Inborn errors of metabolism
Overview

• Definition and incidence
• Types of disorder
• Common clinical features
• Initial investigations
• Specialist metabolic investigations
• Summary
What is an Inborn Error of Metabolism

- Genetic disorder, resulting from defect in a gene of an enzyme or a functional protein
- Autosomal recessive or X-linked
- Generally appear in infancy or early childhood
- Often produce severe metabolic disturbances
- Acute presentation requires immediate management
- There are many specific disorders
Incidence

- Some disorders are more common
  - 1 in 10,000
- Some are very rare
  - 1 in 500,000
- Collectively they can account for 1 in 5-6,000 live births
- Despite rarity – important to consider in the sick neonate
- Important to diagnosis early for appropriate management and care
Types of disorders

- Urea cycle disorders
- Amino acid disorders
- Organic acid disorders
- Fatty acid oxidation disorders
- Carbohydrate disorders
- Peroxisomal disorders
- Purine and pyrimidine disorders
- Lysosomal storage disorders
Urea cycle disorders (UCD)

- There are 6 UCDs
- Ornithine carbamoyl transferase deficiency (OCT) – Prevalence 1:40,000
- Characteristic symptoms:
  - High ammonia (often >800 umol/L)
  - Vomiting, seizures, lethargy
  - Respiratory alkalosis
- May be mis-diagnosed as sepsis
Urea cycle disorders

- Ornithine
- Citrulline
- Arginine
- Arginosuccinate
- Fumarate
- Urea
- NAG & Carbamoyl P
- Aspartate
- Orotic acid
Hyperammonaemia

- Not diagnostic for urea cycle disorders
- May also be increased in sepsis, sick neonates etc
- Requires additional investigation
  - LFTs, APTT
  - Plasma/urine AA and OA
  - Plasma acyl carnitines
Consequences

- Once ammonia >150 μmol/L can lead to permanent neurological damage
- Requires prompt & aggressive treatment
  - Withdraw dietary protein
  - Sodium benzoate/ phenylbutyrate
  - Haemofiltration/dialysis
Long term

- In severe cases the long term outlook is poor
- Protein restriction (1.5g per kg per day)
- Sodium benzoate (conjugates glycine to form hippurate)
- Arginine supplements (becomes essential AA)
- Liver transplant may be an option
Urea cycle disorder: example

- Ornithine carbamoyl transferase (OCT) deficiency
- X-linked inheritance
- Most are affected males (?female carriers)
- Requires life-long protein restriction
- Neurological handicap can be severe
Amino acid disorders: Maple syrup urine disease (MSUD)

- Incidence: rare
- Defective decarboxylation of branched chain amino acids
- Presentation: progressive CNS dysfunction
- Metabolic acidosis & hypoglycaemia
- Diagnosis: increased plasma amino acids
  - leucine, isoleucine, valine
- Treatment: special diet
  - Poor long-term outlook
Biochemical defect in Phenylketonuria

Phenylalanine block → Phenylalanine hydroxylase → Phenylpyruvic acid

Phenylalanine → Tyrosine → 3,4-dihydroxyphenylalanine (DOPA) → Melanin pigments

Tyrosine transaminase → p-hydroxyphenylpyruvic acid

p-hydroxyphenylpyruvic acid → p-hydroxyphenylpyruvic acid oxidase → Homogentisic acid

Homogentisic acid oxidase → Maleylacetoacetic acid

Fumarylacetoacetate → Acetoacetic acid → Fumaric acid → CO₂ + H₂O → Citric acid cycle
Phenylketonuria

Phe hydroxylase

Phe --- deficiency --- Tyr

- Mental Retardation
- Low pigmentation

Phe Accumulation

[Image of a child with phenylketonuria symptoms]
Phenylketonuria

- Deficiency of phenylalanine hydroxylase
- Severe mental retardation, often light color skin
- Can be diagnosed in neonates
- By decreasing phenylalanine in diet, it is possible to prevent mental retardation
Albinism

Tyrosine

Deficiency

Tyrosine hydroxylase

Melanin
Organic acid disorders

- Organic acids are carboxylic acids
- Metabolites of amino acids, carbohydrate and fats
- Disorders affect several pathways
  - Catabolism of branched chain amino acids and propionyl CoA
- Presentation: severe metabolic acidosis
  - Vomiting; hypoglycaemia, hyperammonaemia, ketonuria
- Diagnosis: Urine OAs or carnitines
OA examples

- Methylmalonic acidaemia
- Propionic acidaemia
- Treatment: protein restriction
- Very poor long-term prognosis
- Liver transplantation has had some success
Fatty acid oxidation disorders

- Mitochondrial $\beta$-oxidation of fatty acids
- Major role in energy production
- Especially important during fasting
- Complex process
- Variety of disorders caused by enzyme defects in process
- Commonly present with hypoglycaemia after fasting
MCAD: medium chain acyl CoA dehydrogenase deficiency

- MCAD: affects fatty acids C6-C10
- Clinical severity varies
  - Sudden infant death
  - Asymptomatic adults
- Diagnosis difficult – timing is crucial
  - Hypoglycaemia with inappropriately low plasma/urine ketones
  - High plasma FA: 3HB ratio
Galactosemia

- Incidence approx 1 in 45,000
- Deficiency of galactose-1-phosphate uridyl transferase (Gal-1-PUT)
- Fatty liver, jaundice, hepatomegaly
- Liver failure, sepsis
- Fatal if appropriate treatment not given
Diagnosis

• **Initial screen**
  - Positive urine reducing substances (Clinitest)

• **Confirmed by**
  - Gal-1-PUT measurement in RBCs
  - Invalidated by recent blood transfusion

• **Long term treatment requires a galactose free diet**
  - Even with good compliance, neurological function can deteriorate
Presentation

• Most babies with an IEM are born at term
• Generally are normal at birth – protected by maternal metabolism
• Symptoms commonly develop within 1st week – 24-48hrs after milk feeding
Common clinical features

• Generally non-specific
  – Vomiting, lethargy, hypotonia, fits

• Features which suggest IEM are:
  – Abnormal smell
  – Metabolic acidosis with high anion gap
  – Neurological dysfunction & respiratory alkalosis
  – Dysmorphic features
Initial investigations

• **Biochemical “clues” to an IEM**
  - Hyperammonaemia
  - Hypoglycaemia
  - Acid-base imbalance +/- high anion gap
  - Lactic acidosis
  - Inappropriate ketonaemia or absence of ketones

• **Exclude common causes**
  - Infection, renal disease, congenital heart disease
Specialist metabolic investigations

- When the neonate is acutely ill the following tests should be considered and may be required urgently
  - Ammonia (P)
  - Lactate (P)
  - Amino acids (P and U)
  - Organic acids (U)
  - Acyl carnitines (P or blood spot)
  - Galactose-1-phosphate uridyl transferase (RBCs)
Specimen collection

• In an emergency or with imminent death the following should be collected
  • Urine: 5-10ml (plain bottle) –20ºC
  • Plasma: 1ml heparin & 1ml fluoride oxalate
    – Separate asap and freeze at –20ºC
  • Skin fibroblasts
  • Tissue samples (heart, muscle etc)
Treatment

- **Short term:**
  - supportive, withdraw protein
  - Sodium benzoate: conjugates with glycine
  - Dialysis

- **Long term**
  - Dietary restrictions (growth problems)
  - Amino acid supplements
Prognosis

- Long term outlook often poor
- Prompt treatment can be of benefit
- Difficult to maintain long term
  - Diet unpalatable
- Neurological handicap can be severe
- Importance of pre-natal diagnosis
- Aggressive treatment may not always be best option
Counselling and prenatal diagnosis

• Importance of making a diagnosis
• Allows counselling of family
• Pre-natal diagnosis for future babies
• Or prompt treatment for future affected babies
  - chorionic villus sampling
  - amniocentesis
  - pre-implantation diagnosis
Summary

• Individually rare but collectively important
• Effect different pathways
• Investigation of these disorders
  – Requires complex equipment (GC-MS etc)
  – Specialist knowledge and expertise
• But most babies with these disorders are born in full term
  – Important to be aware of specimen collection requirements
  – Importance of prompt separation & freezing
  – May only get 1 chance