INHERITED METABOLIC DISORDERS (IMD) ● 1/4

RECOGNITION

- Early recognition of IMD and prompt management are essential to prevent death or neurodisability
- diagnosis of IMD in babies is often delayed owing to non-specific nature of clinical presentation and unfamiliarity with diagnostic tests
- seek early advice from regional clinical IMD team at tertiary metabolic centre

Consider IMD at the same time as common acquired conditions, such as sepsis

Differential diagnosis (lists below are not comprehensive, discuss with clinical IMD team)

Presentation	Common conditions
• Encephalopathy without metabolic acidosis	• Urea cycle disorders • Maple syrup urine disease (MSUD)
• Encephalopathy with metabolic acidosis	• Organic acidaemias (e.g. propionic, methylmalonic, isovaleric, glutaric aciduria Type I) • Congenital lactic acidosis
• Liver dysfunction including jaundice, particularly conjugated	• Galactosaemia • Tyrosinaemia • Neonatal haemochromatosis • Alpha$_1$-antitrypsin deficiency • Citrin deficiency • Niemann-Pick disease type C • Mitochondrial disease • Congenital disorders of glycosylation – CDG 1b (uncommon)
• Hypoglycaemia	• Hyperinsulinism • Fatty acid oxidation disorders • Glycogen storage disorders • Gluconeogenesis defects
• Metabolic acidosis	• Organic acidaemias • Congenital lactic acidosis
• Non-immune hydrops	• Lysosomal storage disorders, including: mucopolysaccharidoses I-cell disease Gaucher disease Niemann-Pick disease type A, B or C
• Severe neonatal hypotonia	• Zellweger's syndrome • Non-ketotic hyperglycinaemia (NKHG)
• Cataracts	• Galactosaemia • Zellweger's syndrome • Lowe's syndrome
• Congenital anomalies if developmental delay or neurological signs present with dysmorphism, consider IMD	
• Apnoea or periodic breathing in term baby • Hiccoughing	• NKHG (also likely to have hypotonia, epileptic encephalopathy) • MSUD
• Respiratory alkalosis in a tachypnoeic baby	• Hyperammonaemia
• Intractable neonatal seizures	• Pyridoxine or pyridoxal phosphate – responsive seizures • Peroxisomal biogenesis disorders • Neurotransmitter disorders • Glucose transporter defect (GLUT 1) • NKHG • Sulphite oxidase deficiency and molybdenum cofactor deficiency • Serine synthesis defect

INHERITED METABOLIC DISORDERS (IMD) ● 2/4

Specific indicators

Clinical context

- Unexplained and mysterious deterioration of baby (can be as short as 12 hr but more commonly after a symptom-free interval of 24 hr–14 days)

Family history

- Known metabolic disorders
- Unexplained neonatal or infant deaths
- Parental consanguinity

Obstetric history

- Acute fatty liver of pregnancy and HELLP syndrome in index pregnancy may point towards long chain fatty acid oxidation defect in baby

Non-specific indicators suggestive of metabolic disorder in an encephalopathic baby

- Encephalopathy in low-risk baby, or onset after period of normality
- Fluctuating consciousness and muscle tone
- Changes in muscle tone:
  - axial hypotonia with limb hypertonia
  - 'normal' tone in comatose baby
- Abnormal movements:
  - myoclonic or boxing movements
  - tongue thrusting
  - lip smacking
  - unexplained seizures/burst suppression/hypsarrythmia
  - seizures are uncommon or occur late in babies with metabolic encephalopathy compared to hypoxic-ischaemic encephalopathy

INITIAL INVESTIGATIONS

- Whenever IMD suspected, perform required investigations **without delay**
  - in a sick child request urgent processing of investigations by metabolic biochemistry laboratory
- Seek early advice about appropriate investigations and management from IMD team at tertiary metabolic centre

Urine

- Smell
- Ketostix: presence of large amounts of urinary ketones is usually abnormal in babies and could suggest IMD, especially organic acidaemias
- Freeze 15–20 mL urine for amino and organic acid analysis
- Metabolic screen (amino acids, organic acids, ketones, sugars)

Blood

- FBC, U&E, infection screen
- Glucose
- Blood gas (calculate anion gap)
- Ammonia
- Lactate
- Acylcarnitines, including free and total carnitine (bloodspot on Guthrie card/2 mL Li-Hep)
- Plasma amino acids (lithium heparin 2 mL)

Imaging

- Cranial ultrasound scan
- Ophthalmic examination

SPECIFIC INVESTIGATIONS

Discuss with clinical IMD team at tertiary metabolic centre before initiating specific investigations as not all tests may be indicated in all babies with similar presentation

Unexplained/prolonged jaundice or liver synthetic dysfunction

Blood

- Galactosaemia screen [galactose-1-phosphate uridytransferase (GALIPUT)/Beutler test] (urinary reducing substances can be negative after short period of galactose exclusion)
  - cannot be performed reliably if transfused ≤90 days: measure galactose-1 phosphate (Gal-1-P) and urine galactitol (urine organic acids)
- Total and conjugated bilirubin, liver function tests, including clotting studies
- Blood spot – succinyl acetone (tyrosinaemia I)
- Ferritin
- Plasma – very long chain fatty acids only if dysmorphic and hypotonic*
- Plasma quantitative amino acids
- Alpha$_1$-antitrypsin (quantitative)
- Transferrin isoelectric focusing* (CDG)
- Consider Niemann-Pick disease type C (chitotriosidase, DNA- mutation analysis)*

Urine

- Organic acids (succinylacetone in tyrosinaemia I)
- Reducing substances: use Clinitest™
  - urinary dipsticks are glucose specific and miss galactose in babies with galactosaemia
  - negative Clinitest™ does not exclude galactosaemia

Encephalopathy/epileptic encephalopathy/neonatal intractable seizures

Discuss with IMD team – some of the following investigations may be advised and a trial of treatment with pyridoxine/pyridoxal phosphate may be required in certain cases

- Urgent quantitative plasma amino acids and urine amino acids
- Paired blood and CSF amino acids (glycine, serine), (NKHG, serine synthesis deficiency)
  - CSF glucose, lactate (GLUT I, mitochondrial disorder). Paired blood and CSF lactate with blood sample taken before CSF
- Plasma – very long chain fatty acids (peroxisomal disorder)
- Urine:
  - dipstick for ketones
  - sulphite test for sulphite oxidase deficiency
- Plasma – uric acid (low in molybdenum cofactor deficiency)
- Pyridoxine responsive epilepsy (antiquitin deficiency)
- Pyridoxal phosphate responsive seizures
  - consider CSF amino acids, CSF neurotransmitters, urine organic acid analysis
  - urine alpha-aminoadipic semialdehyde (AASA) (freeze urine and CSF samples **immediately**)

Hypoglycaemia (most informative when obtained at time of hypoglycaemia)

- Plasma non-esterified free fatty acids (FFA)
- Beta-hydroxybutyrate (ketones)
- Insulin and C-peptide
- Acylcarnitine profile, free and total carnitine
- Cortisol, growth hormone
- Urine for organic acids and ketones

Post-mortem (plan how best to use these precious samples in consultation with IMD team)

- Plasma (2–5 mL), urine (10–20 mL) and CSF (1 mL) frozen at −20°C
- Red cells: blood (5 mL) in lithium heparin stored at 4°C (fridge)
- Blood (5 mL) in EDTA: stored at 4°C (fridge) for DNA analysis
- Tissue biopsies
  - skin: store in viral culture medium or sodium chloride 0.9% at 4°C (fridge) (see **Skin biopsy** guideline)
  - muscle and liver: take within 1 hr of death, snap freeze in liquid nitrogen
- Post-mortem examination
- Bile for acylcarnitine analysis – stable for longer than other body fluids

IMMEDIATE MANAGEMENT

Commence emergency management of suspected IMD while awaiting results of initial investigations and discuss with IMD team as early as possible

- Attend to **A**irway, **B**reathing and **C**irculation; ventilate if necessary
- Omit all protein, fat and galactose/lactose (milk) intake, including PN and lipid
- Commence glucose 10% IV infusion to provide 6–8 mg glucose/kg/min
  - if hyperglycaemic (>15 mmol/L) or catabolic, start insulin infusion, under guidance from IMD team
  - if hypertonic (concentration of glucose >10%) infusion necessary, insert central line
- Correct dehydration, acid-base and electrolyte disturbances
- Cover for infection
- Control seizures (avoid sodium valproate)
- When stable and appropriate, consider early transfer to tertiary metabolic centre

SPECIFIC MANAGEMENT

- Must be led by IMD team
- Use following as guide to general principles of management
- Check regularly that metabolic emergency medications mentioned below are in stock and available for emergency use

Neonatal hyperammonaemia

Medical emergency requiring prompt intervention to lower ammonia concentration

- Renal replacement therapy (haemofiltration more efficient than peritoneal dialysis)
- Sodium benzoate
- Sodium phenylbutyrate
- L-arginine
- Carglumic acid (Carbaglu®)

Organic acidaemia

- Reduce/stop protein intake
- Glucose 10% infusion +/- insulin
- L-carnitine
- Carglumic acid (Carbaglu®)

Fatty acid oxidation disorders

- Avoid prolonged fast
- Specific management guided by IMD team

Lactic acidosis

- Dichloroacetate
- Biotin
- L-carnitine
- Thiamine

Galactosaemia

- Dietary exclusion of galactose

For further information on IMD, www.bimdg.org.uk/guidelines.asp, Emergency protocols and follow through

LOCAL CONTACT

- Birmingham Children's Hospital metabolic team (0121 333 9999)