Primary immunodeficiency

Genetically determined diseases arise as a result of mutations. From the point of view of immunology, those mutations that cause disturbances in the synthesis of proteins, participating in a certain way in the function of the immune system, are significant. The consequences of these mutations are variously serious "congenital dysfunctions" of the immune system, referred to as "primary immunodeficiency".

Immunodeficiency is a condition where, due to a certain cause, the individual's immune system is not 100% functional and this individual is more susceptible to infectious diseases. In contrast to secondary immunodeficiencies, in which the cause of the disease is only acquired during the individual's life, 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 itself.

Immunodeficiency in general

- a condition where, due to a certain *cause*, the individual's immune system is not 100% functional and this individual is more susceptible to *infectious diseases*
- is the result of a '*malfunction* of one of the many components of the immune system
- genetically determined diseases arise as a '*result of mutations*
- from the point of view of ""immunology"" such mutations are significant, which cause disturbances in the synthesis of proteins, participating in a certain way in the ""function of the immune system""
- the consequences of these mutations are **variously 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 only acquired during the individual's life
- therefore, 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 itself"

Etiology and pathogenesis

Currently, more than 100 primary immunodeficiencies have already been described. Advances in molecular genetics in recent years have helped to definitively locate the responsible gene and shed light on the mechanism of a number of immune system disorders.

Diagnosis

Most of these immunodeficiencies show the **recessive type of inheritance'**; dominant type of inheritance is known but very rare. In some very rare types of primary immunodeficiencies, only **sporadic occurrence** has been recorded without a described familial occurrence. There are also types with presumed multifactorial heredity, which thus stand at the interface between primary and secondary immunodeficiencies. A relatively large number of responsible genes are located on **X chromosome**. In humans, this leads to the fact that boys are affected by primary immunodeficiencies twice as often as girls. However, some clinical manifestations of the relevant immunodeficiency may also manifest in girls - carriers; as with other X-linked diseases, this also depends on how the process of lyonization took place in the particular girl. Other genes responsible for the development of primary immunodeficiencies are located on autosomes.

Some complex syndromes, whose manifestations also include certain dysfunctions of the immune system, cannot be neglected. Due to the cause, it is some microdeletion syndromes or chromosomal instability syndromes.

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

Mutated DNA → mRNA with a non-standard sequence → dysfunctional (possibly no) protein → impaired function

According to the damaged function, which can be part of the system of specific and non-specific immunity, primary immunodeficiencies are then classified. We distinguish:

- Antibody deficits.
- Cellular deficiencies.
- Combined deficiencies.
- Disruptions of the complement system.
- Disorders apoptosis.

- Disorders phagocytosis.
- Deficiencies as part of other typical syndromes.
- Other (eg disorders of cytokines and cytokine receptors).

In order to accurately understand the manifestation of the relevant mutation, it is necessary to take into account the *complexity* of the immune system. A defect in one part of the immune system can be manifested by a simultaneous defect in another part, the synthesis of which is not directly disrupted by the mutation. For example, in some combined immunodeficiencies we do not find T-lymphocytes. B-lymphocytes are formed in normal amounts, but without the possibility of interaction with T-lymphocytes, their function is impaired. whereas primary immunodeficiencies are genetically conditioned, their **cause is present from birth''*. Manifestations of some immunodeficiencies can thus be recognized in very early childhood. The onset of symptoms is different for different types of immunodeficiency – severe combined disorders manifest very early and violently, while some disorders of complement and phagocytosis may remain undetected until adulthood. In antibody deficiencies, the onset of symptoms is delayed due to the 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 that do not concern the immune system.

If the relevant immunodeficiency is already present in the family, the diagnosis is usually known and tests for a specific disease can be performed on the newborn (if prenatal diagnosis was not performed for some reason or did not yield satisfactory results). In cases of new mutations, we cannot rely on family history, and therefore a **comprehensive examination** must be performed.

Generally, they serve as prompts for examination of **frequent and repeated infections,** *children often do not thrive*, and are **smaller in stature** than their healthy peers. Another symptom is the repeated *complicated course of infectious diseases*, which respond relatively poorly to standard therapy.

Examination methods are different, they include differential blood count examination, determination of the concentration of individual types of immunoglobulins or complement components in the serum, or functional tests of immunocompetent cells. Microbiological examinations are also beneficial, where the identification of a specific microorganism can be an important guide to establishing a final diagnosis. Great possibilities for the diagnosis of primary immunodeficiencies are offered by *DNA diagnostics*, when we can use hybridization probes to unequivocally confirm one of the known mutations and definitively establish the diagnosis. In the case of unknown mutations, the determination of the sequence of certain genes is also considered.

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 an immunodeficiency, it can be dangerous to give a vaccine, especially if it is a live vaccine. Therefore, the administration of all live vaccines in persons with congenital immunodeficiencies is **contraindicated*. In our case, it is mainly the** *BCG vaccine''* against tuberculosis, which is administered shortly after birth (usually on the 3rd-5th day). In view of this, it is precisely the reaction to this vaccine that may indicate immunodeficiency. For children from families where one of the primary immunodeficiencies can be expected due to family anamnesis, it is advisable to wait until the appropriate diagnostic tests are performed before taking the BCG vaccine. Other commonly used live vaccines in the Czech Republic are vaccines against measles, rubella and mumps. The contraindication of other vaccines depends on the type of primary immunodeficiency. For some types of immunodeficiency, on the other hand, it is advisable to supplement the basic with some above-standard vaccinations.

Genetic counseling

From the point of view of genetic counseling and prenatal diagnosis, the following facts are interesting:

- For a number of primary immunodeficiencies, we know the exact responsible gene, its location and sequence. We can thus accurately identify the mutation and confirm the diagnosis using direct DNA diagnostic methods.
- Thanks to the known type of inheritance, we can estimate possible risks using genealogical method based on family anamnesis. To refine the estimate, we can also use methods of indirect DNA diagnostics (RFLP).
- For autosomal recessively inherited primary immunodeficiencies, the increased risk for marriages between related individuals and for marriages in population isolates must be taken into account.
- For X-linked primary immunodeficiencies, it is necessary to take into account a different incidence in boys and girls. Determining the sex of the fetus can thus be of great importance for answering the question of whether the born child will suffer from the relevant immunodeficiency.
- Cordocentesis is a very beneficial method for prenatal diagnosis of primary immunodeficiencies, because we can not only isolate DNA from the obtained umbilical cord blood for DNA diagnosis (other invasive methods are usually chosen for this purpose, which can be used with less risk and earlier - AMC, CVS), but we also obtain cellular elements of the fetus that can be examined from the phenotype side.
- Even in the diagnosis of primary immunodeficiencies, the future lies in the routine use of DNA chips, thanks to which it will be possible to perform a test (not only) for a number of different types of immunodeficiencies at once.

Therapy Options

For genetic diseases such as primary immunodeficiency '*there is no real causal therapy*. This would consist in targeted repair of the mutated gene (primary DNA sequence). Advances in gene therapy give hope for the future; however, current methods of gene therapy most often use retroviral carriers that insert a sequence into the genome more or less randomly. In '*X-linked SCID* (severe combined immunodeficiency), gene therapy was performed as the first human disease. However, some patients treated in this way subsequently developed leukemia, probably due to disruption of tumor-suppressor genes by retroviral carriers. Due to these complications, it is not yet possible to introduce this therapy into routine practice. Experimental treatment with gene therapy for '*ADA deficiency* (adenosine deaminase) has also met with some success.

Bone marrow stem cell transplantation remains the most widespread treatment for severe primary deficiencies. This method is especially demanding because of **providing a suitable donor' *with the greatest possible match in HLA antigens. Family members, especially of the same sex, are preferred as donors. Finding an unrelated donor is very* challenging** and moreover, a satisfactory match in minor HLA antigens cannot be expected. Since it is a transplant of immunoactive tissue, the risk of a *GVH reaction* (GHVR = graft versus host reaction) must be taken into account.

'*Replacement therapy **includes** intravenous administration of immunoglobulins'**; there are also therapies based on** substitution of the defective enzyme*, as is the case with ADA deficiency.

An appropriate part of the therapy is **preventive administration of antibiotics**', possibly also a virostatic or antifungal agent. Depending on the type of immunodeficiency, you can consider some "above-standard vaccinations". If the patient is threatened by autoimmune manifestations of the disease, "immunosuppressive therapy" comes into play.

Overview of Primary Immunodeficiencies

Antibody immunodeficiency

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

Combined and cellular immunodeficiency

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

Immunodeficiency caused by phagocytosis disorders

- Chédiak-Higashi syndrome.
- Chronic granulomatous disease.
- Shwachman-Diamond syndrome.
- Severe congenital neutropenia (Kostmann 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 syndrome.

Immunodeficiency as part of microdeletion syndromes

- DiGeorge syndrome.

Links

Related Articles

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

References

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