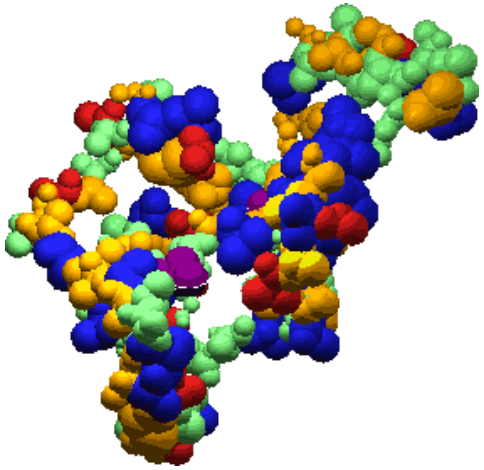
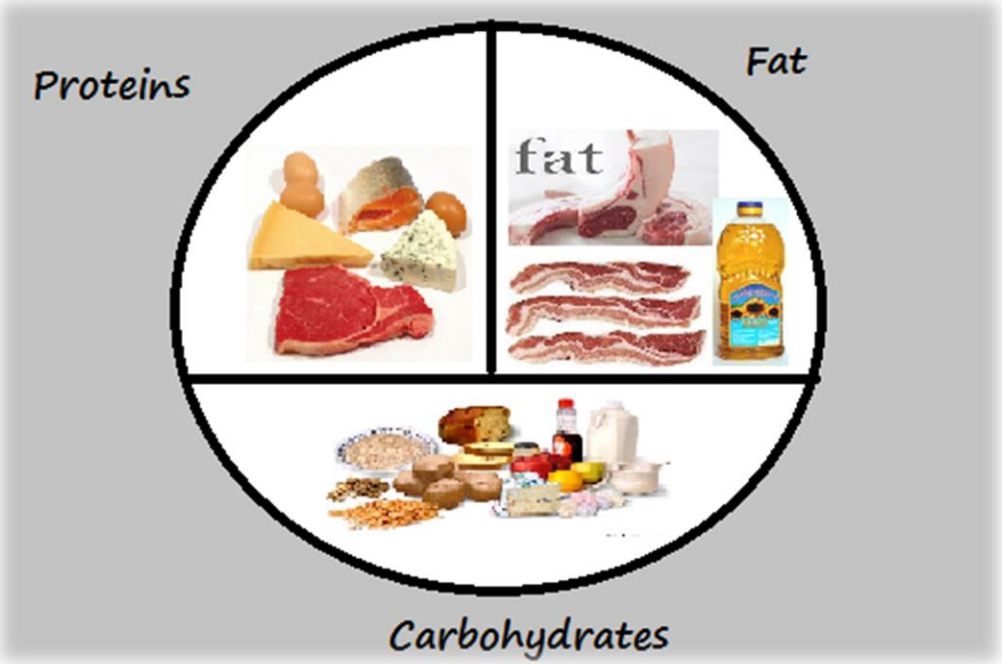
The most frequent metabolic failures in childhood





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Inborn error of metabolism (IEM)

1. Inborn errors of metabolism (IEM) are disorders in which there is a block at some point in the normal metabolic pathway
2. IEMs occur due to mutations in DNA
3. While particular diseases are rare, they collectively account for a significant proportion of neonatal and childhood morbidity and mortality
4. IEMs incidence is 1 in 2000 infants
5. Diagnosis is important not only for treatment but also for genetic counselling and antenatal diagnosis in subsequent pregnancies
6. An inborn error of metabolism may be suspected before birth from a positive family history or previous unexplained deaths in the family

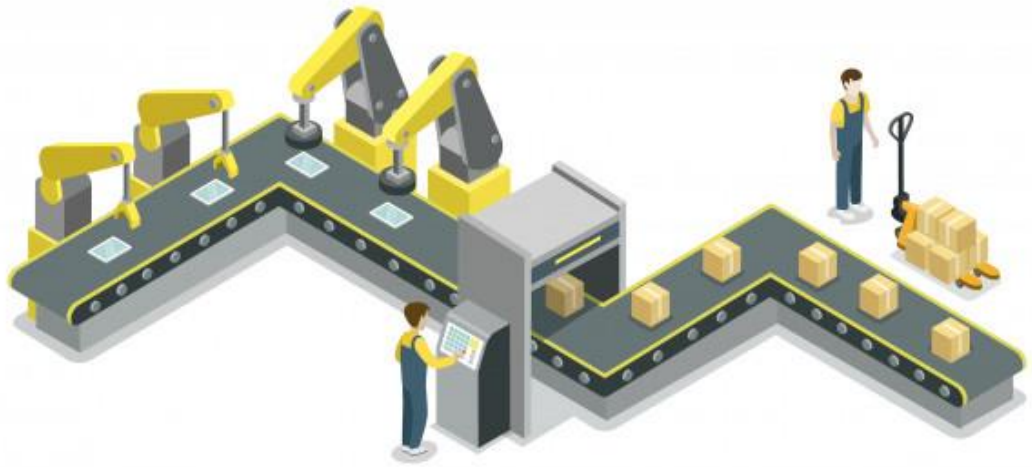
Map of the known metabolic pathways

- Very complex – more complex than the most coplicated subway in the world (New York)
- Error in one pathway may also influence on others

New York subway map

Metabolic pathways

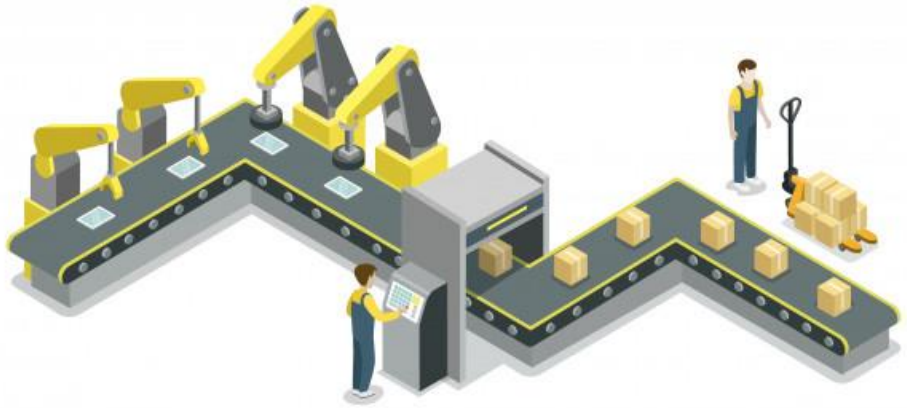
- Metabolic pathways are a complex „factory/production line” with many crossing-points between particular pathways
- The product of one cycle may be the substrate for another etc.



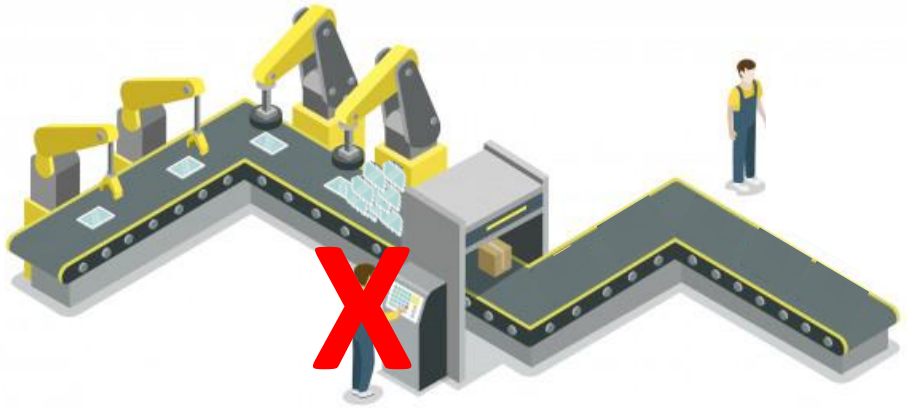
Metabolic errors

- Genetic mutations cause errors at some point of the „production line”
- Usually dysfunction of some enzymes
- For example: deficiency of one enzyme will result in blockade of the pathway -> deficiency of the products beyond the blockade and accumulation of substrats before the blockade

Normal state



Metabolic disease



Accumulation of some substances (to toxic levels)

Deficiency of some substances

Clinical symptoms

Symptoms of metabolic diseases usually begin after birth

Clinical presentation

After birth, inborn errors of metabolism usually, but not invariably, present in one of the way:

1. As a result of **newborn screening**, e.g. phenylketonuria (PKU)
2. After a short period of normal, healthy activity, with symptoms as: **poor feeding, vomiting, encephalopathy, acidosis, coma and death,** e.g. organic acid or urea cycle disorders
3. As an infant or older child with symptoms similar to that described above but with **hypoglycaemia** as a prominent feature or as an ALTE (acute lifethreatening episode), e.g. a fat oxidation defect such as medium-chain acyl-CoA dehydrogenase deficiency (MCADD)
4. In a subacute way, after a period of normal development, with **regression, neurological symptoms, organomegaly and coarse facies,** e.g. mucopolysaccharide disease or other lysosomal storage disorder or with **hepatosplenomegaly/ splenomegaly,** with or without accompanying biochemical upset such as hypoglycaemia, e.g. glycogen storage disease
5. As a **dysmorphic syndrome**

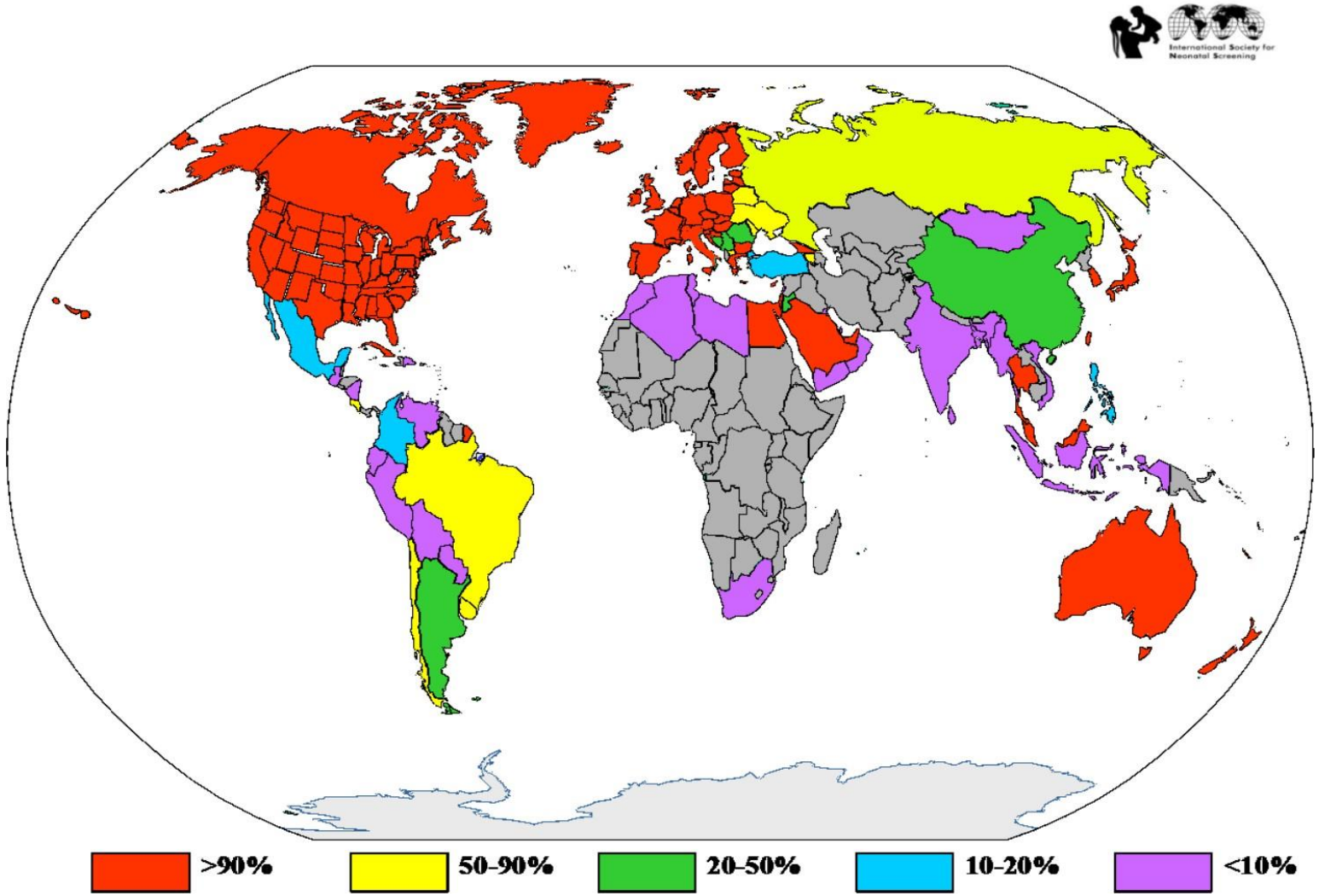
Newborn screening

All babies born in Poland have a screening test to detect some diseases, including metabolic diseases, especially those that can be treated:

1. Hypothyroidism
2. Phenylketonuria (PKU)
3. Cystic fibrosis (CF)
4. other metabolic disorders such as organic acidemias, a fat oxidation defect, aminoacidopathies - MSUD, homocystinuria, citrulinemia, tyrosinemia – by tandem mass spectrometry

The tests are done on a spot of blood from a heel-prick collected onto a filter paper.

Number of children included into screening test



Clinical indicators of IEM

1. Symptoms appear when the child diet is changed (e.g. galactosemia, fructosemia)
2. Deterioration after a period without alarming symptoms
3. Parental consanguinity (increased risk of autosomal recessive diseases)
4. Family history of neonatal deaths
5. Rapidly progressive encephalopathy and seizures of unexplained cause
6. Recurrent vomiting
7. Unusual odour of urine

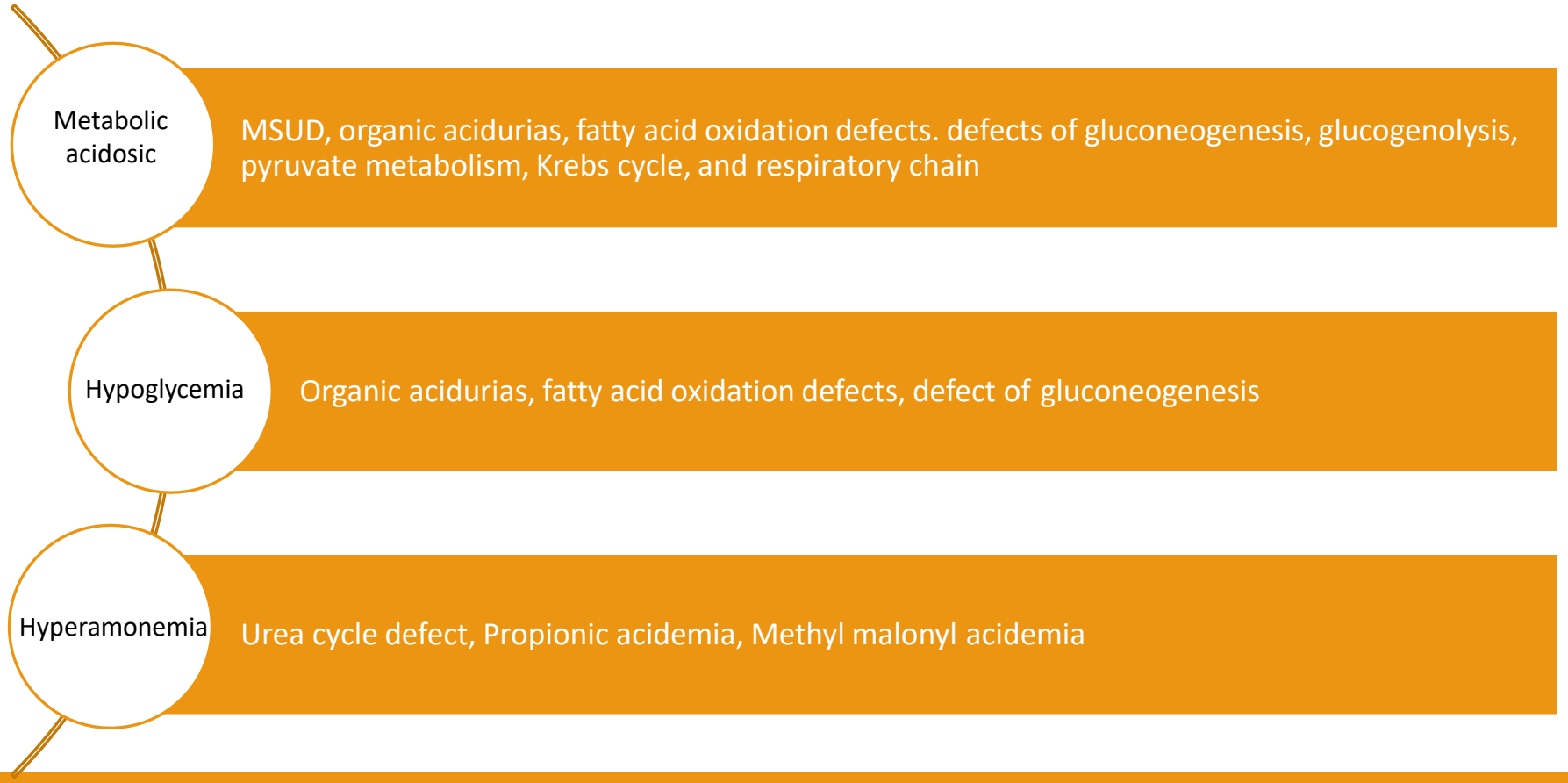
Symptoms of IEM

IEM must be considered in the differential diagnosis of:

- Critically ill newborns
- Neurodegeneration, developmental delay or regression
- Coarse facies, dysmorphic features
- Acute liver disease
- Cardiomyopathy
- Organomegaly
- Corneal opacity, cataract or dislocation of lens
- Hyperammonemia, unexplained acidosis, hypoglycemia

Clinical finding	Disorder
Coarse facies	Lysosomal disordes
Cataract	Galactosemia
Cherry red spot	Lipidosis
Hepatosplenomegaly	Urea cycle defects
Abnormal kinky hair	Menkes disease
Decreased pigmantation	Phenyloketonuria
Urine odour	**Disorder**
Maple syrop	Maple syrop urine disease
Boiled cabbage	Hypermethioninemia
Mousey, musty	Phenyloketonurmia
Boiled cabbage, rancid butter	Tyrosinemia
Rotting fish	Trimethylaminuria
Sweaty feer	Isovaleric acidemia

Neurological detoriation with…

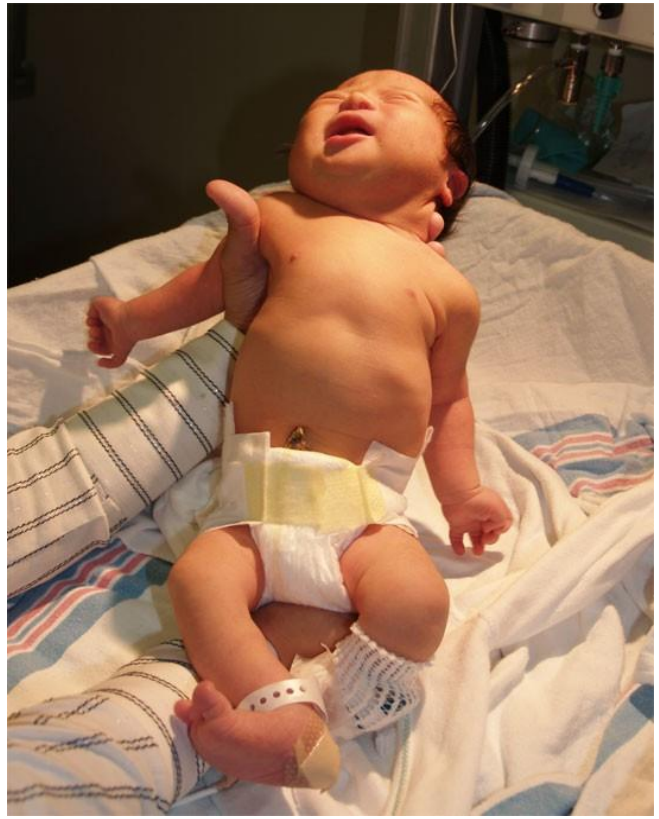


Hypotonia

- Mitochondrial respiratory chain defects

  Peroxisomal disorders

- Non-ketotic hyperglycinemia
- Sulfite oxidase/molybdenum co-factor defect
- Other…



Seizures

- Pyridoxine – responsive seizures, 1st day Pyridoxal phosphate responsive seizures 1t day Folinic-acid responsive seizures 1st day
- Sulfite oxidase/molybdenum co-factor defect Peroxisomal disorders
- Disorders of creatine biosynthesis & transport

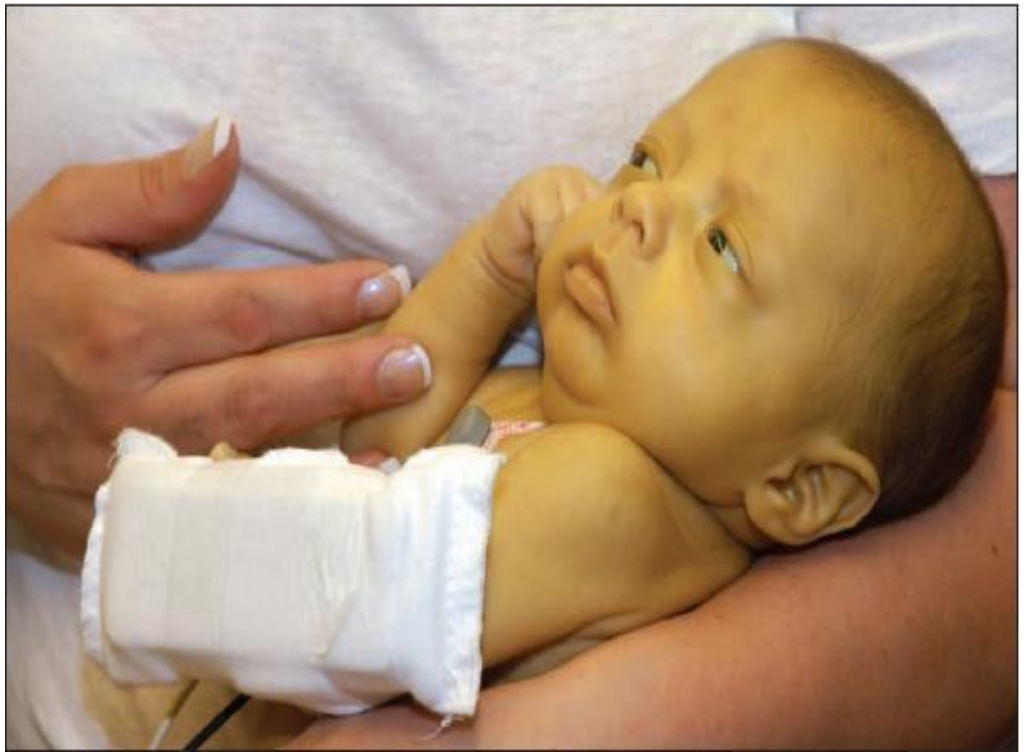
Liver dysfunction

Liver failure

- Galactosemia
- Hereditary fructose intolerance
  Tyrosinemia type I
- Fatty acid oxydation defects Mitochondrial respiratory chain defects

Cholestatic jaundice with failure to thrive:

- Alpha-1-antitrypsin deficiency
- Niemann-Pick disease type C
- Peroxisomal disorders



IME diagnosis

- Laboratory studies including metabolic studies e.g. GC/MS and TANDEM
- Lumbar puncture
- Genetic studies
- Other

IEM – diagnosis
Laboratory studies

- Complete blood count
- Arterial blood gases and electrolytes- acidosis/ alkalosis
- Blood glucose
- Plasma ammonia
- Arterial blood lactate
- Liver function tests
- Urine ketones if acidosis or hypoglycemia present
- Urine reducing substances
- Serum uric acid (low in molybdenum cofactor deficiency).
- Plasma amino acids

Collecting samples

Should be collected before specific treatment is started or feeds are stopped

Samples for blood ammonia and lactate should be transported in ice and immediately tested.

Lactate sample should be arterial or central line and should be collected afer 2 hours fasting in a preheparinized syringe.

Collecting samples

Samples have to be obtained in infant with suspected IEM especially when diagnosis is uncertain and death seems inevitable

Blood: 5-10 ml; frozen at -200C; both heparinized (for chromosomal studies) and EDTA (for DNA studies)

Urine: frozen at –20oC

CSF: store at –20oC

Skin biopsy: including dermis in culture medium or saline with glucose. Store at 4-80C. Do not freeze.

Liver, muscle, kidney and heart biopsy: as indicated.

Clinical photograph (in cases with dysmorphism)

Infantogram (in cases with skeletal abnormalities)

Treatment

Aims of treatment

1. Decreasing substrate availability e.g. by proper diet
2. To provide adequate calories
3. To enhance the excretion of toxic metabolites
4. To institute co-factor therapy for specific diseases and also empirically if diagnosis is not established
5. Supportive care - treatment of seizures (avoid sodium valproate – may increase ammonia levels), maintain normoglycemia and normothermia, fluid, electrolyte & acid-base balance, treatment of infection, mechanical ventilation if required

Early intervention is the most important -> therefore, early diagnosis is pivotal

Long term therapy

- Dietary treatment: this is the mainstay of treatment in some diseases eg.g phenylketonuria, maple syrup urine disease, homocystinuria, galactosemia, and glycogen storage disease type I & III.

Some disorders like urea cycle disorders and organic acidurias require dietary modification (protein restriction) in addition to other modalities.

- Enzyme replacement therapy (ERT): ERT is now commercially available for some lysosomal storage disorders.

However, these disorders do not manifest in the newborn period, except Pompe's disease (glycogen storage disorder Type II) which may present in the newborn period and for which ERT is now available.

Cofactor replacement therapy

The catalytic properties of many enzymes depend on the participation of non-protein cofactors, such as vitamins or microelements

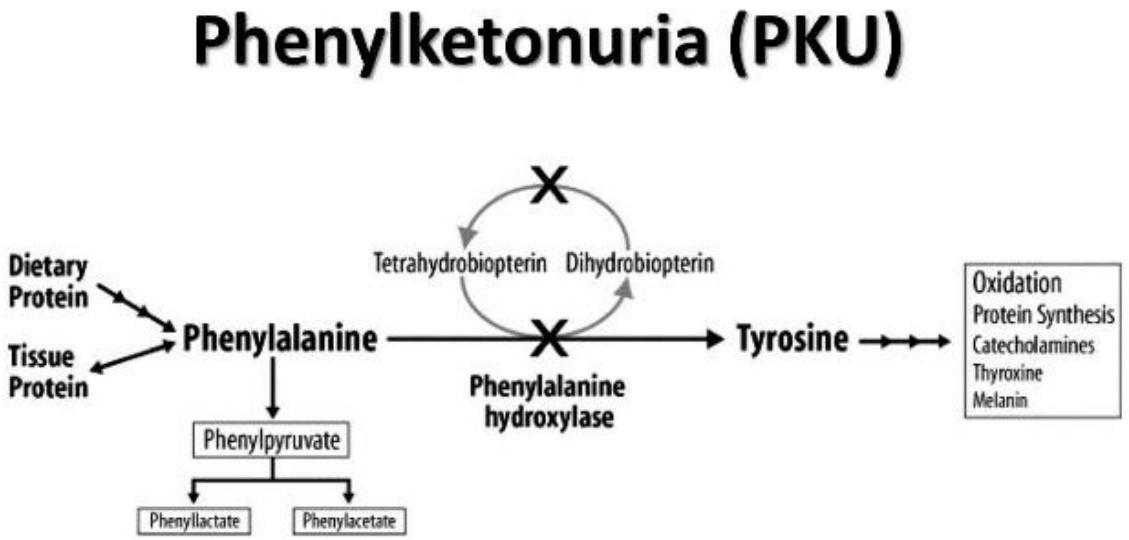
Disorder	Cofactor
Maple syrup urine disease	Thiamine
Homocystinuria	Pyridoxine, folic acid, vitamin B12
Biotinidase deficiency	Biotin
Hartnup disease	Nicotinic acid
Propionic acidemia	Biotin
Methylmalonic acidemia	Hydroxycobalamin
Respiratory chain disorders	Riboflavin
Glutaric acidemia	Riboflavin

Prevention

- Most of the IEM are single gene defects, inherited in an autosomal recessive manner, with a 25% recurrence risk in offspring when two parents are carriers of the mutation.
- When the diagnosis is known and confirmed, prenatal diagnosis can be offered wherever available for the subsequent pregnancies.
- The samples required are Chorionic Villous tissue or Amniotic fluid
- Substrate or metabolite detection: Phenylketonuria, Peroxisomal defects
- Enzyme assay: lysosomal storage disorders like Niemann-Pick disease, Gaucher disease
- DNA based (molecular) diagnosis: Detection of mutation in proband/carrier parents

Phenylketonuria

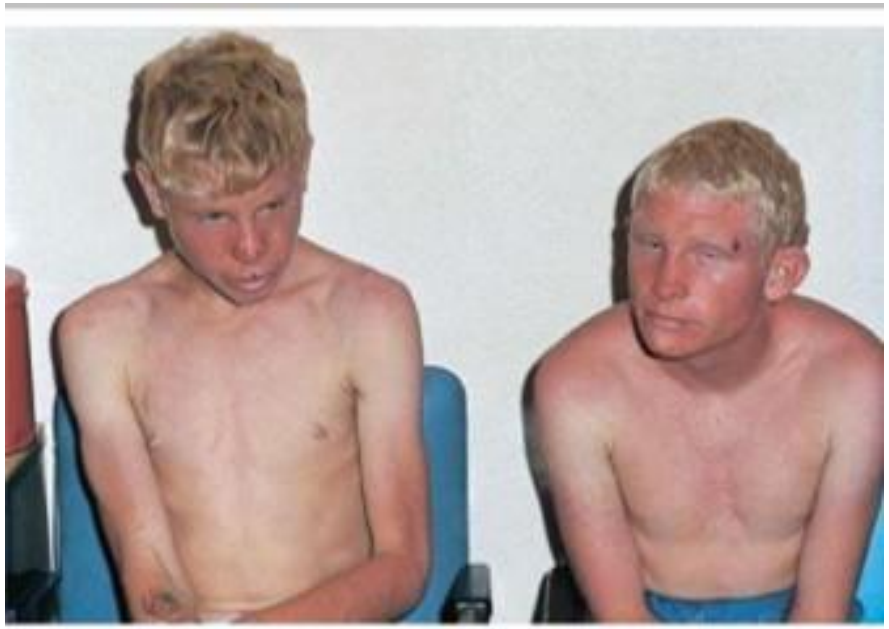
- It occurs in 1 in 7 000 live births. The most common metabolic disease of aminoacids.
- Inherited in autosomal recessive way.
- Deficiency of the enzyme **phenylalanine hydroxylase** (classical PKU) or in the synthesis or recycling of the biopterin cofactor for this enzyme -> disturbed metabolism of phenyloalanine to tyrosine -> accumulation of phenyloalanine

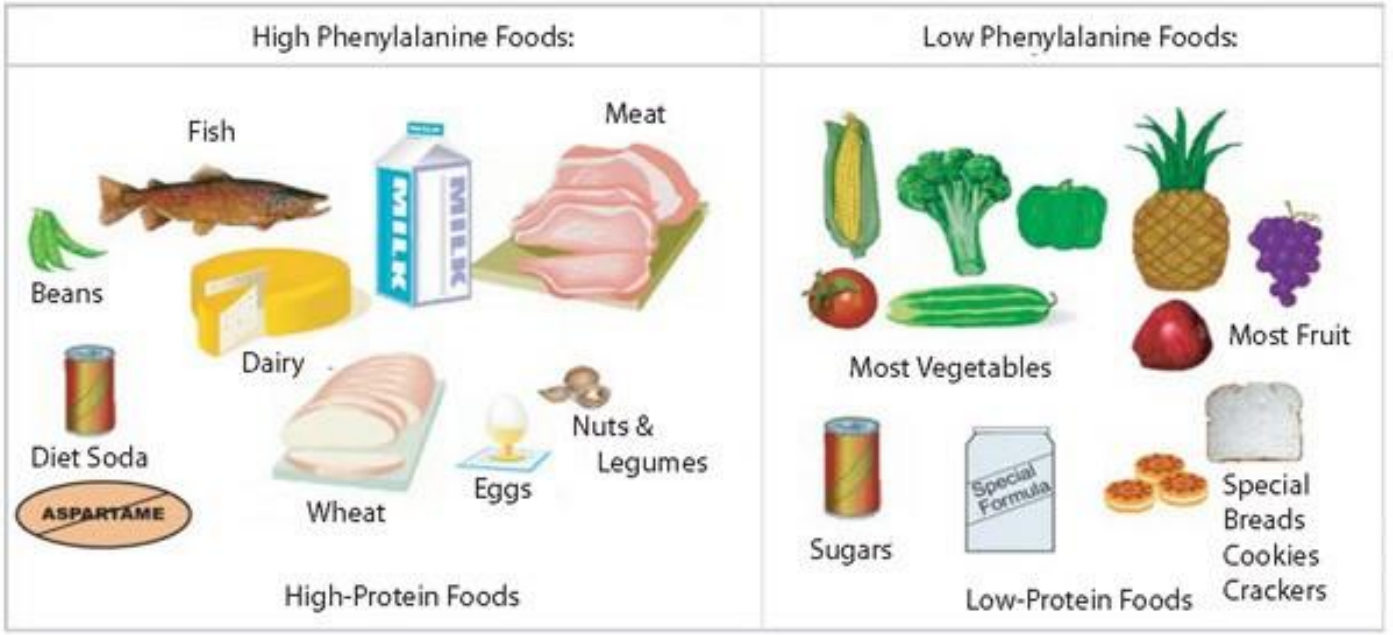


Phenylketonuria

- It may be treated with proper diet (low phenyloalanine products) – prevention of symptoms
- If untreated, irreversable symptoms will develop in infancy:
  - eczema
  - vomits
  - developmental delay
  - epilepsy
  - microcephaly
- Many affected children are fair-haired and blue-eyed
- The blood plasma phenylalanine should be monitored regularly.
- The current recommendation is to maintain the diet throughout life.
- In adults higher levels of phenyloalanine may not cause the symptoms, but maintaining the diet is particularly **important during pregnancy**, when high maternal phenylalanine levels may damage the fetus.
- Cofactor defects, which have a much poorer prognosis than classical PKU, are treated with a diet low in phenylalanine and neurotransmitter precursors.

Phenyloketonuria





Tyrosinemia

- Tyrosinemia (type 1) is a rare autosomal recessive disorder caused by a deficiency of fumarylacetoacetase
- Accumulation of toxic metabolites results in damage to the liver (leading to liver failure) and renal tubules (resulting in Fanconi syndrome)
- Untreated is fatal
- Treatment – drug Nitisinone (NTBC), which inhibits an enzyme required in the catabolism of tyrosine, with a diet low in tyrosine and phenylalanine.

Galactosemia

This rare, recessively inherited disorder results from deficiency of the enzyme galactose-1-phosphate uridyltransferase, which is essential for galactose metabolism.

When lactose – disaccharide build from glucose and galactose, found in milk are introduced, it causes:

- problem with feeding
- vomits
- jaundice
- hepatomegaly and hepatic failure

Untreated galactosemia lead to: chronic liver disease, cataracts and developmental delay.

Management is with a lactose and galactose - free diet for life.

Even if treated early, there are usually moderate learning difficulties (adult IQ 60–80).

Galactosemia is a contraindication to the breast feeding

Refferences and sources

Nelson textbook of Pediatrics, 19th Edition Illutrated textbook of Pediatrics, 4th Edition

Nelson textbook of Pediatrics, 19th Edition, Kliegman, Behrman, Schor, Stanton, St. Geme

www.mz.gov.pl/___data/assets/pdf_file/0004/27733/aktualny-projekt-programu-przesiew-w-PDF-na-strone.pdf