WHEN TO CONSIDER AN INHERITED METABOLIC DISORDER

Aims:

- To guide clinicians about when to consider the presence of an inherited metabolic disorder in neonates, infants, children, adolescents or adults based on clinical presentation or initial laboratory test results.
- To recommend the first-line laboratory tests needed to identify a metabolic disorder in life threatening conditions.

Clinical signs and symptoms suggestive of inherited metabolic disorders:

- **Presentation can occur at any time, including adulthood.**
- **A high index of suspicion is important.**

FLAGS

- Any critically ill neonate, with apparent “sepsis”, who has no risk factors for an infection.
- Recurrent vomiting, poor feeding, failure to thrive in an infant.
- Episodes of lethargy, altered consciousness.
- Severe global developmental delay, especially with loss of skills.
- Illness out of proportion to the immediate precipitating cause (such as a childhood viral illness) and if siblings recover much more quickly.
- Subtle neurological or psychiatric abnormalities in older children (>5) or adolescents.
- Hepatomegaly, cirrhosis, liver failure, cholestatic jaundice.
- Dysmorphic syndromes.
- Hypertrophic cardiomyopathy.
- Skin signs: ichthyosis, light sensitivity.
- Eye abnormalities - cataract, corneal opacities, pigmentary retinopathy.
- Chronic muscle weakness with pain.
- Renal stone disease in children.
- Renal tubular disease in children.
- An unusual smell from skin or urine: sweaty feet, cheese, burnt maple syrup, rotten fish, “tomcat urine”.

Hints to metabolic disorders from patient history or family history

- *Symptoms during infection, fever or fasting?* – may mean impaired glucose synthesis or glycogen breakdown, impaired amino acid breakdown, impaired fatty acid oxidation, impaired ketone production or use.
- *Symptoms on weaning?* – increased protein intake, exposure to fructose in food.
- *Symptoms on exposure to drugs?* – porphyria , G6PD deficiency, exposure to fructose or glycerol in medicines.
- *Family consanguinity?* – higher likelihood of autosomal recessive disorders
- *Are there any related symptoms in parents or other family members?*
- *Unexplained neonatal or cot deaths?*

ACUTE, LIFE THREATENING INBORN ERRORS

Most will have **encephalopathy** and at least 1 of the following laboratory abnormalities:

- **Metabolic acidosis**
- **Hypoglycaemia**
- **High blood ammonia**

Exceptions include:

- **Encephalopathy, apnoea , intractable seizures, but none of the above:** glycine
- cleavage defect: (non-ketotic hyperglycinaemia)
- **Severe hyponatraemia, hyperkalaemia:** congenital adrenal hyperplasia:

First line investigations for suspected, acute life threatening metabolic disease

- *Urea, electrolytes and bicarbonate* (hypokalaemia, uraemia, low bicarbonate).
- *Liver function tests* (elevated transaminases in liver disease, fat oxidation defects, some myopathies).
- *Creatine kinase* (raised in metabolic myopathy and fatty acid oxidation defects)
- *Glucose* (high or low).
- *Lactate* (high in shock, may be high in organic acidaemia, some glucose disorders, some fatty acid oxidation disorders).
- *Capillary blood gas* (acidosis; alkalosis is rare but may occur early in Hyperammonaemia).
- *Ammonia*. (high in urea cycle defects, organic acidaemia or fatty acid oxidation defects)
- *Two blood spots on a "Guthrie" card for acylcarnitines* (may be diagnostic in fatty acid oxidation disorders).
- *Full blood count* (neutropenia in organic acidaemias).
- *Urinalysis for ketones* (test for acetoacetate: presence is highly significant in the newborn).
- *Coagulation Studies*

Keep a sample frozen for subsequent organic acid analysis, if required later.

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WHEN TO CONSIDER AN INHERITED METABOLIC DISORDER
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Original publication: September 2008. Last revision: September 2016. Date of next revision: September 2019.

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SOME IMPORTANT ACUTE, LIFE-THREATENING DISORDERS

Result / Diagnosis	***Metabolic Acidosis***	***Glucose***	***Ketonuria***	***Lactate***	***Ammonia***
Organic Aciduria	+++	↓ - ↑	Yes ++	↑	↑↑
Urea cycle defect *	No	Normal	No	Normal	↑↑↑
Fatty acid oxidation defect	+/-	Normal or ↓↓	Usually No	Normal - ↑	Normal -↑↑
Neonatal sepsis	Possible	Normal or ↓	No	Yes ↑↑	Normal or ↑
Congenital Lactic acidosis	+++	Normal	No	Yes ↑↑↑↑	Normal

* In any neonate with respiratory alkalosis, hyperammonaemia should be considered.

Please note:

- This table describes typical patterns.
- Variations in presentation and severity are common.