Inborn errors of metabolism

When to screen

- Unexplained symptoms including:
    - severe or unexplained metabolic acidosis
    - hypoglycaemia
    - collapse or shock
    - unexplained neurological symptoms –hypertonia/hypotonia/lethargy
    - apparent “birth asphyxia” but with unusual clinical features
    - persistent vomiting
    - apnoeic episodes
    - jaundice with unusual features
    - hepatosplenomegaly
    - abnormal urine colour (yellow/black -conjugated jaundice/alkaptonuria)
    - unusual odour
    - dysmorphism suggestive of specific syndrome (eg Zellweger, Smith-Lemli-Opitz)

- Ill baby with family history of inborn error of metabolism or of unexplained illness or death in infancy or developmental delay.

Acute symptoms may be indistinguishable from those of sepsis, cardiorespiratory failure or CNS disease. Symptoms can be present from birth but this is unusual and in many the signs and symptoms develop after a period of apparent good health - e.g. after introduction of feeds or a change in diet. Consider metabolic disease especially if signs persist or progress with no supportive evidence of another explanation (e.g. sepsis) or following usual therapy for conditions such as sepsis.

What to do

N.B. This is not a chronological sequence. In seriously ill babies and those with a high level of suspicion of inborn error, it is better to take samples for investigation at the time of resuscitation, before feeds stopped, transfusion given or antibiotics started.

1. **Escalate to Consultant Neonatologist**
2. **Discuss with Metabolic Medicine Consultant (available through QEUH switchboard)**
3. **Discuss with Biochemistry RHSC**
4. **Immediate management and resuscitation:**

    - Routine supportive treatment of breathing and circulation
    - Ensure good hydration with iv fluids
    - Stop milk feeds - milk challenge may be used later to help with diagnosis
    - Correct biochemical abnormalities: acidosis, hypoglycaemia and clotting
    - Give antibiotics until sepsis excluded
    - If there is hyperammonaemia please follow separate guideline

    Further management will be guided by biochemical abnormalities including:

    - Elimination of toxic metabolites: chelators, hemofiltration
    - Cofactor supplementation

4. Investigations

It is usually best to perform these investigations at the time when the baby is clinically ill, since this improves the chances of finding an abnormality

a. General –the following should be considered:

- Glucose
- Gases
- Urea & electrolytes
- Liver function tests
- Coagulation screen
- Ammonia

b. Specific – discuss with Consultant before sending:

- Urine reducing substances
- Blood amino acids
- Urine amino acids
- Urine organic acids
- Blood and CSF lactate
- Very long chain fatty acids
- Galactosaemia screen

If in doubt or in a hurry, take the following:

- Lithium heparin ON ICE -amino acids, ammonia, galactosaemia investigations
- Lithium heparin -routine biochemistry and hypoglycaemic endocrine screen if indicated
- Fluoride oxalate -glucose, lactate, 3-hydroxybutyrate, free fatty acids
- EDTA -DNA, VLCFA, lysosomal and peroxisomal enzymes (5ml minimum for these)
- Urine -amino acids, organic acids, mucopolysaccharides, sugars

5. Further management

a. Ascertain

- Any consanguinity
- Full family history including name and detailed information about possibly affected relatives

b. Consider

- Specialist opinion from neurologist/ gastroenterologist/ geneticist
- Tissue biopsy during life or immediately PM
- Special post or perimortem investigations (discuss with pathologists at RHSC)
- Storage of blood for DNA analysis (EDTA sample to Clinical Genetics, WGH)

6. Tissue biopsy

Always contact the relevant labs before arranging any tissue biopsy. Out of normal office hours, the biochemistry lab MLSO will contact one of the Senior Biochemists to provide advise, and also discuss how to obtain the necessary kit.

a. Skin biopsy

- For fibroblast culture.
- Discuss with Metabolic Biochemist
- Skin biopsy packs with the correct medium can be obtained from biochemistry
- Take 2 samples from well-perfused skin on the upper leg or trunk. Clean skin well but wash off all cleaning solution with sterile saline. If no medium immediately available then place skin in sterile saline using sterile forceps.

b. Liver and muscle biopsy

- Discuss differential diagnosis with Metabolic Biochemist, Metabolic Medicine and Pathologist.
- Liver biopsy is usually done for storage disorders.
- Muscle biopsy is helpful particularly if a respiratory chain defect suspected.
- For liver and muscle biopsy during life contact the surgeons and pathology.

7. The baby who is dying

It is important to get a diagnosis to help with genetic counseling. An autopsy is the gold standard but it is also vital to get "fresh" specimens either before or just after death. Obtain the following samples when appropriate and where this does not result in pain or distress to the baby:

- Blood– heparinised, fluoride oxalate, EDTA: send to biochemistry RHSC to be separated and frozen
- Heparinised blood for karyotype and EDTA for DNA analysis to cytogenetics, WGH
- Urine: refrigerate until it can be sent to biochemistry laboratory
- CSF: refrigerate until it can be sent to biochemistry laboratory
- Tissue biopsies