remain undiagnosed until adulthood. However, such heterogeneous and nonspecific symptoms often lead to misdiagnoses, requiring different treatment approaches that can negatively impact patients' quality of life and cause social discomfort[12,13].

Here, we present the clinical and metabolic characteristics of our cohort of 14 patients with HFI, referred to the Adult Metabolic Disease Clinic at Careggi University Hospital in Florence, Italy.

PATIENTS AND METHODS

We conducted a retrospective observational analysis of a cohort of adult patients with HFI referred to the Adult Metabolic Disease Clinic at Careggi University Hospital (Florence, Italy) as part of a larger transition program with Meyer Children's Hospital involving adult patients with IEM. Demographic, clinical, laboratory, and anthropometric data were collected for each patient. The study was approved by the Ethics Committee of Toscana Area Vasta Centro (CEAVC), registration number 24807_bio of 16/04/2024, and each patient provided written informed consent to participate.

Statistical Analysis

Data are shown as mean±SD. Given the descriptive nature of our observational study, no further statistical analysis was needed.

RESULTS

Clinical history, molecular diagnosis, and main clinical findings are shown in Table I.

Fourteen patients (10 women) were analyzed with a median follow-up of 8 years[6,13]. In eight cases, the diagnosis was made in adulthood (mean age at diagnosis 37±15) and in two cases during adolescence. Four patients were diagnosed during childhood after clinical investigation for gastrointestinal symptoms associated with hepatomegaly and failure to thrive, and their history revealed an aversion to fruits since weaning.

Symptoms were invariably present from early childhood in all patients, confirming an important collective diagnostic delay.

Table 1. Clinical history, molecular diagnosis, and main clinical findings of the entire cohort.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at diagnosis (years)	41	12	39	24	43
Age at last follow-up (years)	46	26	48	46	48
Clinical onset (years)	Weaning	3	Weaning	4	21
Symptoms at onset	Hypoglycemia and vomiting	Sweet and fruit aversion	Fruit aversion	Abdominal discomfort and fruit aversion	Post-prandial flushing and malaise
ALDOB mutations	p.Ala150Pro/ p.Ala150Pro	p.Ala150Pro/ p.Ala150Pro	p.Ala150Pro/ p.Asn335Lys	p.Ala175Asp/ p.Ala150Pro	c.-214G>A/ c.-244 G>A
Familial	+ (daughter)	+ (brother)	–	+	–
Growth deficits during childhood	–	+	–	–	–
Hepatomegaly or steatosis at diagnosis	+	+	–	–	–
Hepatomegaly or steatosis at the last visit	+	–	–	–	–
Elevated liver function tests overall	–	–	–	–	–
Symptomatic hypoglycemia overall	+	–	+	–	+
Gastrointestinal symptoms overall	Vomiting, bloating	Bloating, diarrhea	Abdominal pain, diarrhea	–	Bloating
Dietary self-restriction	+	+	+	+	–
Misdiagnosis	Anorexia	–	Epilepsy	Anorexia	Dumping syndrome/ reactive hypoglycemia
Comorbidity	Renal malignancy	Ovarian teratoma	Cutaneous melanoma	Fibromyalgia	Hiatal hernia
Vitamin B12 or folate deficiency	–	–	–	–	+
Urinary fructose excretion detectable by TLC at the last visit	+	+	–	+	+

Continued

Table 1 *(Continued).* Clinical history, molecular diagnosis, and main clinical findings of the entire cohort.

	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age at diagnosis (years)	66	5	41	14	36
Age at last follow-up (years)	69	20	48	51	50
Clinical onset (years)	2	3	Weaning	Weaning	Weaning
Symptoms at onset	Sweet and fruit aversion	Incidental finding of hepatomegaly	Post-prandial hypoglycemia	Vomiting after sweet or fruit ingestion	Vomiting and malaise after sweet or fruit ingestion
ALDOB mutations	p.Ala175Asp/ p.Ala175Asp	p.Ala150Pro/ p.Ala175Asp	p.Ala150Pro/ p.Ala150Pro	p.Ala175Asp / c113-1_115	Gross exon deletion (2–6)
Familial	–	–	–	–	+
Growth deficits during childhood	–	–	+	–	–
Hepatomegaly or steatosis at diagnosis	+	+	–	–	+
Hepatomegaly or steatosis at the last visit	+	+	–	+	+
Elevated liver function tests overall	–	–	–	–	+
Symptomatic hypo-glycemia overall	–	–	+	–	+
Gastrointestinal symptoms overall	–	–	Abdominal pain	Vomiting	Abdominal pain, diarrhea
Dietary self-restriction	+	–	+	+	+
Misdiagnosis	–	–	Celiac disease and hyperinsulinism	–	IBD
Comorbidity	Osteoporosis, pre-diabetes, dyslipidemia, scleroderma	Congenital primary megaureter	Fibromyalgia	Nephrolithiasis	Crohn's disease, osteopenia uveitis, IPB
Vitamin B12 or folate deficiency	–	–	–	–	–
Urinary fructose excretion detectable by TLC at the last visit	–	–	–	–	–

Continued

Seven different variants were present in the *ALDOB* gene of our cohort. The most frequent mutations were p.Ala150Pro and p.Ala175Asp (Table I). Other known mutations were p.Asn335Lys, p.Tyr204Ter, c113-1_115del, c.625-2A>G, and c.940dup, each found in one patient. One patient was homozygous for a large deletion encompassing *ALDOB* exons 2–6, previously identified by Ferri et al[10], and another patient presented compound heterozygosity for the known pathogenetic variant c.-214G>A and the novel c.-244 G>A of uncertain significance.

Gastrointestinal symptoms and symptomatic hypoglycemia were the most frequent clinical manifestations overall, occurring in nine and seven patients, respectively.

All patients had an aversion to sweet foods and fruit since early childhood and continued with self-imposed dietary restrictions into adulthood. Moreover, at time of diagnosis and during subsequent follow-up, each patients received dietary recommendations to avoid exceeding a fructose intake of 2 g/day.

Table 1 *(Continued).* Clinical history, molecular diagnosis, and main clinical findings of the entire cohort.

	Patient 11	Patient 12	Patient 13	Patient 14
Age at diagnosis (years)	5	25	4	7
Age at last follow-up (years)	18	32	24	18
Clinical onset (years)	Weaning	Weaning	2	5
Symptoms at onset	Hypoglycemia, growth deficit, and selective fruit aversion	Vomiting and malaise after sweet or fruit ingestion	Abdominal pain, diarrhea and hypoglycemia	Vomiting and abdominal pain
ALDOB mutations	p.Ala175Asp/ p.Ala175Asp	p.Ala150Pro/ p.Ala150Pro	p.Ala175Asp/ c.940dupT	p.Ala175Asp/ p.Ala175Asp
Familial	–	–	–	–
Growth deficits during childhood	+	–	–	–
Hepatomegaly or steatosis at diagnosis	+	+	+	+
Hepatomegaly or steatosis at the last visit	+	–	+	+
Elevated liver function tests overall	+	+	+	+
Symptomatic hypoglycemia overall	+	+	–	–
Gastrointestinal symptoms overall	–	Vomiting, abdominal pain, diarrhea	Abdominal pain, diarrhea	–
Dietary self-restriction	+	+	+	–
Misdiagnosis	–	–	–	–
Comorbidity	–	–	Vesicoureteral reflux sx (surgery)	Migraine
Vitamin B12 or folate deficiency	–	–	–	–
Urinary fructose excretion detectable by TLC at the last visit	+	–	–	–

Hepatomegaly was present in nine patients at diagnosis and eight at the last follow-up, confirming that this is one of the most important features of the disease. Among laboratory findings, a modest increase in liver function parameters was the most common feature and was reported in five patients in our cohort. In six cases, erroneous diagnoses were made, including eating disorders, epilepsy, chronic intestinal diseases, and glucose intolerance. Three patients experienced solid malignancies (kidney, ovarian, and cutaneous). At the last evaluation, patients had a mean body mass index (BMI) of 21.7±2.5 kg/m^2, and liver enzymes, creatinine, fasting plasma glucose, and lipid profiles were all within the normal range (Table II). Osteoporosis/osteopenia was reported in two patients. Nutritional deficiency of vitamin B12 and folate developed in only one patient despite vitamin supplementation. At the last follow-up visit, TLC detected urinary fructose in five patients, suggesting incomplete adherence to dietary prescriptions.

Table 2. Biochemical characteristics of the study cohort at the last follow-up.

Biochemical characteristics	Mean±SD
BMI (kg/m^2)	21.5±2.4
GOT (U/L)	24±12
GPT (U/L)	24±17
Creatinine (mg/dL)	0.78±0.18
eGFR (mL/min/1.73 m2)	96.8±27.0
Fasting plasma glucose (mg/dL)	80±8
Total cholesterol (mg/dL)	217±22
HDL cholesterol (mg/dL)	91±22
LDL cholesterol (mg/dL)	121±10
Triglycerides (mg/dL)	70±21

DISCUSSION

Misdiagnosed HFI is associated with heterogeneous manifestations, making comparisons among patients difficult. Despite this, the history-taking performed in our cohort showed that the most recurrent clinical features were gastrointestinal symptoms, hepatomegaly/liver steatosis, and hypoglycemia.

Liver disease is a common finding among patients with HFI[11]. Tissue damage is attributed to the accumulation of F-1P, which subsequently leads to an increase in hepatic fat content[14]. Although fatty liver disease has traditionally been linked to poor metabolic control and a high BMI, it is not always related to obesity. As shown in our cohort, it can also be found in young patients with good adherence to a fructose-free diet[15].

HFI should be suspected in adult patients with isolated hepatomegaly and steatosis, even if they are asymptomatic and have normal liver function[16].

The cornerstone of HFI treatment is lifelong adherence to a fructose-free diet and avoiding any medications containing fructose. This can be especially challenging because of the hidden presence of fructose in many foods, drugs, additives and preservatives[17]. A limited fructose intake (less than 6 g/day) is generally tolerated in adults[11], although some studies suggest a lower threshold of 1.5 g/day[4,18].

With strict adherence to treatment, the prognosis is generally favorable, but hepatomegaly and steatosis may persist over time, as we observed in our cohort. Additionally, vitamin C deficiency is a common concern and requires regular monitoring and supplementation, as we did for our patients[19].

The small intestine plays a pivotal role in fructose metabolism, primarily through the action of GLUT5, which facilitates fructose absorption. Moreover, the small intestine expresses enzymes involved in fructolysis and gluconeogenesis, similar to those expressed in the liver. A large portion of fructose is metabolized into glucose and lactate within the small intestine and then transported to the liver for further processing. Only a small fraction of fructose bypasses hepatic metabolism and enters the systemic circulation directly. The extent to which unmetabolized fructose passes through the small intestine to the liver depends on the amount of fructose ingested: low doses are almost entirely metabolized, while higher doses overwhelm the intestine's capacity to absorb and metabolize fructose, leading to increased processing by the liver and gut microbiota[11,20-24]. Notably, self-imposed dietary restrictions can alleviate gastrointestinal symptoms but may not fully prevent complications, particularly hepatomegaly, as previously described[11].

Another aspect that clearly emerged in our cohort is that HFI is often diagnosed late, typically after numerous specialist evaluations and multiple examinations, which negatively impact patients' quality of life and disease management. Moreover, because of the complexity of manifestations, HFI is frequently misdiagnosed as other conditions, making it even more difficult for patients to cope with their disease[25].

CONCLUSIONS

HFI is an inherited metabolic disease, largely unknown to adult clinicians, with significant variability in the severity of clinical manifestations. The diagnosis can be challenging and requires thorough history-taking about dietary habits as well as the timing of symptoms in relation to food ingestion, aspects often overlooked by adult clinicians. Patients often develop self-imposed dietary restrictions on fructose-containing foods, which contribute to delayed diagnosis until adulthood.

Early diagnosis and the introduction of appropriate diet therapy can help prevent complications. However, patients may develop chronic morbidity even with strict dietary adherence. Therefore, periodic clinical and metabolic monitoring is required to assess adherence, general health, and possible diet-related nutritional deficiencies.

Artificial intelligence-assisted technologies:

No artificial intelligence-assisted technologies were used in the production of this article.

Authors' contributions:

Study conception and design: Edoardo Biancalana, Domenico Prisco, Maria Alice Donati; collection and interpretation of data: Edoardo Biancalana, Amelia Morrone, Lorenzo Ferri, Anna Caciotti, Rodolfo Tonin; statistical analysis: NA; manuscript drafting: Edoardo Biancalana, Cinzia Pistolesi, Noemi Duratti, Debora Paoli, Francesca Pochiero, Michele Sacchini, Giulia Bruni, Amelia Morrone, Lorenzo Ferri, Rodolfo Tonin, Silvia Funghini, Anna Caciotti, Anita Nannoni, Giacomo Emmi, Elena Procopio; manuscript editing: Edoardo Biancalana, Amelia Morrone, Domenico Prisco, Maria Alice Donati; approval to submit: Edoardo Biancalana, Maria Alice Donati.

Availability of data and material:

All data generated or analyzed during this study are included in this published article.

Conflicts of interest:

The authors declare that they have no conflict of interest to disclose.

Consent for publication:

Each patient provided consent to participate in the current data collection.

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