

METABOLIC DISORDERS

(INBORN ERRORS OF METABOLISM)

RECOGNITION

- Early recognition of inborn errors of metabolism (IEM) and prompt management are essential to prevent death or neurodisability
- diagnosis of IEM in neonates is often delayed owing to non-specific nature of clinical presentation, and unfamiliarity with diagnostic tests
- seek advice from local and regional clinical chemistry services

Consider inborn errors of metabolism at same time as common acquired conditions, such as sepsis

Differential diagnosis

Presentation	Common conditions
Encephalopathy without metabolic acidosis	<ul style="list-style-type: none"> • Urea cycle disorders • Maple syrup urine disease (MSUD) • Zellweger syndrome • Non-ketotic hyperglycinaemia (NKHG) • Molybdenum cofactor deficiency
Encephalopathy with metabolic acidosis	<ul style="list-style-type: none"> • Organic acidaemias (propionic, methylmalonic, isovaleric) • Glutaric acidaemia type II
Liver dysfunction	<ul style="list-style-type: none"> • Galactosaemia • Tyrosinaemia • Neonatal haemochromatosis • Zellweger syndrome • α_1-antitrypsin deficiency • Smith-Lemli-Opitz syndrome • Fatty acid oxidation disorders (MCAD) • Congenital disorders of glycosylation – CDG 1b
Hypoglycaemia	<ul style="list-style-type: none"> • Fatty acid oxidation disorders • Galactosaemia • Glycogen storage disorders • Fructose-1, 6-bisphosphatase deficiency
Metabolic acidosis	<ul style="list-style-type: none"> • With raised lactate • Pyruvate dehydrogenase (PDH) deficiency • Pyruvate carboxylase deficiency • respiratory chain disorders • organic acidaemias • With normal lactate • organic acidaemias
Non-immune hydrops	<ul style="list-style-type: none"> • GM1 gangliosidosis • Mucopolysaccharidosis type VII and IV • Gaucher's • Niemann-Pick A & C • I-Cell disease
Odour : maple syrup (burnt sugar) sweaty feet odour	<ul style="list-style-type: none"> • MSUD • Isovaleric acidaemia or • Glutaric acidaemia type II
Cataracts	<ul style="list-style-type: none"> • Galactosaemia • Zellweger syndrome

	<ul style="list-style-type: none"> • Lowe syndrome
Dislocated lens	<ul style="list-style-type: none"> • Homocystinuria • Sulphite oxidase deficiency
Congenital anomalies <ul style="list-style-type: none"> • hypotonia, epicanthal folds, Brushfield spots, simian creases, large fontanelle, renal cysts • hypertelorism, low set ears, high forehead, abdominal wall defects, large kidneys • appearance similar to fetal alcohol syndrome • facial dysmorphism, cleft palate, poly- or syndactyly, congenital heart disease 	<ul style="list-style-type: none"> • Zellweger syndrome • Glutaric acidemia type II • PDH deficiency • Smith-Lemli-Opitz syndrome
Agenesis of corpus callosum	<ul style="list-style-type: none"> • NKHGPDH deficiency
Apnoea or periodic breathing in term infant	<ul style="list-style-type: none"> • NKHG
Respiratory alkalosis in a tachypnoeic baby	<ul style="list-style-type: none"> • Hyperammonaemia
Jaundice (particularly conjugated) and liver dysfunction	<ul style="list-style-type: none"> • Galactosemia • Tyrosinaemia • α_1-antitrypsin deficiency
Hypoglycaemia in a low-risk infant, or persistent/recurrent, with neurological symptoms	<ul style="list-style-type: none"> • Fatty acid oxidation defects • Glycogen storage disorders • Galactosaemia
Metabolic acidosis with increased anion gap	<ul style="list-style-type: none"> • Organic acidemias
Persistent vomiting	<ul style="list-style-type: none"> • Hyperammonaemia
Hiccoughing	<ul style="list-style-type: none"> • NKHG

Specific indicators

- Clinical context:
 - unexplained and mysterious deterioration of baby (can be as short as 12 hr but more commonly at 48 hr)
- Family history of:
 - 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 neonate

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

- Encephalopathy in low risk infant, 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
- True seizures occur late in metabolic encephalopathies except in NKHG

INITIAL INVESTIGATIONS

- Whenever IEM suspected, perform required investigations without delay
- Seek early advice about appropriate investigations and management from inherited metabolic diseases (IMD) team at tertiary metabolic centre

Urine

- Smell
- Ketostix – presence of large amounts of urinary ketones is always abnormal in neonates and suggests IEM, especially organic acidaemias
- Reducing substances – use Clinitest – urinary dipsticks are specific for glucose and miss galactose in babies with galactosaemia
- Freeze 15-20 mL urine for amino and organic acid analysis

Blood

- Full blood count, U&Es, Infection work up
- Glucose
- Blood gas
- Ammonia
- Lactate
- Total and conjugated bilirubin, liver function tests including clotting studies
- Acylcarnitines, including free and total carnitine
- Uric acid
- Amino acids

Imaging

- Cranial ultrasound
- Ophthalmic examination

SPECIFIC INVESTIGATIONS

Jaundice

Blood

- Galactosaemia screen (urinary reducing substances can be negative after short period of galactose exclusion)
- Ferritin
- Very long chain fatty acids
- α_1 -antitrypsin (quantitative)
- 7-dehydrocholesterol
- Transferrin isoelectric focusing

Urine

- Succinylacetone
- Skin (and liver) biopsy after discussion with metabolic team

Encephalopathy

- Paired blood and CSF glycine
- CSF lactate
- Very long chain fatty acid profile
- Urine for orotic acid
- Urine – Sulfitest for sulphite oxidase deficiency

Hypoglycaemia (most informative when obtained at the time of hypoglycaemia)

- Plasma non-esterified fatty acids
- β -hydroxybutyrate
- RBC galactosaemia screen
- Insulin and C-peptide
- Acylcarnitine profile, free and total carnitine
- Cortisol, growth hormone
- Urine for organic acids

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 for DNA analysis
- Tissue biopsies
- skin – store in culture medium or saline at 4°C (fridge)
- muscle and liver – take within hour of death, snap freeze in liquid nitrogen
- Post-mortem examination

IMMEDIATE MANAGEMENT

Commence emergency management of suspected IEM while awaiting results of initial investigations

- Attend to **A**irway, **B**reathing and **C**irculation; ventilate if necessary
- Omit all protein intake, including TPN and lipid
- Commence intravenous glucose infusion to provide 6-8 mg glucose/kg/min
- start insulin infusion if hyperglycaemic (>15 mmol/L) or catabolic
- if hypertonic glucose infusion necessary, insert central line
- Correct dehydration, acid-base and electrolyte disturbances
- Cover for infection
- Control seizures (avoid sodium valproate)
- Consider transfer to tertiary metabolic centre if stable and appropriate

SPECIFIC MANAGEMENT

- Must be led by IMD team
- Use following as guide to general principles of management
- Neonatal hyperammonaemia – a medical emergency requiring prompt intervention to lower ammonia concentration
- renal replacement therapy (haemofiltration more efficient than peritoneal dialysis)
- sodium benzoate
- sodium phenylbutyrate
- L-arginine
- L-carnitine
- Organic acidaemia
- reduce/stop protein intake
- hypertonic glucose infusion ± insulin
- L-carnitine
- glycine
- biotin
- Fatty acid oxidation disorders
- avoid prolonged fast
- L-carnitine
- Lactic acidosis
- dichloroacetate
- biotin
- L-carnitine
- thiamine
- Galactosaemia
- dietary exclusion of galactose