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**

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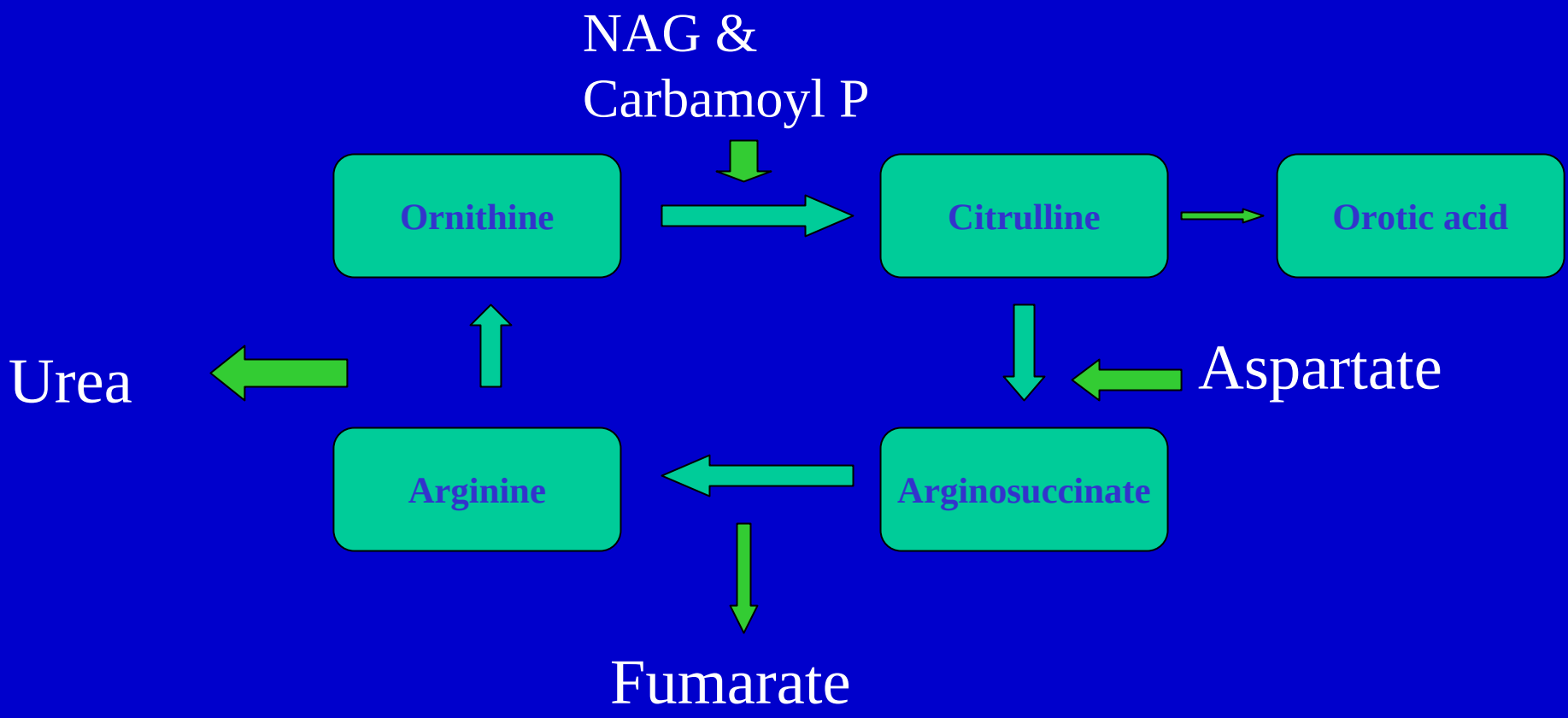
Types of disorders

- 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



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

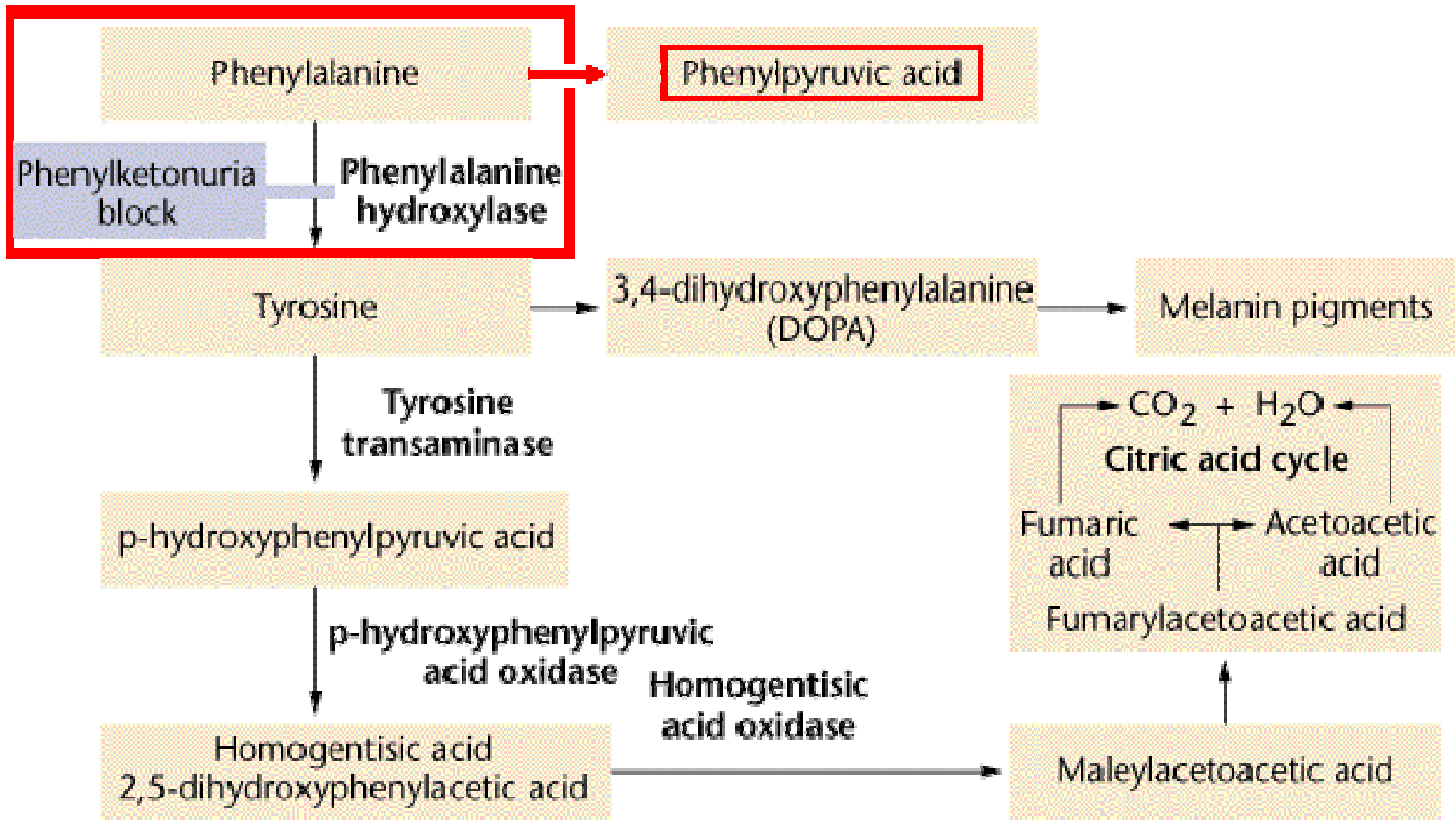
Urea cycle disorder: example

- 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



Phenylketonuria

Phenylketonuria

Phe → **Phe hydroxylase** → **Tyr** (deficiency)

Phe → Phe Accumulation

- **Mental Retardation**
- **Low pigmentation**

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 etardation

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 β-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) –20°C
- Plasma: 1ml heparin & 1ml fluoride oxalate
  - Separate asap and freeze at –20°C
- 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