WHEN TO CONSIDER GLUTATHIONE SYNTHETASE DEFICIENCY

THREE PHENOTYPES HAVE BEEN DESCRIBED. BASED ON THE SEVERITY AND THE MAIN IMPAIRMENTS PRESENTED:
Isolated haemolytic anaemia (HA) in the mild phenotype
HA and metabolic acidosis in the moderate phenotype
HA, metabolic acidosis, neurological impairment and vulnerability to infections in the severe phenotype

Clinical signs

Haematological diseases
Always present

Haemolytic anaemia:
Most frequently with neonatal onset
Recurrent
Sometimes with favouring medication-related factors

Tendency to bleed due to platelet dysfunction

Metabolic abnormalities
Moderate, severe phenotypes

Metabolic acidosis most frequently with neonatal onset

Potential acute flare-ups, sometimes triggered by infections

Neurological impairment
In severe phenotypes
Severity of symptoms can vary depending on patients
Most frequently-reported symptoms:
Intellectual disability Epilepsy

Other possible impairments:
Ataxia, dysarthria, tremors
Pyramidal syndrome
Possible microencephaly

Vulnerability to infection
Severe phenotypes
Recurrent bacterial infections

Inconstant ophthalmological impairment
Progressive retinal dystrophy causing poor sight
Opaque corneas

Haematological diseases

Non-specialist laboratory workup: results that may indicate this diagnosis:

- Elevated free bilirubin, other indications of haemolysis
- Haemolytic anaemia with negative Coombs test
- High anion gap metabolic acidosis

Specialist workup

Glutathione synthetase deficiency?

Specialist metabolic assessment
In collaboration with a centre of excellence, at the same time as looking for other potential differential diagnoses[1]

Urinary organic acid chromatography
(inconstant abnormalities, particularly in mild phenotypes): elevated 5-oxoproline = pyroglutamic acid[2]

Possible measurement of enzyme activity (erythrocyte, fibroblasts)

Less frequently performed: erythrocyte glutathione test (reduction)

Confirmatory genetic analysis to be carried out by a specialist centre

Seek specialist advice quickly from a Centre of Excellence: Rare Disease Centre of Reference / Competence:

Inherited metabolic diseases
https://www.filiere-g2m.fr/annuaire/

Healthcare network for rare constitutional diseases of red blood cells and erythropoiesis: https://filiere-mcgre.fr/ou-consulter

Start the parallel treatment

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

Specialist care, specific treatment coordinated by a Centre of Excellence

Genetic counselling, family screening in a specialist centre

Specialist medical opinion and reference laboratory

[1] Other causes of haemolytic anaemia, and depending on the clinical picture.
[2] Non-specific abnormality, possible moderate secondary elevations (**medication including paracetamol**, dietary factors, malnutrition, prematurity, other pathologies, etc.). The intensity of urine excretion appears to correlate with phenotype severity.

Maladies rares Héréditaires du Métabolisme
Filière nationale de santé