Diagnosis, Management & Ongoing Impacts of Hereditary Fructose Intolerance

A review of the current knowledge and practice

Background

Basics of the condition

Hereditary fructose intolerance (HFI) [1] or Fructosemia [2] (OMIM #229600) is a rare, potentially fatal autosomal recessive disorder caused by deficiencies in Aldolase B (*ALDOB*) activity resulting in an inability to metabolise fructose and its cognate sugars, sucrose and sorbitol, but a retained ability to metabolise glucose and lactose[1]. HFI commonly presents in newborns during weaning from breast milk with the baby showing symptoms of severe abdominal pain vomiting, hypoglycaemia, hyperuracemia, fructosemia and phosphaturia which if undiagnosed or untreated can lead to long term complications of liver and renal failure, mental and growth retardation [3] [4]. These long-term conditions are a burden on the individual, their families and the healthcare system as it impairs their quality of life and their ability to work or live independently.

Outcomes for HFI sufferers

With dietary restriction of fructose and its cognate sugars the complications of HFI can be avoided and successful development and longevity can be achieved, particularly with early diagnosis. Diagnosis previously relied on oral fructose challenges and/or liver biopsies which are both risky procedures for the patient's survival [5]; however the addition of molecular genetics and newborn screening are improving diagnostic safety [6] [5]. Across the globe patients are still being misdiagnosed with fatal consequences, indicating the ability to detect the condition early and provide adequate treatment needs improvement[1]. There is currently no cure but HFI sufferers who do survive an episode of fructose exposure have been known to develop to adulthood even if they are undiagnosed, as they develop a self-protective aversion to the taste of sugars[7]. The absence of dental carries is also noted in almost all cases of HFI as a result of markedly decreased sugar consumption [8].

Prevalence

All of the early literature on HFI was based on case studies making it difficult to accurately determine population statistics. As more HFI cases are identified and diagnosis techniques improve, larger scale cohorts have become available for analysis and genetic screening and counselling is becoming a significant way of detecting the likelihood of HFI occurrence [1]. In 2005, Santer and colleagues identified 15 different mutations via PCR analysis of *ALDOB* across 80 European patients and screened 2,000 randomly selected newborns finding 21 had heterozygous *ALDOB* mutations[6]. Santer concluded an estimated 1 in 26,000 rate of homozygous *ALDOB* mutations and 1 in 70 heterozygous carriers in all live births in Europe [6]. Many subsequent publications have quoted Santer's statistics rounding to 1/20,000[2]. There is scarce data on the prevalence of HFI in other regions of the world however multiple studies have indicated differences to specific mutation frequencies across ethnic groups including Italian [9], French [10], Polish [5] and Chinese [11] cohorts. The accuracy of these conclusions is limited by the small cohort sizes.

Elucidating the genetic & molecular basis

post glucose administration [7]. Chambers & Pratt did not have the knowledge to identify the genetic and molecular cause of the condition but they paved the way for further investigations into this condition. Through advancements in genetics and molecular biology in 1988 Cross and colleagues analyzed the *ALDOB* gene, that was sequenced and mapped by Tolan & Penhoet in 1986 [12], in an adult presenting with HFI symptoms and found homozygous alleles for a single base mutation they described as 'molecular lesions' [13]. This was the first study to link the function of Aldolase B with the symptoms of HFI and has been supported by multiple studies [3 4 7] . To date, over 54 subtle point mutations and a handful of deletions have been sequenced in the *ALDOB* gene located on chromosome 9 by PCR analysis [12] across HFI sufferers [1] . Aldolase B is an important enzyme catalyzing key processes in gluconeogenesis and glycolysis and is expressed in the liver, kidney and small intestines [3 4 7]. As more insight into the disease is gained it provides clinicians with a greater ability to diagnose and manage the condition and avoid long term complications or fatalities [2 14 15].

Normal Fructose Metabolism

Chemical basics

Fructose is a hexose saccharide with a chemical formula identical to glucose (C6H12O6) but with a different chemical structure and function[16]. Fructose is found abundantly in fruits, vegetables, honey, processed foods [16 14] and can be ingested as free fructose; sucrose which is split into fructose and glucose, or as sorbitol which is oxidised to fructose in the liver by sorbitol dehydrogenase [17 16]

Absorption, Transport & Metabolism

Post ingestion, fructose is absorbed in the small intestine via facilitated diffusion utilising GLUT5 receptors [17 16]. Fructose is then transferred through the portal blood to the hepatocytes where it is converted to fructose-1-phosphate by fructokinase and split into the dihydroxyacetone phosphate (DHAP) and glyceraldehyde by Aldolase B[16]. The trioses can then enter gluconeogenesis to be delivered to tissues as glucose through the circulation or converted to glycogen and triglycerides for energy storage in the liver, muscle and adipocytes respectively [16 14]. Under normal conditions fructose does not enter the blood circulation and the detection of fructose in the blood, known as fructosemia indicates defects in the carbohydrate metabolic pathways[16]. Small amounts of these trioses are converted to glyceraldehyde-3-phosphate (G-3-P) and enter glycolysis to provide energy for the hepatocytes [16]. Entering glycolysis as G-3-P bypasses the ATP and phosphofructokinase feedback mechanism and relying only on negative feedback regulation from high F-1-P levels, resulting in a faster rate metabolism compared to glucose [14]. Fructose also acts as an integral stimulator of nucleotide turnover through the uric acid pathway, which releases uric acid through the kidneys[18].

Molecular Basis of HFI

Elucidating defects in Aldolase B

The molecular links between Aldolase B mutations and the molecular basis of the presenting symptoms post fructose consumption have been continually investigated over the last 60 years [1]. In the early 1960s, Hers & Joassin identified the underlying mechanism of Aldolase B and it's link with the symptoms of HFI through pathological analysis of liver biopsies obtained from two unrelated patients with HFI [19]. The liver biopsies showed that Aldolase B had lost its

Although this basic mechanism is common to all cases of HFI, the severity is in part influenced by the nature of the mutation and how this affects the protein folding capacity of the Aldolase B enzyme and therefore its function [20]. In 2005 Malay & Allen, published a paper summarising the impacts of the nature of the mutation in it's effect on various functional aspects of the Aldolase B enzyme [20]. These molecular studies help bridge the gaps in knowledge between the genotype and phenotype of HFI leading to varying severities of long and short-term symptoms.

Changes in serum and stored glucose

The hypoglycaemia observed in response to fructose consumption in HFI patients was puzzling for many clinicians and scientists until a man was analysed in a Toronto hospital in the 1970s with both insulin dependent diabetes mellitus and HFI [8]. Analysis by Steiner and colleagues on the man's plasma biochemistry, post independent glucose and fructose tests, led to the conclusion that the hypoglycaemia was independent of insulin and beta cell function and was uniquely due to decreased hepatic release of glucose [8] . F-1-P is an important up regulator of glucokinase in the catalysis of glucose phosphorylation in order to trap glucose in the hepatocyte for the production of energy or glycogen[3]. When F-1-P is in excess it continues to increase the action of hexokinase which phosphorylates glucose to glucose-6-phosphate (G-6-P) trapping it in the hepatocyte, inhibiting gluconeogenesis and increasing intracellular glycogen [21]. Increased hepatic glycogen in HFI was first reported in a 1971 case study by Cain & Ryman after a liver autopsy of a 2 year old girl with HFI that had been misdiagnosed with glycogen storage disease [22]. Increased hepatic glucose uptake and decreased output leads to hypoglycaemia which peaks ~60-90mins after ingestion [21]. Glucose reabsorption in the kidneys is also reduced due to renal dysfunction further attenuating hypoglycaemia[23]. Prolonged hypoglycaemia can lead to seizures, coma, brain damage or death especially in infants[21].

Liver complications

The liver is the site of fructose metabolism and liver failure is a major long term complication of HFI and primarily due to ATP depletion leading to hepatic apoptosis[21]. The phosphorylation of fructose to F-1-P sequesters large quantities of inorganic phosphate (Pi) depleting phosphate stores, reducing ATP production and increasing sugar phosphates [8]. Without a source of energy, hepatocyte apoptosis and AST and elevate [21]. In chronic cases liver cirrhosis cannot be reversed with diet correction unlike many other symptoms of HFI [4]. Quintana et al report of a child with HFI who was required a liver transplant[4], a costly procedure for all parties [24], as a result of initial misdiagnosis[4].

Kidney complications

Renal failure is a devastating complication of HFI that is commonly treated with ongoing dialysis and severely impacts an individual's quality of life and is costly for them and the healthcare system [25]. As ATP stores deplete, energy dependent reactions slow, and ADP is hydrolysed to AMP which increases the rate of nucleotide turnover and production of uric acid excreted through the kidneys[21] [16] . The kidneys cannot keep up with the rate of uric acid production resulting in hyperuricemia & ucosuria, leading to formation of urate crystals, which form gout, and renal calculi inducing renal tube damage. [4] [26]. Ucosuria also hinders insulin's vasodialating actions and reduces the uptake of glucose by skeletal muscle cells leading to fatigue and malaise [16] [26]. These metabolic alterations in the kidney lead to bicarbonate wasting causing to tubular acidosis [8]. Mock and colleagues studied the kidney function of two unrelated children with HFI and found the impairments to renal function could be reversed with early removal of fructose from the diet [23] Their study also found that the breakdown of nucleotides in the unregulated uric acid

Management of HFI

Immediate treatment post fructose consumption

When an individual with HFI ingests fructose the immediate treatment should focus on preventing hypoglycaemia through intravenous administration of unflavoured milk or a glucose only solution, as was established by Chambers & Pratt and supported by many subsequent studies[3 17]. Post blood glucose stabilisation and emesis, supplementation of vitamin D or analogues such as calcitriol should be provided due to the quantities lost during reduced kidney function [27]. Vitamin D supplementation will help stabilise blood calcium, phosphate, parathyroid hormone and alkaline phosphatase levels and prevent the onset of rickets or osteopenia [23 27]. If acidosis continues additional bicarbonate supplementation may be required [27].

Long-term recommendations

Dietary elimination of many fructose containing fruits and vegetables often results in dietary deficiencies of important nutrients and vitamin C supplementation is commonly suggested to prevent the onset of scurvy[27]. Caution should be taken in assessing any medications or supplements due to the extensive use of sorbitol and fructose as a coating to pills and tablets or an addition to syrups [3].

Conclusion

HFI is a potentially fatal genetic condition that can be prevented and managed with the strict dietary exclusion of fructose and its cognate sugars, sucrose and sorbitol leading to successful development and longevity in patients. Unfortunately, as demonstrated in many of the literature examples within this review, HFI is too commonly misdiagnosed or left undiagnosed with long term or fatal consequences. The long-term consequences after chronic fructose exposure of renal and liver failure and mental and physical retardation have significant impact on the individual's quality of life and ability to work and live independently. This puts a large strain on the individual's family or guardians as well as the healthcare system. Molecular and biochemical research continues to increase the ability to provide early diagnosis and treatment however increased awareness of this condition amongst medical practitioners will likely aid consideration of HFI in similar presenting conditions and improve time to diagnosis.

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