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METHODS OF BIOLOGICAL EXAMINATION OF THE ORIGIN OF AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME AND ITS DETECTION

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Annotation: Autoimmune lymphoproliferative syndrome is a group of genetically determined diseases that occur due to hereditary or somatic mutations in the genes responsible for various stages of FAS-related apoptosis. Symptoms can be variable and most often include lymphadenopathy, splenomegaly, and various autoimmune lesions of the blood, liver, and thyroid systems. Diagnosis of autoimmune lymphoproliferative syndrome is based on the results of general and biochemical blood tests, lymph node biopsies, and genetic studies. There is currently no specific treatment for the disease, but a combination of immunosuppressive and cytotoxic therapy is used.

Key words: Autoimmune lymphoproliferative syndrome , lymphadenopathy, splenomegaly.

Autoimmune lymphoproliferative syndrome (ALS, ALPS, Canale-Smith syndrome) is a group of immunodeficiency conditions characterized by autoimmune cytopenias, lymphadenopathy, and splenomegaly. The first data on the disease began to arrive in 1968, after which a rapid study of pathology soon began. Initially, ALS was classified as primary immunodeficiency, but over time, forms of the syndrome caused by somatic mutations in the child and adolescent body were discovered.

Data on the occurrence of different researchers are quite different, to date, more than 500 cases of various forms of autoimmune lymphoproliferative syndrome have been described. Hereditary forms of the disease are transmitted by an autosomal dominant type, while spontaneous mutations also play a fairly large role in the development of congenital forms. Among the patients, both boys and girls are found with the same frequency.

Reasons

It was found that the cause of any type of ALS is a violation of FAS-mediated apoptosis of lymphocytes. During the formation of T-lymphocytes, those lines that can attack their own tissues are destroyed by activating CD-95 receptors (Fas-receptors) on the surface of their membrane. Activation of CD-95, which belongs to the group of tumor necrosis factor receptors, triggers a multi-stage reaction involving caspases, which ends in apoptosis of the cell.

In autoimmune lymphoproliferative syndrome, genetic mutations block this process at a certain stage, which is why the elimination of potentially dangerous T-cell clones does not occur, and they begin to accumulate in the lymph nodes. In addition, conditions are created for autoimmune damage to organs and tissues.

Hereditary and spontaneous mutations in the TNFRSF6 gene, which encodes the Fas receptor itself, are most common. In this case, a violation of the protein structure (especially the domain responsible for interaction with the FADD molecule) leads to the fact that it becomes unable to perform its receptor functions and activate apoptosis. Somatic mutations in the FAS gene are also possible, which fully manifest themselves in late childhood or adolescence, and therefore they belong to a separate group of ALS.

The second most common variant of autoimmune lymphoproliferative syndrome is caused by a mutation in the CASP10 gene encoding the cystine-asparagine acid protease (caspase-

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10). This protein plays a key role in signaling apoptosis from the cell membrane to the cell nucleus. This variant also includes mutations of the CASP8 gene.
The third most common is autoimmune lymphoproliferative syndrome, which is caused by a mutation in the FASLG gene encoding the Fas ligand or CD-178 receptor. It plays an auxiliary role in the recognition of factors that stimulate apoptosis, and is involved in signal transmission to the cell.
Some forms of ALS are caused by a mutation of the NRAS gene, which encodes a "small G protein" that takes part as a secondary messenger in the transmission of signals from the membrane to the cell, including the nucleus. In about a third of cases of autoimmune lymphoproliferative syndrome, immunologists are unable to determine the immediate cause of the disease.
Classification of autoimmune lymphoproliferative syndrome
Using the methods of modern genetics, it was possible to identify six main forms of ALS:
ALPS 1A – caused by a mutation of the TNFRSF6 gene located on chromosome 10, most often has a congenital character, inherited by an autosomal dominant type. According to statistics, more than 40% of ALS belong to this particular type.
ALPS 1B-is caused by a mutation of the FASLG gene, and also quite often leads to congenital autoimmune lymphoproliferative syndrome. This type includes about 10% of all clinical cases of ALS.
ALPS 1m-it is caused by somatic mutations in the FAS gene that occur in childhood or adolescence and therefore lead to late forms of ALS. In this case, gene damage must occur in a polypotent progenitor cell, which can give rise to many lymphocyte lines. In this form, sudden spontaneous remission of the disease most often occurs.
ALPS 2 – is caused by a mutation in the CASP10 and, according to some sources, CASP8 genes, which encode the caspase proteins that transmit the apoptosis signal from the receptor to the cell nucleus. This form of autoimmune lifoproliferative syndrome accounts for approximately 25% of all cases of the disease, and can be either congenital or manifest itself at an older age.
ALPS 3 - mutation of which gene and the nature of its inheritance in this form are unknown. The peculiarity of this variant of ALS is a violation of not only FAS-, but also IL2-mediated apoptosis, as well as a more severe course.
ALPS 4-is caused by a mutation of the NRAS gene, which also encodes intracellular signal transmitter proteins. This type of autoimmune lymphoproliferative syndrome is characterized by a more benign course and moderate severity of symptoms.
Symptoms of autoimmune lymphoproliferative syndrome
The symptoms of ALS are quite variable due to the large number of mutations that can lead to this condition. The onset of the disease can be noticed as early as the 15th day after birth (in congenital forms), in childhood or adolescence in the case of somatic mutations in the FAS, CASP10 or NRAS genes. Usually, the first manifestation of the disease is lymphadenopathy – the axillary, inguinal or cervical lymph nodes increase in size, but they are painless and not soldered to the surrounding tissues. Splenomegaly is registered, in some cases it is accompanied by an enlarged liver (hepatosplenomegaly).
Autoimmune manifestations of ALS are usually recorded some time after lymphadenopathy and enlargement of the spleen. These are mainly lesions of blood sprouts-thrombocytopenia, hemolytic anemia leading to jaundice, and occasionally neutropenia. In addition to blood, autoimmune damage can affect the digestive tract (gastritis, pancreatitis, colitis, autoimmune hepatitis). The skin may show signs of vasculitis, making the autoimmune lymphoproliferative syndrome clinic similar to that of systemic lupus

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erythematosus. In addition, autoimmune forms of thyroiditis, glomerulonephritis may occur, joints and eye tissues may be affected (iridocyclitis, uveitis). Common lesions of the central nervous system are epileptic seizures, myelitis, and cerebellar ataxia.

The severity of symptoms and their number can vary significantly for each individual patient. In addition, with autoimmune lymphoproliferative syndrome, the risk of developing malignant tumors increases tenfold, since tumor clones of lymphocytes are also eliminated by apoptosis.

In approximately 20% of cases, ALS leads to non-Hodgkin's lymphomas (Burkitt's lymphoma, follicular lymphoma), and other oncological diseases have been described. Because of this, the manifestations of ALS can be mistakenly identified as a consequence of tumor infiltration of lymphoid tissue. Among other complications of autoimmune lymphoproliferative syndrome, the most common are traumatic rupture of the spleen, sepsis, and other infectious lesions.

Diagnostics

Diagnosis of ALS is made on the basis of examination, as well as laboratory, immunological and genetic studies. Examination reveals an increase in more than three groups of lymph nodes, splenomegaly, and liver enlargement. A blood test may show a decrease in the number of certain cells (anemia, thrombocytopenia), and some patients have high (up to 30%) eosinophilia. The Coombs test is positive, and a biochemical blood test shows severe hypergammaglobulinemia.

One of the highly sensitive methods of immunological diagnosis of autoimmune lymphoproliferative syndrome is flow immunocytofluorometry, which is performed to detect the number of lymphocytes with an atypical set of receptors (CD3+CD4-CD8 -). In ALS, the number of such cells exceeds 1% of all lymphocytes. In the biopsy of the lymph nodes, follicular hyperplasia is determined, and the result of histological examination of the spleen is lymphoid hyperplasia.

The FAS gene can be sequenced by a geneticist to identify mutations that have caused autoimmune lymphoproliferative syndrome. Given the significant size of this gene, to speed up and reduce the cost of the procedure, the search can be performed only in individual exons of the FAS gene, in which violations are most often detected – these areas are called "hot spots". Thus, only types 1A, 1B, and 1m ALS can be determined by genetic diagnosis. Methods for determining other forms of ALS by genetic methods have not yet been developed. The study of hereditary history in some cases will be ineffective due to a significant proportion of forms of the disease caused by somatic mutations.

Treatment of autoimmune lymphoproliferative syndrome

Etiotropic treatment of autoimmune lymphoproliferative syndrome has not been developed, pathogenetic therapy is limited to the use of immunosuppressive and cytotoxic agents. Corticosteroids (prednisone, dexamethasone) are most often used as agents that suppress autoimmune activity. Specific drugs that limit the rate of lymphocyte proliferation include mycophenolate mofetil, sirolimus. Also, traditional cytotoxic agents-methotrexate, cyclosporine A and others-are actively used in autoimmune lymphoproliferative syndrome.

With a significant increase in the spleen or no effect from conservative treatment, splenectomy is resorted to. Bone marrow transplants and the use of stem cells in the long run gave only a temporary effect. With significantly pronounced hematological disorders, hemotransfusions, the introduction of red blood cells or platelets are used. The patient should avoid physical exertion, use a high-vitamin diet.

Forecast

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The prognosis of the disease, due to the high variability and severity of symptoms, is uncertain or unfavorable. In most patients, the manifestations of the disease gradually increase, eventually leading to fatal anemia, thrombocytopenia, and biliary cirrhosis of the liver. Immune disorders also play an important role in the prognosis, as sepsis and other infectious lesions are often the cause of death. The prognosis of autoimmune lymphoproliferative syndrome should also take into account the increased risk of cancer, about a fifth of patients die from various types of lymphomas. In some cases, spontaneous and prolonged remission of the pathology occurs.

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