Primary immunodeficiencies

Genetic diseases arise as a result of mutations. From the point of view of immunology. The consequences of these mutations are variously severe **innate dysfunctions** of the immune system, referred to as **primary immunodeficiency**.

Immunodeficiency is a condition in which an individual's immune system is not 100% functional due to a cause and this individual is more susceptible to infectious diseases. Thus, unlike secondary immunodeficiencies, in which the cause of the disease is acquired only during the life of the individual, in primary deficiencies, **the cause is present from the very beginning** and depends only on the nature of the disease, when and how it manifests.

Immunodeficiency in general

- a condition in which an individual's immune system is not 100% functional due to a certain **cause**and that individual is more susceptible to **infectious diseases**
- is the result of **dysfunction of** some of the many components of the immune system
- genetic diseases arise as a **consequence of mutations**
- from the point of view of **immunology**, such mutations are significant that cause disorders of protein synthesis, which in some way participate in the **function of the immune system**.
- the consequences of these mutations are **severely severe** - congenital dysfunctions of the immune system, referred to as **primary immunodeficiency**
- in contrast to **secondary immunodeficiencies**, in which the cause of the disease is acquired only during the life of the individual
- therefore, in **primary deficits,** the cause is present from the very beginning and depends only on the nature of the disease, when and how **it manifests**

Etiology and pathogenesis

More than 100 primary immunodeficiencies have been described to date. Advances in recent years in molecular genetics have helped to definitively locate the responsible gene and elucidate the mechanism of a number of immune system disorders.

Most of these immunodeficiencies exhibit a **recessive type of inheritance**; the dominant type of inheritance is known, but very rare. In some very rare types of primary immunodeficiencies, only a **sporadic incidence** has been reported without a familial incidence. There are also types with presumed multifactorial inheritance, which thus stand at the interface between primary and secondary immunodeficiencies. A relatively large number of responsible genes are located on the **X chromosome**. In practice, this means that boys are up to **twice as likely** to have primary immunodeficiencies as girls. However, even in carrier girls, some clinical manifestations of the respective immunodeficiency may manifest; as with other X-linked diseases, this depends on how the lyonization process took place in a particular girl. Other genes responsible for the development of primary immunodeficiencies are located on autosomes.

For some reasons, some complex syndromes cannot be neglected, the manifestations of which include certain dysfunctions of the immune system. Due to the cause, there are some microdeletion syndromes or chromosomal instability syndromes.

Primary immunodeficiencies reduce the functionality of the immune system, and thus the body's defenses, which make it more susceptible to various pathogens. As already mentioned, the cause of these deficiencies is a mutation in human genetic information. Substituting into the central dogma of molecular genetics, we then obtain the following scheme (simplified):

Mutated DNA → mRNA with non-standard sequence → dysfunctional (possibly none) protein → impaired function

Primary immunodeficiencies are then classified according to impaired function, which may be part of the system of specific and non-specific immunity. We distinguish:

- Antibody deficits.
- Cell deficiencies.
- Combined deficits.
- Disorders of the complement system.
- Disorders apoptosis.
- Disorders phagocytosis.
- Deficiency is part of other typical syndromes.
- Other (eg disorders of cytokines and cytokine receptors).

To accurately understand the manifestation of a given mutation, the **complexity** of the immune system needs to be considered. A defect in one part of the immune system can manifest itself in a simultaneous defect in another part, the synthesis of which is not directly disturbed by the mutation. For example, we do not find T-lymphocytes in some combined immunodeficiencies. B-lymphocytes are formed in normal amounts, but without the possibility of interaction with T-lymphocytes, their function is also impaired.

Diagnostics

Because primary immunodeficiencies are genetically determined, their **cause is present from birth**. Manifestations of some immunodeficiencies can be recognized in very early childhood. The onset of symptoms is different for different types of immunodeficiencies - severe combined disorders manifest very early and drastically, while some complement and phagocytosis disorders may remain undetected until adulthood. In antibody deficits, the onset of manifestations is delayed due to a period when the newborn is still protected by **maternal antibodies**. Complex syndromes (associated with a disorder of the immune system) are often diagnosed on the basis of their other manifestations, which do not concern the immune system.

If the family already has the relevant immunodeficiency, the diagnosis is usually known and the newborn can be **tested for a specific disease** (if the prenatal diagnosis has not been performed for some reason or has not produced satisfactory results). In cases of new mutations, we cannot rely on family history, and therefore a **comprehensive** examination is necessary.

They generally serve as stimuli for **frequent and recurrent infections, children often do not thrive** and are **smaller** than their healthy peers. Another symptom is a recurrent **complicated course of infectious diseases** that respond relatively poorly to standard therapy.

Assay methods are diverse, including **differential blood counts**, serum concentrations of immunoglobulins or complement components, or immunocompetent cell functional assays. Microbiological examinations are also beneficial, where the identification of a specific microorganism can be an important guide for determining the final diagnosis. Great possibilities for the diagnosis of primary immunodeficiencies are offered by **DNA diagnostics**, where we can use hybridization probes to unambiguously confirm any of the known mutations and definitively establish the diagnosis. For unknown mutations, it is also possible to determine the sequence of certain genes.

Early and correct diagnosis of immunodeficiencies is important for the timely initiation of treatment and for the correct approach to vaccination of the affected person. For a person with immunodeficiency, **the administration of a vaccine** can be dangerous, especially with a **live vaccine**. Therefore, the administration of all live vaccines in people with congenital immunodeficiencies is **contraindicated**. In our country, it is mainly a **BCG vaccine** against tuberculosis, which is given shortly after birth (usually on the 3rd or 5th day). Because of this, it is the reaction to this vaccine that may indicate immunodeficiency. In children from families where one of the primary immunodeficiencies can be expected due to family history, it is advisable to wait for the appropriate diagnostic tests with the BCG vaccine.

Other live vaccines commonly used in the Czech Republic are vaccines against measles, rubella and mumps.

Contraindications to other vaccines depend on the type of primary immunodeficiency. For some types of immunodeficiency, on the other hand, it is appropriate to supplement the basics with some above-standard vaccinations.

Genetic counselling

From the point of view of genetic counselling and prenatal diagnostics, the following facts are interesting:

- For many primary immunodeficiencies, we know the exact gene, its location and its sequence. We can accurately identify the mutation and confirm the diagnosis using direct DNA diagnostic methods.
- Thanks to the known type of inheritance, we can use family history to estimate potential risks using genealogy methods. We can also use methods of indirect DNA diagnostics (RFLP) to refine the estimate.
- In autosomal recessively inherited primary immunodeficiencies, an increased risk should be taken for related marriages and for marriages in population isolates.
- In X-linked primary immunodeficiencies, different incidences should be expected in boys and girls. Determining the sex of the fetus can thus be of great importance in answering the question of whether the newborn will suffer from the relevant immunodeficiency.
- Cordocentesis is a very useful method for prenatal diagnosis of primary immunodeficiencies because from the obtained umbilical cord blood we can not only isolate DNA for DNA diagnostics (for this purpose, other invasive methods are usually chosen that can be used at lower risk and earlier - Amniocentesis (AMC, CVS), but we also obtain cellular elements of the fetus that can be examined phenotype.
- Even in the diagnosis of primary immunodeficiencies, the future lies in the routine use of DNA chips, which will make it possible to test (not only) a number of different types of immunodeficiencies at once.

Therapy options

There is **no real causal therapy** for genetic diseases such as primary immunodeficiency. This would involve targeted repair of the mutated gene (primary DNA sequence). Advances in gene therapy give hope for the future; however, current gene therapy methods most commonly use retroviruses carriers that insert the sequence into the genome more or less randomly.

X-linked SCID (severe combined immunodeficiency) was the subject of gene therapy as the first human disease. However, some patients treated in this way developed subsequent leukemia, presumably due to disruption of tumor suppressor genes by retroviral carriers. Due to these complications, it is not yet possible to put this therapy into practice. Experimental gene therapy treatment for **ADA deficiency** (adenosine deaminase) has also met with some success.

Thus, **bone marrow stem cell transplantation** remains the most common treatment for severe primary deficiencies. This method is particularly challenging to secure a suitable donor with the greatest possible agreement in HLA antigens. Family members, especially of the same sex, are preferred as donors. **Finding an unrelated donor** is very **challenging** and, moreover, satisfactory agreement in minor HLA antigens cannot be expected. As this is the transplantation of immunoactive tissue, the risk of a **GVH reaction** (GHVR = graft versus host reaction) must be taken into account.

Substitution treatment includes intravenous immunoglobulin administration; there are also therapies based on **defective enzyme substitution**, as is the case with ADA deficiency.

A suitable part of the therapy is the **preventive administration of antibiotics** or even antiviral or antifungal drugs. Depending on the type of immunodeficiency, some **above-standard vaccinations** may be considered. If the patient is threatened with autoimmune manifestations of the disease, it is time for **immunosuppressive therapy**.

Overview of primary immunodeficiencies

Antibody immunodeficiency

- Autosomal inherited agammaglobulinemia.
- Bruton's agammaglobulinemia.
- Selective IgA deficiency.
- Common variable immunodeficiency.
- IgM hyperimmunoglobulinemia syndrome.

Combined and cellular immunodeficiencies

- Severe combined immunodeficiency.
- Reticular dysgenesis.
- Omenn's syndrome.
- X-linked lymphoproliferative syndrome.
- Wiskott-Aldrich syndrome.

Immunodeficiency caused by phagocytosis disorders

- Chediak-Higashi syndrome.
- Chronic granulomatous disease.
- Shwachman-Diamond Syndrome.
- Severe congenital neutropenia (Kostmann's syndrome).
- Glucose-6-phosphate dehydrogenase deficiency [1].
- Myeloperoxidase Defect [2].

Immunodeficiency caused by complement disorders

- Hereditary angioedema.
- Mannose-binding lectin deficiency.

Immunodeficiency caused by apoptosis disorders

- Autoimmune lymphoproliferative syndrome.

Immunodeficiency as part of chromosomal instability syndromes

- Ataxia telangiectasia.
- Bloom's syndrome.

Immunodeficiency as a part of microdeletion syndromes

- DiGeorge's syndrome.

Links

Related Articles

- Complement component deficiency
- Neutropenia in children
- Primary immunodeficiency / case report

Reference

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