# WHEN TO CONSIDER ISOVALERIC ACIDEMIA (IVA)-TYPE OF ORGANIC ACIDURIA

## Neonatal screening in France since 1st January 2023:

This clinical picture should no longer be seen in children born in France after January 2023 who have been screened[1]

## Clinical signs

### NEONATES
### ACUTE ONSET
### Symptom-free interval
**Starting at 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

**Unusual smell**

**Sweaty feet smell**

### INFANTS, CHILDREN, ADOLESCENTS, ADULTS: ONSET REVEALED BY ACUTE OR CHRONIC IMPAIRMENT, WITH BOTH KINDS OFTEN BEING ASSOCIATED
**Association and severity of symptoms vary depending on patients**

#### ACUTE IMPAIRMENT

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

**Risk of multiorgan failure, death or severe disability during decompensation**

**Neurological impairment**

**Altered consciousness leading to coma**

Abnormal movements

**Digestive impairment**

**Anorexia, nausea, vomiting, pancreatitis**

#### CHRONIC IMPAIRMENT

**Neurological impairment**

*Inconstant and variable depending on patients*

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

**Digestive impairment and feeding/eating disorders**

Chronic anorexia, nausea and vomiting, aversion to high-protein foods, oral fixation, growth retardation

## 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[2]**
**High anion gap metabolic acidosis**
**With hyperammonaemia[3]**
+/- Hyperlactataemia

Specialist medical opinion and reference laboratory

## Isovaleryl-CoA dehydrogenase deficiency?

**Specialist metabolic assessment[4]**

**Plasma**: **acylcarnitine profile**, amino acid chromatography
**Urine: organic acid chromatography (uOAC)**

→ **Telltale abnormalities** →

**Confirmatory genetic analysis** to be carried out subsequently by a specialist centre

Seek urgent 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 under preparation: French National Authority for Health - French National Diagnosis and Treatment Protocols (has-sante.fr)**

[1] Neonatal screening (https://depistage-neonatal.fr/) **makes it possible to identify affected neonates and initiate treatment at an early stage to prevent the onset of clinical symptoms.**

[2] **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.**

[3] **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**

[4] **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.**

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