Natural history and complications of hereditary fructose intolerance in adult patients

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Background

Hereditary fructose intolerance (HFI) (OMIM#229600) is an autosomal recessive disorder of fructose metabolism, caused by aldolase B deficiency which catalyses the cleavage of fructose 1,6-bisphosphate and fructose 1-phosphate (Fru-1-P) to triose molecules. In patients with HFI, ingestion of fructose results in accumulation of Fru-1-P and depletion of ATP. This leads to inhibition of glycogenolysis and gluconeogenesis resulting in hypoglycaemia (1,2) (Fig 1).

Clinical presentations include hypoglycaemia and gastrointestinal symptoms (nausea, vomiting and abdominal pain) after ingestion of fructose, sucrose or sorbitol. Ingestion of large amounts can lead to hypoglycaemic seizures, encephalopathy, acute liver injury and kidney failure (3). Patients develop a strong aversion to sucrose and fructose and can avoid recurrence of symptoms by remaining on fructose and sucrose free diet (1).

Based on the UK population prevalence of the p.Ala150Pro variant, the estimate for the prevalence of HFI was 1:18,000 (4).

Diagnosis requires a combination of clinical features and genetic diagnosis (ALDOB gene). Hepatic aldolase B activity on liver or intestinal biopsy is rarely required now for diagnosis. Fructose tolerance testing (fructose challenge) should be avoided because it is dangerous and, when used in the past, could result in death (1).

Definitive treatment requires a strict exclusion diet (restriction of fructose, sucrose and sorbitol) (2).

Herein, we present the complications and long-term course of HFI in adult patients in our centre.

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Fig. 1: Metabolic consequences of aldolase B deficiency in the liver. The catabolism of Fru 1P and Fru 1,6-P2 are blocked (red bars). Accumulation of Fru 1P has several acute downstream effects denoted in yellow circled letters as follows:

1) Depletion of intracellular inorganic phosphate (Pi) and ATP, leading to formation of IMP and urate (A).
2) Hypoglycaemia due to impairment of glycogenolysis (by inhibition of GP and loss of Pi) (B) and gluconeogenesis (by inhibition of G6Pi) (C).
3) Hyperlactatemia due to stimulation of PK activity and impaired gluconeogenesis (D).
4) Fructose produced endogenously from sorbitol (via the polyol pathway) may contribute to the accumulation of Fru 1P (E).
5) Blue crosses indicate blocked pathway as a consequence of Fru 1P accumulation. - Adapted from Buziu AM et al, (2).
Patients and Methods

We recorded the clinical manifestations, biochemistry, radiological and molecular genetics of ALDOB in adult HFI patients. Dietary Assessment was through Dietplan7 analysis of patient-filled food diary.

Results

Clinical Features:
This study included 14 patients with HFI and epilepsy, with median age 62 yrs (range 17-83 yrs). Four (28.6%) patients were males and ten (71.4%) were females.

Clinical characteristics of HFI
All patients in the study presented with clinical features of sugar aversion and feeding difficulties in infancy. Symptoms with inadvertent intake of fructose, sucrose or sorbitol were reported in 10 patients (71.4%). These included gastrointestinal symptoms in seven (50%) patients and episodic hypoglycaemia in five (35.87%) patients.

Dietary intake data
All patients in the study continued on self-restricted diets (fructose, sucrose and sorbitol restricted). Seven-day food diaries were analysed for 7 patients.

Daily fructose/sucrose intake was within recommended in 2/6 patients (Fig 2). Median (range) = 1.78 (0.9-2.1) g/day. Recommended daily intake of fructose/sucrose is 1.0-2.0 g/day in adults.

Daily saturated fat intake was within recommended in 3/7 patients (Fig 3). Median (range) = 9.55 (8.06-13.6) %/day. Recommended daily saturated fat intake is <10% of total energy requirements (TER) in adults.

Daily vitamin C intake was within recommended in 1/7 patients (Fig 4). Median (range) = 31 (15-51) mg/day. Recommended daily vitamin C intake is >40 mg/day in adults.

Daily folate intake was within recommended in 1/7 patients (Fig 5). Median (range) = 170 (131-1168) µg/day. Recommended daily folate intake is >200 µg/day in non-pregnant adults.
Liver surveillance
Liver ultrasound was performed in 12 patients. Hepatosteatosis was detected in 6 (50%) patients. One (8.3%) patient was found to have hepatic fibrosis in addition (fig 6 A&B). None of the patients had liver cirrhosis or focal solid lesions. Patients with hepatosteatosis/fibrosis were slightly older in age, had marginally higher BMI and had higher daily saturated fat intake compared to patients without steatosis. Both group had similar daily fructose/sucrose intake (table 1).

Kidney surveillance
Kidney ultrasound was performed in 11 patients. Renal calculi were detected in 4 (36.36%) patients. Renal calculi were symptomatic in two (18.18%) patients, asymptomatic in one patient (9.09%) (fig 6 B) and one patient (9.09%) had nephrocalcinosis. Three (21.43%) patients had hypertension. eGFR was reduced ≤ 60 mL/min/1.73 m² in two (14.29%) patients.
None of the patients had generalised aminoaciduria or glucosuria on urine tests. One patient had hypercalciuria with associated kidney stones. One patient had increased urine potassium excretion.

Genetic data
Confirmation of diagnosis by genetic testing of ALDOB gene was performed in all patients. The most common variant was c.448G>C p.(Ala150Pro) detected in 13 (92.86%) patients, followed by c.524C>A p.(Ala175Asp) and c.1013C>T p.(Ala338Val) detected in four (28.57%) and two (14.29%) patients respectively. Genetic results are shown in table 2.

### Table 1: Surveillance liver imaging results

<table>
<thead>
<tr>
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<th>Hepatic steatosis/fibrosis (n=6)</th>
<th>No steatosis (n=6)</th>
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<tbody>
<tr>
<td>Age (median/range)</td>
<td>62.5 (56-73)</td>
<td>50 (17-83)</td>
</tr>
<tr>
<td>BMI (kg/m²) (median/range)</td>
<td>26.075 (24-30.33)</td>
<td>23.65 (19.7-26.5)</td>
</tr>
<tr>
<td>Daily fructose/sucrose intake (g/day) (median/range)</td>
<td>1.9 (0.9-2.1)</td>
<td>2.0 (2.0-2.0)</td>
</tr>
<tr>
<td>Daily saturated fat intake (% of TER/day) (median/range)</td>
<td>11.49 (9.12-13.6)</td>
<td>8.81 (8.06-9.55)</td>
</tr>
</tbody>
</table>

Mildly elevated ALT was seen in one (8.3%) patient. None of patients had elevation of GGT or bilirubin.

### Table 2: ALDOB gene testing results

<table>
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<th>Variants</th>
<th>No (%)</th>
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<tr>
<td>Homozygous c.448G&gt;C p.(Ala150Pro)</td>
<td>8 (57.14%)</td>
</tr>
<tr>
<td>c.448G&gt;C p.(Ala150Pro); c.524C&gt;A p.(Ala175Asp)</td>
<td>3 (21.43%)</td>
</tr>
<tr>
<td>c.448G&gt;C p.(Ala150Pro); c.1013C&gt;T p.(Ala338Val)</td>
<td>2 (14.29%)</td>
</tr>
<tr>
<td>homozygous c.524C&gt;A, p.(Ala175Asp)</td>
<td>1 (7.14%)</td>
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Discussion

This study describes a group of adult patients with HFI. Symptoms with inadvertent intake of fructose, sucrose or sorbitol were common despite patients being on self restricted diet. Obesity and overweight were seen in 43% of patients, less than the prevalence in UK adults which is estimated at 63% (5). This supports previous reports where the Body Mass Index (BMI) of paediatric and adult HFI patients was found to be lower than the average for their age (6).

Dietary micronutrient deficiencies in form of vitamin C and folate was common. This supports previous observations (7).

Hepatic steatosis was common despite dietary restriction and was detected in 50% of patients who had liver ultrasound. This is higher than the estimated prevalence of non-alcoholic fatty liver disease (NAFLD) in the general population in Europe which is about 20–30% (8). Hepatic steatosis in our study was not correlated with BMI or daily fructose intake. This supports previous reports where NAFLD has been reported to be not related to obesity in HFI patients (6). NAFLD developed despite dietary restriction (9) and was reported to be not related to dietary fructose intake (10).

Kidney stones were common and were detected in 36% of patients who had kidney ultrasound. This is higher than the estimated prevalence of urolithiasis in the general population in Europe which is estimated at 10-15% (11).

The most common genetic variant was c.448G>C p.(Ala150Pro) which is the common European variant. This is the most common ALDOB gene variant reported in UK (4).

Conclusions

Adults with HFI require ongoing medical and dietetic support. Inadvertent fructose/sucrose exposure is common. The prevalence of hepatic steatosis is higher than expected for BMI. It is unclear whether the prevalence of asymptomatic/symptomatic renal calculi is higher than expected for population. Although it is possible to restrict fructose intake to <2g/day, patients will benefit from long term access to dietary advice and metabolic monitoring. The most common genetic variant was the common European variant.

References