Investigation methods in IMD

Investigative methods inherited metabolic disorders are a set of biochemical, genetic, physical examination, anamnestic, and other procedures to determine a specific inherited enzyme disorder, transport or other protein deficiency.

Meaning of diagnosis

The diagnosis has a particular impact on the choice of treatment, which is fundamentally different from the diseases that fall under the differential diagnosis of some inherited metabolic disorders (oncological diseases, neurodegenerative diseases, etc.). However, it is also important when there is no treatment for the disease other than symptomatic treatment, which can be carried out without knowledge of the diagnosis. In addition to adjusting the treatment, its importance also lies in improving the patient's psychological state after the causes of the disease have been explained and in alleviating anxiety and uncertainty, as well as in preventing symptoms that have not yet manifested, unnecessary further examinations and determining the risk to the proband's relative.

Diagnosis of IMD

- **Diagnosis of a specific patient**

🔎 *For more information see Diagnosis.*

  Based on the presenting problems, history and physical examination, investigations are indicated to confirm or refute the initial **hypothesis**. In the first case a diagnosis is made, in the second case a new hypothesis is expressed and the process is repeated.

- **Selective screening**

  In a selected group of people in whom some manifestations of inherited metabolic disorders are manifested, laboratory tests for some diseases are performed.

- **Population-wide screening**

  It is an active search for diseases in the whole population, allowing presymptomatic diagnosis.

🔎 *For more information see Newborn Screening.*

  Laboratory tests for markers of high-incidence disease are performed in all newborns. The benefit (high incidence, severe disease) must outweigh the cost (financial cost, burden on patient and family in case of false positive result).

Diagnostic levels

An inherited metabolic disorder can be diagnosed in a patient at several levels, which are derived from the pathogenesis of IMD: the cause is a gene mutation that manifests itself as an enzyme deficiency; this causes substrate accumulation and the absence of the product of the metabolic pathway, which then manifests itself as tissue, organ or general damage to the organism.

Tests used

Process: organism level → metabolite level → enzyme level → nucleic acid level.

- **genetic level** (DNA, mRNA): determination of a specific mutation by DNA diagnostic methods - polymerase chain reaction with primers specific for the mutation; sequencing (common methods sequencing, next generation sequencing)
- **Enzymatic level:** determination of the presence or better activity of a given enzyme - biochemical determination of enzyme activity: measured over time by photometry, radiometry, fluorimetry or mass spectrometry, loss of substrate or cofactor or formation of the product of the reaction being determined or coupled. (Note: ELISA does not measure activity, but enzyme concentration.)
- **Metabolite level:** determination of substrate accumulation and missing product, sometimes indirectly (e.g. $NADH + H^+$ accumulation in oxidative phosphorylation disorders by lactate and 3-hydroxybutyrate determination) - biochemically, immunochemically, by chemical analysis methods:
  - for ***small molecules*** high-performance liquid chromatography, gas chromatography, tandem mass spectrophotometry widely used in screening
  - for ***complex molecules*** electrophoresis, immunochemistry
- **Organism level:** physical examination, medical history, imaging (e.g. MRI in diseases of complex molecules mimicking neurodegenerative diseases example!) - Indispensable. The physician and his/her opportunity and ability to indicate selective screening plays a major role.

The available laboratory tests have different sensitivities determined by the nature of the laboratory method and the analyte. The output is a complex picture of results that are difficult to interpret and require specialisation.

Clues to suspect IMD

A physician will be given the reason to perform laboratory tests at the genetic, enzymatic and metabolite levels, especially if:

- hereditary disorder is suggested by **family history** - consanguinity, similar manifestations in relatives, unexplained deaths in the family,
- a disease considered common **does not respond** to usual treatment,
- the disease is **multisystemic**,
- the disease is influenced by factors typical of IMD - catabolic states (fever, muscle strain), fasting, protein or carbohydrate intake,
- unexplained abnormalities of routine laboratory tests are found,
- manifested manifestations of the disease are rare and typical of IMD - odour, urine colour, specific dysmorphic symptoms (gargoylism) etc.

The manifestations differ between Small molecule metabolic disorders and IMD of complex molecules.

Links

Related articles

- Inherited metabolic disorders

External Links

- KOŽICH, Viktor: Diagnostika a terapie monogenně podmíněných poruch metabolismu. [přednáška z patobiochemie], 2.11.2010