Ministry of Health of Ukraine
Poltava State Medical University

Approved"
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Minutes № from
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METHODOLOGICAL RECOMMENDATIONS FOR CONDUCTING AND PREPARING FOR PRACTICAL CLASSES

Academic discipline	Clinical immunology and allergology
*Module **4***	Clinical immunology and allergology
Content module	Clinical immunology and allergology
*Topic **№6***	Immune aspects of autoimmune pathology
Course	5
Hours	2

Poltava 2023

Methodological recommendations for the practical training for independent work of students in preparation for the practical training and during the class were prepared by:
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Methodological recommendations were re-approved at the meeting of the Department of Internal Medicine of Internal Medicine №3 with Phthisiology_____
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1. Relevance of the topic.

The urgency of the problem is due to the rapid increase in the prevalence of autoimmune pathology in Ukraine. To date, there are 80 diseases that belong to autoimmune pathology. The latest studies prove that it belongs to the class of autoimmune diseases such as endometriosis, autism, duodenal ulcer, epilepsy, schizophrenia, hypertension, alopecia.

Recently, a huge amount of scientific research has been conducted in the field of autoimmune diseases, but new modern methods of diagnosis and treatment of autoimmune pathology are not yet widely used clinically. Despite the large number of scientific developments, the etiology and immunopathogenesis of autoimmune pathology have not been sufficiently studied.

In connection with the high prevalence of autoimmune pathology, doctors of any specialty (and especially district or family doctors, because most often the patients first turn to them) must thoroughly know the clinical manifestations of autoimmune diseases, be able to carry out a timely and complete diagnosis, prescribe adequate therapy in depending on the etiology and immunopathogenesis of the autoimmune disease. In order to carry out differential diagnosis and choose further patient management tactics, every graduate of a higher medical educational institution must have sufficient modern knowledge of immunopathogenesis, clinical and laboratory diagnosis of autoimmune pathology.

Autoimmune diseases most often affect young people, which often leads to early disability and disability of patients. This significantly complicates and exacerbates the situation, and therefore leads autoimmune pathology to a number of current social and economic problems.

The general goal: to master the method of collecting anamnestic and clinical data necessary for a timely diagnosis of an autoimmune disease; method of diagnosing an autoimmune disease, taking into account the clinical form, localization, prevalence, stage of the pathological process, variant of the course of the disease; the method of prescribing and evaluating the results of additional research methods (laboratory and instrumental); the method of prescribing an adequate scheme of therapy, taking into account the received data, modern developments in the field of autoimmune pathology and data on the assessment of immune status.

Specific goals:

1. Evaluate the results of determining the immunological criteria of autoimmune pathology.

2. Prescribe immunosuppressive therapy and evaluate its effectiveness in autoimmune diseases

Theoretical questions for practical training:

1. Mechanisms of tolerance breakdown.

2. The role of tolerance breakdown in the development of autoimmune diseases, clinical examples.

3. Features of immunopathogenesis of autoimmune pathology.

4. Laboratory criteria for diagnosis of autoimmune diseases.

5. Rheumatoid arthritis: immunopathogenesis, immunodiagnosis, principles of immunotherapy.

6. Systemic lupus erythematosus: immunopathogenesis, immunodiagnosis, principles of immunotherapy.

7. Insulin-dependent diabetes: immunopathogenesis, immunodiagnosis, principles of immunotherapy.

8. Multiple sclerosis: immunopathogenesis, immunodiagnosis, principles of immunotherapy.

9. Dermatomyositis: immunopathogenesis, immunodiagnosis, principles of immunotherapy.

10. Myasthenia gravis: immunopathogenesis, immunodiagnosis, principles of immunotherapy.

11. Organ-specific autoimmune diseases: autoimmune thyroiditis, nonspecific ulcerative colitis: immunopathogenesis, immunodiagnosis, principles of immunotherapy.

Approximate basis of action

Autoimmune reaction is a form of immune response that is induced by autoantigenic determinants under normal or pathological conditions and is one of the important mechanisms for maintaining homeostasis. Autoimmune reactions, expressed to one degree or another, accompany almost any immune response, acting

as a regulator of its intensity. Excessively pronounced autoimmune reactions can lead to clinically significant self-harm, moving from the regulatory to the pathological.

Autoimmune disease is a disease of the immune system associated with a violation of the formation or maintenance of immune tolerance, which manifests itself in the form of clinically manifest immune-mediated self-damage of organs and tissues of the body. Autoimmune disease, unlike autoimmune reactions, is not a consequence, but a cause of damage to various somatic organs.

It is known that normally the lymphocyte population contains so-called autoreactive cells, capable of recognizing the body's own molecules (autoantigens) and inducing the development of an immune response against them. In this regard, an important function of the immune system is the maintenance of immune tolerance, the main principle of which is the absence of effector reactions against autoantigens even if they are recognized by autoreactive lymphocytes. To maintain tolerance to autoantigens, aggressive autoreactive T-cells are destroyed by apoptosis in the thymus during their maturation (so-called negative selection). Autoreactive B lymphocytes undergo deletion during maturation in the red bone marrow. "Dangerous" immunocytes that have survived are in the peripheral lymphoid organs in a state of certain inactivity - anergy. Thus, the main mechanisms of immune tolerance are apoptosis and anergy of autoreactive lymphocytes.

It is quite clear that autoimmune diseases develop as a result of a violation of the mechanisms of maintaining immune tolerance. The first theory that explained the development of autoimmune diseases was the theory of genetic predisposition. Today, it is believed that genetic predisposition is not a direct cause, but a favorable background for the disruption of immune tolerance.

1. The theory of "forbidden clones". According to this theory, autoimmune diseases are initiated by autoreactive T-lymphocytes - representatives of the so-called forbidden clones, which should have died by apoptosis while maturing in the thymus (see above).

Inferiority of the thymus as an organ, where the central mechanisms of immune tolerance are implemented, can have both congenital and acquired genesis. In the latter case, important importance is given to viral infections that affect this organ, as well as hormonal disorders, since the thymus functions in a close relationship with the glands of internal secretion, acting as an antagonist of the hypothalamus - pituitary - adrenal cortex - gonads system.

2. Theory of immune defects. According to this theory, autoimmune diseases are a type of immunodeficiency diseases, that is, diseases based on a specific immune defect. According to classical concepts, the presence of an immune defect leads to a violation of the maintenance of immune tolerance through a decrease in the activity of cells (so-called T-suppressors), which control potentially dangerous autoreactive lymphocytes.However, so far no specific immune defects have been identified, the presence of which in 100% of cases would lead to the development of autoimmune reactions.

According to modern concepts, immune defects lead to the breakdown of immune tolerance in an indirect way - in connection with a decrease in immunity to microorganisms, a patient with IDZ develops chronic or recurrent infections, in connection with which a protective background is maintained for an unnaturally long time, which protects activated lymphocytes from apoptosis (see section "Apoptosis"). In such conditions, "impunity" activation of autoreactive cells is possible, which is not accompanied by the induction of their programmed death. Persistent viral infections are especially dangerous in terms of provoking a breakdown of tolerance - they run subclinically, in connection with which the patient may not suspect the fact of infection for a long time and may not seek medical help.

Recently, various disorders of the apoptosis cascade in autoreactive T-cells in patients with autoimmune diseases have been discovered, so it is believed that the indicated immune defects may be at the basis of the breakdown of tolerance.

According to the theory of immune defects, adequate treatment of immunodeficiency diseases is a prevention of the development of autoimmune diseases.

3. Theory of barrier antigens. It is known that some organs (brain and spinal cord, organ of vision, thyroid gland, testes) develop and function behind physiological barriers that are relatively impenetrable for immunocompetent cells. However, when the integrity of such barriers is violated, the development of autoimmune reactions against the antigens of these organs is possible, since immune tolerance to them is not supported due to spatial isolation.

4. Theory of polyclonal activation of B-lymphocytes. Polyclonal activation of B-lymphocytes is deliberately caused by various pathogenic microorganisms (for example, Epstein-Barr virus) in order to reduce the targeting of the immune response. Directly stimulated by the pathogen, various non-specific clones of B-cells synthesize correspondingly non-specific antibodies to the pathogen. In this way, a huge number of immunoglobulins are aimlessly produced, which do not

play any role in the immune response against a specific pathogen, and the production of antibodies specific to it is carried out in an insufficient amount, since the intensity of the synthesis of immunoglobulins in the body has its functional limits. As a result of pathogen-induced polyclonal stimulation, activation of some autoreactive B-lymphocytes, capable of mediating the development of autoimmune reactions, is possible.

Autoimmune diseases can be divided according to the type of autoreactive T-helpers, through which autoaggression is carried out.

• mainly type 1 T-helpers: rheumatoid arthritis, reactive arthritis, Wegener's granulomatosis, Lyme arthritis, giant cell arteritis.

• T-helpers type 2: Charge-Strauss syndrome.• mainly type 2 T-helpers: systemic lupus erythematosus, dermatomyositis, systemic scleroderma, Sjogren's syndrome.

In addition, autoimmune diseases are divided into organ-specific, in which the pathological process is concentrated mainly in one organ, and organ-nonspecific, in which diffuse (generalized) autoimmune damage occurs. Organ-specific include, for example, myasthenia gravis, insulin-dependent diabetes, Hashimoto's thyroiditis, etc., and organ-nonspecific - systemic lupus erythematosus, rheumatoid arthritis, systemic scleroderma, etc.

The main approaches to immunodiagnosis of autoimmune diseases:
1. The most significant is the detection of autoantibodies to one's own antigens (table 1). For example, in SLE, autoantibodies to native DNA are detected, in multiple sclerosis - to the main myelin protein.
2. As a rule, the immunogram reveals an increase in the level of immunoglobulins of class G, an increase in the immunoregulatory index is often noted due to a decrease in the suppressive function of T-lymphocytes, an increase in the number of B-lymphocytes, a decrease in the content of complement, an increase in the level of circulating immune complexes (CIC).
Taking into account that autoantibodies to one's own antigens (as well as other changes on the part of the immune system) are also found in other diseases (autoimmune reactions in many pathological conditions), to confirm the diagnosis of an autoimmune disease, it is necessary to study all indicators in dynamics.
3. During organ biopsy, the deposition of immune complexes and fibrin in the affected organ is determined.
4. Characteristic tissue infiltration by lymphoid cells.
The main approaches to the therapy of autoimmune diseases:
1) Combined appointment of cytostatics, glucocorticoids and plasmapheresis.

2) In some autoimmune diseases (autoimmune thrombocytopenic purpura, myasthenia gravis, etc.), intravenous administration of immunoglobulin preparations is advisable.
3) Currently, specific peptides have been synthesized that are used for the treatment of autoimmune diseases.

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease that is caused by immune-mediated autoaggression against joint tissues and manifests itself in the form of erosive arthritis, which leads to joint deformations, fibrosis and ankylosis. With RA, the development of visceropathies is possible, but the key, after all, is damage to the joints.

Etiology. The etiology of the disease has not been established. It is assumed that chronic (often subclinical) infection (paramyxoviruses, Epstein-Barr virus, mycoplasmas, chlamydia) in genetically predisposed individuals or in conditions of immune defects can cause a breakdown of tolerance in RA.

Pathogenesis. In the pathogenesis of rheumatoid arthritis, it is customary to distinguish the main mechanism of autoaggression and the secondary one. The first is associated with a violation of tolerance to autoantigens of articular cartilage tissue, in connection with which antigenic presentation of autoantigen peptides and activation of autoreactive T-lymphocytes is carried out in the joints, with subsequent proliferation of the latter and differentiation mainly into type 1 T-helpers.

Macrophages, dendritic cells and chondrocytes play the role of antigen-presenting cells in RA. The latter initiate the expression of HLA class II molecules under the influence of proinflammatory cytokines. Activated cells produce pro-immune cytokines: IL-1β, TNF-α, IL-6. These cytokines cause a series of biochemical changes both at the level of the joint and throughout the body. In particular, IL-1β activates osteoclasts, promoting bone osteoporosis in the joint area, which determines the characteristic radiological picture of the disease. This cytokine also causes local vasodilation and plasmarrhagia in the synovium by inducing the release of prostacyclin by endotheliocytes.On the other hand, under the influence of IL-1β, endotheliocytes increase the expression of adhesion molecules, which promotes the influx of neutrophils, macrophages, and lymphocytes to the focus. All these changes lead to hyperemia (which means local hyperthermia) and swelling of joint tissues, and also facilitate transendothelial migration of cells (that is, contribute

to cell infiltration of the synovial membrane). TNF-α exhibits a synergistic effect with IL-1β in many respects. IL-6 promotes the synthesis of acute-phase proteins (in particular, C-reactive protein) by hepatocytes, and also acts as a kind of counter-regulator of the activity of these cytokines.

Activated by antigen presentation and IL-1β, type 1 autoreactive T-helpers, in turn, synthesize an appropriate set of cytokines (IL-2, TNF-α, lymphotoxin, INF-γ, migration inhibitory factor [MIF]), which contribute to both direct damage cartilage tissues (lymphotoxin, TNF-α), as well as the reinforcement of macrophages and neutrophils, activation of fibroblasts, proliferation of endothelial cells and active formation of new vessels.

Due to the massive infiltration of the synovial membrane by lymphocytes, lymphoid clusters are formed in the latter, resembling the follicles of the peripheral organs of the immune system. It is believed that these changes lead to the transformation of the synovial membrane of the joint into a peculiar organ of immunogenesis, where reactions of antigen-dependent differentiation of autoreactive lymphocytes (B cells) occur. Thus, at a certain stage of the immunopathogenesis of the disease, not only the immune system as a whole, but also the damaged joints themselves can completely autonomously support the course of the autoimmune process.

It should be noted that autoreactive lymphocytes that mature in the tissues of the joint or arrive here from the vascular bed do not have direct access to the cartilage, since the latter is devoid of blood vessels. In this regard, they initially accumulate in the synovium of the joints. So, the first signs of inflammation are swelling and cellular infiltration of the synovial membrane itself. As a result of the proliferation of fibroblasts, proliferation of endotheliocytes, increasing lymphoid-histiocytic infiltration, the synovial membrane of the affected joints transforms into a pannus - a hypertrophied connective tissue in a special way, which has at least two key properties. First, pannus cells lack sensitivity to keylons (natural agents that limit proliferation), so the latter has the ability of steadily progressive growth. The reason for reduced sensitivity to keylons is not well understood. It is assumed that this happens in connection with frequent cell divisions and a changed microenvironment. Second, the pannus is an extremely aggressive tissue, as it produces high concentrations of metalloproteinases and free radicals. It is these factors that determine the development of erosive changes in RA. Aggressive properties of pannus are due to its cellular composition - primarily, macrophages activated by INF-γ and MIF, as well as neutrophils and fibroblasts. The latter initiate the production of proteolytic enzymes under the influence of pro-inflammatory cytokines.

It was established that RF does not have an independent value in the induction of tolerance breakdown in RA, since the introduction of RF from sick individuals to healthy ones does not cause the development of the disease in the latter. At the same time, the transfer of autoreactive T-lymphocytes provokes the development of RA symptoms in healthy individuals. The reason for the high frequency of the combination of autosensitization to Fc-fragments of immunoglobulins and rheumatoid arthritis is not fully understood. In practice, the rheumatoid factor (more precisely, one of its fractions directed against IgM) is determined in the Waaler-Rose reaction or by the latex test.

The presence of RF is not a mandatory sign of rheumatoid arthritis. Depending on the presence or absence of RF, seropositive and seronegative forms of the disease are distinguished. At the same time, seropositive forms are more aggressive, since the rheumatoid factor promotes faster generalization of the autoimmune process and the development of visceropathies. Sometimes, RA follows a seronegative variant, but later transforms into a seropositive form, which is regarded as an unfavorable prognostic sign. It should be noted that RF can also be found in other autoimmune diseases, but in lower concentrations (that is, it is not pathognomonic for RA). RF is especially often found in systemic lupus erythematosus and nodular periarteritis.

Insulin-dependent diabetes

Insulin-dependent diabetes is one of the most common organ-specific autoimmune diseases. There are three main forms of the disease: virus-induced, autoimmune and slowly progressive.

In the first case, the development of the disease is associated with damage to the islets of Langerhans by various viruses tropic to β-cells of the pancreas (acute viral pancreatitis). Some of them have a direct damaging effect (Coxsackie viruses, epidemic parotitis), others cause damage indirectly, contributing to the breakdown of immune tolerance to β-cell autoantigens (viruses of the herpes group). It is known that complex viruses have a membrane-like envelope. Its formation occurs from virus-modified areas of the cytolemma of the host cell. Therefore, it is believed that the breakdown of tolerance to β-cell antigens during viral infections occurs by the mechanism of molecular mimicry - in the conditions of recognition of virus molecules complexed with cell surface structures, effector immune reactions are implemented both against viral and cellular antigens. This means that maintenance of the autoimmune reaction is possible even after the elimination of the viral infection.

Autoimmune reactions occur due to the accumulation of type 1 autoreactive T-helpers, i.e., the immunopathological process in insulin-dependent diabetes develops mainly by cell type. Actually, the effector mechanism is represented by specific and "non-specific" (in fact, it is no less specific than the first) components. The first is carried out due to the activity of autoreactive cytotoxic T-lymphocytes, and the second - reinforced macrophages. Autoantibodies are necessary to provide the latter with a mechanism of specific recognition of pancreatic β-cells (reactions of antibody-dependent cell-mediated cytotoxicity), so a certain amount of T-helper type 2 is formed, which promotes the proliferation and maturation of autoreactive B-lymphocytes.

The virus-induced form of the disease most often affects men, the debut of the disease is noted at a young age. The presence of histocompatibility antigens B8, B12, DR3 and DR4 is characteristic.

It should be noted that the insulin-dependent form of diabetes mellitus is a self-limiting autoimmune disease due to the organ specificity of the pathological process - with the complete destruction of β-cells, autoimmune reactions stop. In conditions of viral damage, the kinetics of the autoimmune process is very high. Most of the cells die during the period of infection, others are destroyed after the elimination of the infectious agent by an autoimmune mechanism that unfolds with the help of specific autoantibodies. In practice, it is difficult to detect such antibodies, since they exist only 3-4 months after the elimination of the pathogen - approximately this period is necessary for the complete destruction of β-cells of pancreatic islets. During the specified period, patients feel satisfied (the so-called honey moon), since the endocrine part of the pancreas has a huge functional reserve and the first clinical manifestations of the disease develop only after the destruction of 80-90% of β-cells.

The autoimmune form of the disease progresses more slowly, autoantibodies to β-cells are determined within 1-2 years. The reason for the breakdown of tolerance in this case is not sufficiently understood, but it has been established that it is not related to acute viral pancreatitis. Violation of tolerance in this form of diabetes is more profound, therefore, in parallel with autoimmune pancreatitis, lesions of other organs are observed (Hashimoto's thyroiditis, Addison's disease, etc.).The disease occurs more often in women, the onset falls on middle age. The most characteristic histocompatibility antigens are HLA DR4, DR8, DRw3.

Slowly progressive insulin-dependent diabetes mellitus starts late (at 40-50 years old), so most often such patients are initially diagnosed with the non-insulin-dependent form of the disease. However, the determination of antibodies to β-cells of pancreatic islets and the detection of insulinopenia force a review of the clinical

diagnosis. This form of the disease is rare, and is observed with the same frequency among men and women. A characteristic narrow spectrum of histocompatibility molecules has not been established.

Clinical manifestations. The clinical picture includes polydipsia, polyuria, polyphagia, pollakiuria and weight loss. In severe cases, the development of coma (ketoacidotic, hyperosmolar or lactatacidemic genesis) is possible.

Treatment. Treatment consists in lifelong use of insulin drugs. Many immunomodulators have been tested for insulin-dependent diabetes, but no convincing results have been obtained using any of them.

Multiple sclerosis

Multiple sclerosis is an autoimmune disease, the basis of which is demyelination of the fibers of the central nervous system, which is manifested by organic symptoms scattered in place and time. The etiology of the disease remains unknown. It is assumed that the breakdown of tolerance occurs as a result of a viral neuroinfection. At the same time, there are two hypotheses that explain the connection between neuroinfection and the development of MS. According to the first, chronic neuroinfection (measles, herpes simplex viruses, cytomegalovirus, etc.), which most often remains subclinical, leads to increased permeability of the blood-brain barrier and changes in the antigenic composition of nervous tissue. According to another, the disease develops as a result of a violation of relationships in the system of integrated viral genes and own genes of nerve cells. It is known that about 5% of the genes of the cells of the human body are acquired as a result of the integration of nucleic acids of various viruses into the genome of target cells. However, this does not lead to the development of autoimmune reactions, since immune tolerance is maintained to viral integrated genes. Violation of such tolerance can lead to the development of an autoimmune disease. At the same time, infection with a certain infection is optional, since most of the integrated viral genes are transmitted from generation to generation.

Today, it has been established that the basis of MS is the synthesis of autoantibodies to some antigens of the myelin sheaths of nervous tissue. The most studied of them are myelin basic protein, proteolipid protein, myelin-associated glycoprotein, and myelin oligodendrocyte glycoprotein.In the late stages of the disease, autoantibodies to antigens of neurons and neuroglia cells are synthesized. The reason for the production of such autoantibodies is the activation of specific autoreactive T-helpers of type 1. The access of antibodies to myelin antigens is ensured by increasing the permeability of the blood-brain barrier under the influence

of pro-inflammatory mediators – γ-IFN, TNF-α, TNF-β, IL-2, which are known to belong to the set of Th 1 cytokines. In numerous studies it is shown that an increase in the level of such cytokines correlates with an increase in clinical symptoms and a worsening of the patient's condition. On the contrary, an increase in the level of Th 2 cytokines (IL-4, IL-5, IL-6 and IL-10) is accompanied by a decrease in the intensity of the pathological process and the occurrence of clinical remission of the disease. However, it is worth realizing that the cause of these changes is not the cytokines themselves, but those immune processes, the reflection of which are changes in the cytokine balance. Since there is no lymphoid tissue in the nervous system, initially, the development of the inflammatory process requires the migration of autoreactive lymphocytes from the outside, but later the synthesis of pro-inflammatory cytokines begins to be carried out by neuroglia cells, which are part of the body's innate resistance. Thus, in the later stages, the pathological process is largely ensured by the resources of the nervous system itself. The effector link in MS is reinforced macrophages, i.e. antibody-dependent cell-mediated cytotoxicity reactions are carried out.

The morphological substrate of the disease is foci of demyelination of nerve fibers (white matter) of the central nervous system (so-called plaques). In conditions of remission, remyelination due to the activity of oligodendrocytes (Schwann cells) is noted. As the disease progresses, not only the destruction of myelin occurs, but also damage to Schwann cells (hypoxia, acidosis, action of free radicals), which slows down the process of remyelination and contributes to the growth of a residual defect that does not disappear even during remission. Slowing down of remyelination as a result of the death of oligodendrocytes in foci of inflammation leads to another tragic consequence. The fact is that the myelin sheath protects axonal cylinders, absorbing the "hit" of aggressive agents (free radicals, toxic peroxides, lysosomal enzymes). When remyelination is disturbed, nerve structures themselves are damaged, which leads to irreversible changes and the formation of astroglial scars at the site of damage due to the compensatory proliferation of astro- and gliocytes. These mechanisms underlie the transformation of the remitting course of the disease into a secondary progressive one.

Clinic.

Main clinical syndromes of MS

1. Syndrome of damage to the pyramidal tract

2. Cerebellar pathway damage syndrome

3. Cranial nerve damage syndrome

4. Syndrome of sensitive disorders

5. Dysfunction of the pelvic organs

6. Visual disturbances

7. Neuropsychological disorders

Treatment. In case of exacerbation of the disease, glucocorticoids and ACTH are used.Prevention of further exacerbations is achieved due to interferon therapy and the use of glatiramer acetate (Copaxone). Interferon-β drugs proved to be the most effective for the treatment of remitting and secondarily progressive forms of the disease. The immunological aspects of their therapeutic effect are associated with a decrease in the production of γ-IFN and TNF-α, as well as with a change in the expression of antigenic presentation and adhesion molecules. Betaferon (interferon β-1b) is administered intravenously at a dose of 8 million IU every other day. Avonex (interferon β-1a) is used in a dose of 6 million IU once a week.

Hashimoto's thyroiditis

Autoimmune thyroiditis (Hashimoto's thyroiditis) is a disease characterized by an immune reaction - both humoral and cellular - to thyroid-specific AH and damage to the gland tissue.

Immunopathogenesis.

Specific thyroid AGs are:

1. Thyroglobulin, the main iodoprotein of the thyroid gland, which is a form of storage of thyroid hormones and their immediate precursors. Most patients with Hashimoto's thyroiditis are prescribed antithyroid drugs.

2. "Second antigen", localized in the colloid. There is an opinion that it is a complex of thyroglobulin with thyroglobulin ATs, which has free areas of attachment of ATs.

3. AG contained in the cytoplasm of cell follicles. This AG is closely related to lipoproteins of microvesicles with smooth contours, which are abundant in the apical zone of thyroid gland cells. These are drops of synthesized thyroglobulin coming from the Golgi complex. It is called microsomal because it was first isolated from the fraction of microsomes.

4. Hypertension of the surface of the cells of the thyroid gland, which are contained in certain areas of the latter. The blood serum of most patients with autoimmune thyroiditis contains autoantibodies capable of reacting in vitro with thyroglobulin, "second AG" and microsomal AG. Hypersensitivity reactions of the delayed type to thyroid autoantigens are determined in the majority of patients with autoimmune thyroiditis. Positive skin reactions characterized by erythema and thickening are observed 24 hours after intradermal injection of thyroid gland extract.Studies with a skin window have shown that after the injection of thyroid gland extract, the content of basophilic leukocytes in the exudate of patients with thyroiditis increases. On the second day after the injection, the concentration of basophils is maximal (4.8% of exudate cells); the content of eosinophils is 2.8%, and the content of neutrophils and macrophages does not increase significantly. These phenomena are the result of a delayed hypersensitivity reaction and indicate the involvement of basophils in autoimmune reactions. In patients with Hashimoto's thyroiditis, antibody-dependent cellular cytotoxicity of lymphoid cells significantly exceeds normal control indicators. Patients with Hashimoto's thyroiditis are mostly women. The connection between HLA-DR3 and HLA-DR5 and the occurrence of the disease is proven. Autoimmune reactions, which are observed in autoimmune thyroiditis, can be considered as normal reactions to one's own thyroid hormones (thyroglobulin, etc.), of course, "sequestered" or inaccessible to the lymphoid system, which got into the bloodstream due to trauma, infection or other influences. According to another opinion, on the contrary, autoimmune reactions to thyroid hormones can be considered normal immune reactions to own AGs, modified by bacteria or viruses, or to introduced AGs that cross-react with thyroid AGs.

There is a hypothesis that the basis of tolerance to "own" thyroglobulin is the tolerance of only one T-cell population, caused by the long-term presence of a small amount of thyroglobulin in the blood. At the same time, B-cells, which have receptors specific for this AG, do not carry out an autoimmune reaction against it due to the lack of a response from T-cells.If T-cells are active enough to force B-cells to respond to AG-determinants that are otherwise ignored, an autoimmune process occurs. Rather, these responses may result from the elimination of suppressor T cells. It is possible that an infectious disease or a strong external influence leads to the stimulation or elimination of T-cells. Some people have immune response genes that give T cells the ability to respond very strongly to certain autoantigens, such as thyroid hyperthyroidism. It cannot be completely excluded that many mechanisms are involved in the development of autoimmune reactions to thyroid hypertension.

Clinical picture.

Enlargement of the thyroid gland is the main clinical manifestation resulting from autoimmune damage, which leads to lymphocytic infiltration, fibrosis and a decrease in the ability of the thyroid gland to synthesize hormones. By the time the diagnosis is made, 20% of patients develop hypothyroidism, but in some it develops later. Sometimes, as with subacute thyroiditis, pain appears, soreness is noted when palpating the gland.

Diagnostics.

The disease is suspected in any patient with a dense, non-thyrotoxic goiter. The diagnosis is confirmed by high titers of antithyroglobulin and antimicrosomal blood pressure. Thyroid function tests are decreased or normal.

Treatment consists in prescribing L-thyroxine sodium, which reduces the size of the goiter.

Inflammatory bowel diseases

Nonspecific ulcerative colitis is a disease that develops in the form of diffuse inflammation of the intestinal mucosa with the formation of widespread shallow ulcers. This pathology is characterized by the formation of autoantibodies against the mucous membrane of the colon. In 50-80% of patients, antibodies to the cytoplasmic antigens of neutrophils are found, and in the lymphoid-cytoplasmic infiltrate of the mucous and submucosa of the colon, among the immunoglobulin-containing cells, 40-50% of cells that synthesize IgG (normally about 5-10%). The same is found in Crohn's disease. Recently, an increased number of lymphocytes expressing receptors for paratuberculosis mycobacteria was found in the colon and blood.

Crohn's disease (granulomatous colitis) is a relapsing disease that mainly affects the colon, but at the same time the pathological process can be localized in other parts of the digestive tract. A characteristic feature is segmental damage to the entire thickness of the colon by lymphocytic granulomas followed by the formation of penetrating slit-like ulcers. The disease occurs with a frequency of 1:4000, young women suffer more often. An increased number of IgG-containing lymphocytes specific for tuberculin was found in the colon.

Immunopathogenesis.

The search for the infectious origin of ulcerative colitis and Crohn's disease has been going on for more than half a century, many of its bacterial species have been discovered, but none of them meet the requirements of Koch's postulates. The presence of unusual bacterial flora does not at all mean that it is the etiological factor,

it can be a secondary element associated with the inflammatory process in the intestine, and not the root cause that causes this pathological condition. Unusual bacterial populations are now seen as epiphenomenal rather than the sole causative factor.

The theory of the viral origin of Crohn's disease and IVC continues to attract the attention of many researchers. The detection of lymphocytotoxic antibodies in the serum of patients with CKD and Crohn's disease and their healthy men, studies showing the existence of a transmissible agent, the cytotoxic effect observed after inoculation of tissue culture of patients with this pathology, confirm the viral origin of these diseases. Effector lymphocytes responsible for the cytotoxic effect are K-cells, but may also include T-cells. Spontaneous lymphocyte cytotoxicity to "target" cells containing the virus significantly increases under the influence of interferon. Along with the potentially important mechanisms responsible for the efficiency of the body's release from viral infection, such immunological reactions may play a significant role in the pathogenesis of chronic tissue damage. For example, the development of chronic hepatitis after a transfer of viral hepatitis B is associated with a cytotoxic effect.Similar mechanisms can probably be recognized as probable in the case of chronic tissue damage in inflammatory bowel diseases. This assumption is based on data on the detection of pathogens that have cytotoxic properties in patients with these diseases, and the exceptional feature of these cytotoxics to destroy only a certain group of host tissues. The selectivity of the action of toxins indicates that the agents that produce them represent a link in the pathogenesis that leads to tissue destruction, while the small and large intestines are able to respond to various stimuli with several appropriate reactions. A number of etiological factors or their combinations can initiate processes that lead to the appearance of diseases. These are viruses or substances they secrete, bacteria or bacterial products, external toxins and (or) food agents. In a susceptible organism of the host, they can stimulate immune mechanisms, which in turn contribute to the manifestation of a cytotoxic effect, which causes the destruction of cells. However, it may turn out that cytotoxins do not play a role in the pathogenesis of ulcerative colitis and Crohn's disease, despite the selective direction of their action.

Studies of immunoglobulins and antibodies in patients with ulcerative colitis and Crohn's disease did not reveal clear abnormalities, although histologically, the number of IgG-containing cells tended to increase, and IgA cells - to decrease. In some patients, the number of IgE cells increased.

Clinical manifestations.

Nonspecific ulcerative colitis is often combined with hypogammaglobulinemia, thymomas, thymic lymphoplasia, SLE, Hashimoto's thyroiditis. Possible development of iridocyclitis, iritis, peritendinitis, erythema nodosum, exanthema, arthritis, spondylitis, amyloidosis, neuritis, liver cirrhosis.

Laboratory data.

The concentration of proteins in the blood is reduced, and the content of α2 and γ-globulins is increased. Increased level of immunoglobulins, especially class A. The concentration of complement in blood serum is normal or slightly increased. ESR is moderately increased, the content of immune complexes is increased, which can cause the development of extraintestinal manifestations.

Treatment.

Immunotherapy of NVK and Crohn's disease depends on the stage of the process. In the early stages of the disease, drugs that improve intestinal microbiocenosis should be prescribed: enzyme drugs (vobenzym is preferred), sorbents. In the later stages of the disease, a surgeon's consultation and an individual scheme of immunotherapy are necessary, taking into account the surgeon's conclusion about the condition of the intestinal wall.

Tasks for self-training

Task No. 1

Patient M., 43 years old, turned to the doctor with complaints about the appearance about 2 months ago of a feeling of stiffness in the small joints of the hands of both hands, which occurs in the morning and disappears within a few hours. The patient also complains of weight loss, constant fever up to 37.7 °C, increasing muscle weakness. The examination revealed swelling and redness of the metacarpal, proximal interphalangeal joints of the right and left hands; subcutaneous nodules on the protruding parts of the bones, deformation of the fingers in the form of a swan's neck, as well as an increase in inguinal lymph nodes.

1. What is the most probable preliminary diagnosis that can be established for this patient?

1) psoriatic arthropathy;

2) ankylosing spondyloarthritis;

3) rheumatoid arthritis;

4) osteoarthritis;

5) Sjogren's syndrome.

2. What additional studies should be conducted first to confirm the diagnosis?

1) general blood analysis with leukocyte formula, immunogram, determination of rheumatoid factor, biochemical blood analysis, synovial fluid research, x-ray of joints;

2) general blood test with formula, immunogram, x-ray of joints;

3) immunogram, biochemical blood analysis, study of synovial fluid, CT scan;

4) general blood test with formula, immunogram, X-ray of joints, MRI;

5) immunogram, biochemical blood analysis, determination of rheumatoid factor, examination of synovial fluid.

3.What X-ray changes will be observed in the early stages of this disease?

1) bilateral sacroiliitis, subchondral sclerosis;

2) subchondral osteoporosis, thinning of the structure of the epiphysis of the bone, compaction and thickening of periarticular tissues, blurring of the contours and structure of the joint, narrowing of the joint space, erosion and wrinkles of the joint surfaces;

3) expansion of the joint gap;

4) thickening of the periosteum, signs of osteoporosis, vertebral compression and the development of osteophytes;

5) osteosclerosis, osteophytosis, wear of bone surfaces of joints, mushroom-like shape of the head of the proximal phalanx.

4. What treatment is most appropriate to prescribe for this patient?

1) glucocorticosteroids, cytostatics, aminoquinolone drugs;

2) intra-articular administration of glucocorticosteroids, long-term use of nonsteroidal anti-inflammatory drugs, plasmapheresis;

3) nonsteroidal anti-inflammatory drugs, sulfasalazine, glucocorticosteroids, midokalm or scutamine C, exercise therapy;

4) nonsteroidal anti-inflammatory drugs, glucocorticosteroids, gold salts, aminoquinolone drugs (chloroquine), antimetabolites (azathioprine or methotrexate), cyclosporin A, systemic enzyme therapy (vobenzym), immunocorrective therapy (levamisole), efferent methods (plasmapheresis);

5) drugs that improve the metabolism of cartilage (rumalon), calcium drugs, vitamin D, non-steroidal anti-inflammatory drugs, osteokin, intra-articular administration of drugs that inhibit the activity of lysosomal enzymes (trasylol, contrical, gordox).

Task No. 2.A 28-year-old woman, after resting on the southern coast of Crimea, noticed the appearance of redness on the skin of the face (in the area of the bridge of the nose and cheeks), complaints of migrating pains in the small joints of the hands and feet, sometimes she notes pains in the elbow and knee joints, pains in the muscles The patient also complains of general malaise, weakness, an increase in body temperature to 37.3-37.5 °C, aching pains in the heart without clear localization. Examination of the patient revealed erythema on the face in the form of a butterfly, spreading to the bridge of the nose and zygomatic arches, slight swelling of the small joints of the hands, during auscultation of the heart, a pericardial friction noise was heard, which did not last long.

1. What is the most likely diagnosis for this patient?

1) rheumatism;

2) rheumatoid arthritis;

3) dermatomyositis;

4) systemic lupus erythematosus;

5) Sjogren's syndrome;

6) systemic scleroderma.

2. What additional studies should be conducted to confirm and clarify the diagnosis?

1) general blood test, general urinalysis, ECG, ultrasound of abdominal organs;

2) general blood test, general urinalysis, immunogram, RIF, serological reaction to syphilis, detection of antinuclear antibodies, LE cells, antibodies to native DNA,

antiphospholipid antibodies, ECG, ultrasound of abdominal organs, X-ray of lungs, hands.

3) detection of antinuclear antibodies, LE cells, antibodies to native DNA, antiphospholipid antibodies, ECG;

4) general blood test, immunogram, RIF, serological reaction to syphilis, X-ray of lungs, hands;

5) immunogram, detection of antinuclear antibodies, LE cells, antibodies to native DNA, antif