WHEN TO CONSIDER FRUCTOSE 1.6 BISPHOSPHATASE DEFICIENCY

Acute onset shortly after birth or in young childhood, some cases of adult onset

patients are asymptomatic between acute episodes[1]

Paroxysmal episodes triggered by infectious episodes, unusual fasting and ingesting large quantities of fructose/sorbitol/sucrose/glycerol (foods and/or medication, etc.)

Clinical signs

Episodes of hypoglycaemia and lactic acidosis[2]

Intermediate to long fasting times > 8-10 hrs (shorter fasting tolerance in neonates and young children)
If left untreated, risk of progression to multiorgan failure

In neonates:
Severe hyperventilation (respiratory acidosis), episodes of apnoea, convulsions and/or coma linked to hypoglycaemia

Episodes become less frequent and less severe with age, with:
Episodes of irritability, tachycardia, hypotonia, sleepiness, dyspnoea and all the other signs of hypoglycaemia

Additional tests

Laboratory:
- During acute episodes: Glucagon-unresponsive **hypoglycaemia** with **lactic acidosis** (with high lactate/ pyruvate ratio), most frequently **with ketosis**, hyperuricaemia, sometimes an increase in free fatty acids, pseudohypertriglyceridaemia (due to high glycerol)
- Between acute episodes: possible intermittent moderate lactic acidosis

Transient acute liver failure

Sometimes massive hepatomegaly, of fluctuating size which may decrease but persist between acute episodes

Reye syndrome

Additional tests

Laboratory:
- During acute episodes: **cytolysis** (sometimes a significant rise in transaminases, X 10), **possible liver failure**
- Between acute episodes: normal liver test results or moderate fluctuating cytolysis

Abdominal ultrasound:
- **Hyperechoic hepatomegaly,** generally uniform, which may persist between episodes

Specialist workup

Fructose 1.6 Bisphosphatase deficiency?

Specialist medical opinion and reference laboratory

Specialist workup
(preferably as an in-patient in a specialist department after an episode of hypoglycaemia, while looking into other potential causes[2, 3] and initiation of general treatment)

Urinary organic acid chromatography[4]: presence of glycerol, glycerol 3-phosphate and ketonuria

Fructose 1,6 bisphosphatase enzyme activity assay in the white blood cells (lower) and **confirmatory genetic analysis**

Seek **specialist advice quickly** from a **Centre of Excellence:**
Rare Disease Centre of Reference / Competence: https://www.filiere-g2m.fr/annuaire/

Start the parallel treatment urgently:
Refer to the emergency protocols **for each symptom and/or disease:**
https://www.filiere-g2m.fr/urgences

Specialist treatment coordinated by a Centre of Excellence

Genetic counselling, family screening in a specialist centre

[1] **No growth retardation, no neurological damage (except if sequelae of hypoglycaemia), no fructose aversion**
[2] **Refer to the emergency protocol for hypoglycaemia: https://www.filiere-g2m.fr/urgences and Hypoglycaemia sheet: https://www.filiere-g2m.fr/media/attachments/2024/12/19/diagnostic-fiche-hypoglycemie.pdf**
Rare cases of paroxysmal episodes with lactic acidosis without hypoglycaemia
[3] **Differential diagnoses: Other causes of hypoglycaemia and lactic acidosis, +/- liver damage (specifically Glycogen storage disease type 1, etc.)**
[4] **If tested during a crisis, the results are normal between paroxysmal episodes**

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