Disorders of cobalamin metabolism

Vitamine B12

- **Cobalamin (vitamine B12)** is a water-soluble vitamin
- It is chemically formed by a *coryne ring* in the center with a cobalt ion
- Cobalamin is synthesized exclusively by microorganisms and must be taken into the diet
  - in the form of **methylcobalamin** is a cofactor of methionine synthase (cytoplasmic enzyme)
  - in the form of **deoxyadenosylcobalamin** is a cofactor of methylmalonyl-CoA mutase (a mitochondrial enzyme involved in the metabolism of succinyl-CoA, valine, threonine, fatty acids with an odd number of carbons

Disorders of cobalamin resorption and transport

- In saliva, cobalamin binds to the R binder (haptocorrin) glycoprotein, which is digested in the gut
- An intrinsic factor (IF) is produced in the stomach, which binds cobalamin after haptocorrin digestion.
- In the terminal ileum, the cobalamin-IF complex enters the enterocyte
- In the blood, cobalamin is bound to transcobalamin, in the portal vein it is slowly released from the binding into the liver parenchyma, where it is stored

Internal factor deficit

- AR inheritance
- The main manifestation is megaloblastic anaemia and then a number of non-specific symptoms
- Start mostly between the first and fifth year of life
- IF is immunologically detectable
- Disorder of IF function is due to decreased affinity for cobalamin, enterocyte receptor or its increased susceptibility to proteolysis
- Treatment with intramuscular hydroxycobalamin 1 mg daily

Cobalamin enterocyte transport disorder (Imerslund-Gräsbeck syndrome)

- AR inheritance
- Megaloblastic anaemia, proteinuria, neurological abnormalities (spasticity, brain atrophy)
- Start mostly between the first and fifth year of life
- The receptor for the IF-cobalamin complex has two components: cubilin, amnionless located in the endocyte apparatus of the enterocyte, mutations can be found in the genes for each of them
- Hydroxycobalamin treatment

Deficit of haptocorrin

- Few described cases, without anaemia
- The role of haptocorrin is not clear, but it could be to remove toxic cobalamin analogues or to protect methylcobalamin from photolysis

Transcobalamin deficiency

- AR inheritance
- Manifestations in the first months of life in the form of paleness, failure to thrive, muscle weakness
- Megaloblastic anaemia and neurological manifestations, immune disorders manifest later
- Treatment by oral or systemic administration of hydroxycobalamin or cyanocobalamin in combination with folate

Disorders of intracellular use of cobalamin

- Based on the biochemical phenotype and genetic analysis, a number of disorders of intracellular cobalamin metabolism, identified as mutated cobalamins (A-H), have been identified.

Combined adenosylcobalamin and methylcobalamin deficiency

- A typical biochemical finding of combined methylmalonic aciduria and homocystinuria
- Hydroxycobalamin treatment

- **Cobalamin deficiency F**
  - Probably a disorder in the transport of the IF-cobalamin complex across the lysosomal membrane of the enterocyte
  - Cobalamin cannot be metabolised to either **adenosylcobalamin** or **methylcobalamin**

- **Cobalamin deficiency C**
  - AR inheritance
  - The most common inherited disorder of cobalamin metabolism
  - Early start
  - Multisystem diseases (kidneys, liver, myocardium)

- **Cobalamin deficiency D**
  - Disorder of the synthesis of **adenosylcobalamin**, **methylcobalamin** or both
  - X-linked inheritance

Adenosylcobalamin deficiency

- Cobalamin A deficiency (Co2-to-Co1- reduction disorder) and cobalamin B (adenosyltransferase deficiency)
- acidosis, methylmalonic aciduria
- Often an acidotic crisis in the first year of life
- Acidosis causes hypotension, lethargy, vomiting, anaemia, leukopenia, thrombocytopenia
- Treatment with protein restriction and hydroxycobalamin

Methylcobalamin deficiency

- **Cobalamin E deficiency** (methionine synthase reductase deficiency) and cobalamin G (methionine apoenzyme activity deficiency)
- insynthase
- **Megaloblastic anaemia**, neurological impairment
- Hyperhomocysteinemia and homocystinuria develop
- Treatment with hydroxycobalamin or methylcobalamin

Pernicious anaemia

Funicular degeneration

- it is a degenerative disease very often associated with pernicious anaemia affecting the posterior and especially the lateral spinal cord
- its cause lies in vitamin B12 deficiency, which cannot be absorbed in pernicious anaemia as autoimmunity is directed against the parietal cells of the gastric mucosa of the antrum and the body, which secrete an intrinsic factor important for protection against vitamin digestion. If the internal factor is missing, the vitamin is not protected and therefore its absorption in the terminal ileum does not occur.
- lack of vitamin B12 leads to funicular myelosis by a relatively complex mechanism. In the absence of vitamin B12, among other things, there is no feedback reaction in the conversion of homocysteine to methionine. As a result, the body does not have enough methionine to form S-adenosyl-methionine, which transfers methyl residues to ethanolamine and thus forms choline, which in turn is essential for lecithin production. Finally, lecithin is one of the important components of sphingomyelin, which is part of the construction of myelin sheaths. As myelin changes over the course of a lifetime, it decreases overall because it fails to appear effectively for these reasons. Therefore, a number of neurological symptoms occur in funicular myelosis, such as central paraparesis of the lower limbs.
- treatment is simple. When the cause is identified, vitamin B12 is substituted

Sources and literature

- FERNANDES, John. *Diagnostika a léčba dědičných metabolických poruch.* 1. vydání. Praha : Triton, 2008. s. 576-580. ISBN 978-80-7387-096-6.

- MURRAY, Robert K., Daryl K. GRANNER a Peter A. MAYES, et al. *Harperova biochemie.* 4. vydání. Jinočany : H & H, 2002. 872 s. ISBN 80-7319-013-3.