Hereditary metabolic disorders of complex molecules

Hereditary metabolic disorders of complex molecules [1] [2] are genetically determined disorders of the synthesis, transport or catabolism of macromolecules. They affect cellular organelles in which their synthesis or degradation occurs, such as lysosomes and peroxisomes, or transport proteins, and then manifest as disorders of cellular transport and processing. These are often sparing diseases. Macromolecules whose metabolism may be affected include[1] sphingolipids, glycosaminoglycans (mucopolysaccharides), oligosaccharides, myelin, very long-chain fatty acids, etherphospholipids (plasmalogens), phytanate, and others.

Pathogenesis

A disorder in the catabolism of a complex molecule leads to its **accumulation**, typically **in a cell organelle**, in which the enzyme responsible for the disease would otherwise be localized, which is manifested mainly by a **membrane abnormality**.

For example, a deficiency of the acid β-glucosidase enzyme in Gaucher's disease as a result of a mutation in the GBA gene leads to the accumulation of glucosylceramide, which then manifests itself as visceral, hematological and bone involvement.[1]

A malfunction in the synthesis of a complex molecule leads to its deficiency, and thus to the absence of its function.

Symptoms

The disease has a slow course, the prodromal phase lasts months, years to decades[2]. The clinical manifestations of these diseases are significantly different from the symptoms of inherited metabolic disorders of small molecules; they are permanent, progressive, independent of diet or concurrent diseases (fever and related catabolic states have no effect). They often affect multiple organs at the same time, symptoms include, for example, psychomotor retardation, facial dysmorphia, organomegaly, disorders of the skeleton, cardiovascular system, vision and hearing.

For some similar symptoms, the differential diagnosis includes, for example, hemato-oncological or other cancer diseases, chromosome aberrations, or neurodegenerative diseases of unclear etiology[2].

Therapy

As with other inherited metabolic disorders, there is currently no permanent causal treatment (gene therapy), however, for some, depending on their nature, there are approaches that at least temporarily remove the cause, or at least slow the progression or mitigate the consequences of the disease[1]:

- **Enzyme replacement therapy'** (*Enzyme replacement therapy*, ERT) - e.g. in Gaucher's disease type I, Fabry's disease or Pompe's disease
- **Restriction of substrate intake** (*substrate reduction therapy*, SRT) - e.g. in Gaucher disease
- **Organ transplant** - e.g. allogeneic bone marrow transplant in some cases in Krabbe's disease

In most cases, however, the treatment is only symptomatic (eg treatment of convulsions in *GM2-gangliosidosis*[1]).
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1. – SAUDUBRAY, Jean-Marie – BERGHE, Georges van den. *Diagnosis and treatment of hereditary metabolic disorders.* 4. edition. Triton, 2008. 607 pp. ISBN 978-80-7387-096-6.
2. KOŽICH, Victor – ZEMAN, George. Hereditary metabolic disorders in pediatrics. *Postgraduate Medicine* [online]. 2010, y. 12, vol. 7, p. 793–799, Available from <https://zdravi.euro.cz/>. ISSN 1214-7664.