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

## Clinical signs

### ACUTE ONSET IN NEONATES

**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,**
Signs **of cerebral œdema**

**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

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**

#### CHRONIC IMPAIRMENTS

**Neurological impairment**
**Hypotonia**
**Neurodevelopmental disorders**
**Intellectual disability**
**Autistic spectrum disorder**
**Learning disabilities**
**Abnormal movements, Dystonia**

**Cardiac impairment (>PA)**
**Cardiomyopathy**
**QT prolongation**

**Haematological diseases**
**Neutropaenia, pancytopaenia,** rare macrophage activation syndrome

**Digestive impairment and feeding/eating disorders**
**Chronic anorexia, nausea and vomiting, oral fixation, aversion to high-protein foods**

**Kidney disease (>MMA)**
**Tubulopathy**
**Chronic kidney disease**

**Other**
**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 workup

**Additional tests**

Standard blood workup
High anion gap metabolic acidosis
+/- frequent hypocalcaemia
**+/- hyperglycaemia** or hypoglycaemia,
+/- **neutropaenia,** pancytopaenia,
+/- cytolysis and high lipase

Standard metabolic assessment[1]
**High anion gap metabolic acidosis**
**With hyperammonaemia[2]**
+/- Hyperlactataemia

Specialist medical opinion and reference laboratory

**MMA? PA?**

Specialist metabolic assessment[3]
Plasma: **acylcarnitine profile**, amino acid chromatography
Urine: **organic acid chromatography (uOAC)**

→ Telltale abnormalities →

**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)**

[1] 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

[2] 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

[3] 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.

Maladies rares Héréditaires du Métabolisme
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