# **Symptom-free interval**

From 48 to 72 hrs, but can be several days/weeks



# Rapidly-worsening neurological impairment

Impaired consciousness up to coma,

Axial hypotonia,

Peripheral hypertonia,



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(1)

### Signs of cerebral cedema **Digestive signs**

Refusal to drink

**Anorexia** 

Nausea Vomiting

**Dehydration** 

Weight loss Sometimes moderate hepatomegaly

# INFANTS, CHILDREN, ADOLESCENTS, ADULTS: ONSET REVEALED BY ACUTE ATTACK OR CHRONIC ILLNESS, BOTH TYPES ARE OFTEN ASSOCIATED

Association and severity of symptoms vary depending on patients

#### **ACUTE IMPAIRMENT**

WHEN TO CONSIDER ORGANIC ACIDURIA - METHYLMALONIC ACIDEMIA (MMA) AND PROPIONIC ACIDEMIA (PA)

> Paroxysmal episodes (metabolic decompensation) Triggering factors: infections, fever, anorexia, vomiting, diarrhoea, excessive protein intake, fasting, insufficient calorie intake, catabolism, surgery

Risk of multiple organ failure, death or severe disability during decompensation



## **Neurological impairment**

Altered consciousness leading to coma, abnormal movements, Leigh syndrome, stroke-like episodes, convulsions



# **Digestive impairment**

Anorexia, nausea, vomiting, pancreatitis



#### **Cardiac impairment** Acute heart failure, arrhythmia



# **Psychiatric disorders**

Hallucinations, psychosis

Standard blood workup High anion gap metabolic acidosis +/- frequent hypocalcaemia

- +/- hyperglycaemia or hypoglycaemia,
- +/- neutropaenia, pancytopaenia,
- +/- cytolysis and high lipase

# **Neurological** impairment

Hypotonia Neurodevelopmental disorders Intellectual disability Autistic spectrum disorder Learning disabilities Abnormal movements, **Dvstonia** 



# Cardiac impairment (>PA)

Cardiomyopathy QT prolongation



Standard metabolic assessment<sup>1</sup>

High anion gap metabolic acidosis

With hyperammonaemia<sup>2</sup>

+/- Hyperlactataemia

# **Haematological** diseases

Neutropaenia, pancytopaenia, rare macrophage activation syndrome



# impairment and feeding/eating disorders

**Digestive** 

Chronic anorexia, nausea and vomiting, oral fixation, aversion to highprotein foods



CHRONIC IMPAIRMENTS

# **Kidney disease** (>MMA)

**Tubulopathy** Chronic kidney disease



**Failure to thrive Neuro-sensory** disorders (+/- sudden loss of hearing and vision with the risk of optical atrophy) **Psychiatric disorders** Skin conditions (especially where there is a protein deficiency)

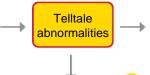


Specialist medical opinion and reference laboratory



(uOAC)

Specialist metabolic assessment<sup>3</sup> Plasma: acylcarnitine profile, amino acid chromatography Urine: organic acid chromatography



## Confirmatory genetic analysis

(and sometimes enzyme study) to be carried out subsequently by a specialist centre

Specialist advice from a Centre of Excellence: Rare Disease Centre of Reference Competence, as soon as the results of the standard metabolic assessment are

received: 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

For more information: PNDS: French National Authority for Health - Organic acidurias: Methylmalonic Acidaemia and Propionic Acidaemia (has-sante.fr)

<sup>2</sup> Pay attention to sample-taking conditions. Always perform tests but do not necessarily wait for test results to start treatment. Standard norms (may vary depending on the laboratories): Neonate: ammonia < 100 μmol/L, Non-neonate ammonia < 50 μmol/L



<sup>&</sup>lt;sup>1</sup> Standard metabolic assessment - Blood: ammonia levels, blood gases, blood sugar, lactate levels, ketosis test (urine dipstick test and/or capillary blood ketones). To be performed immediately where there is no obvious cause, at the same time as looking for other causes: sepsis (neonates), brain damage: trauma-related, vascular, infection-related, encephalitis etc., drug toxicity, other metabolic diseases. Refer to the emergency protocol for coma

It is important to take samples during the acute phase, and as soon as possible, ideally before starting any treatment, though this should not be delayed.

The samples that are essential for diagnosis are in bold, while the others may be useful to interpret the metabolic assessment and eliminate some differential diagnoses.