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INTERRELATION BETWEEN THE NERVOUS AND IMMUNE SYSTEMS IN CHILDREN WITH RHEUMATOID ARTHRITIS (literature review)

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ANNOTATION

Juvenile rheumatoid (ideopathic) arthritis refers to rheumatic diseases that can lead to neurological complications, as well as disorders of the psycho-emotional and cognitive spheres. Damage to the nervous system in JRA includes headaches of various origins, autonomic dysfunction, astheno-neurotic manifestations, impaired cognitive functions, less often neuropathies, compression lesions of the spinal cord and peripheral nerves (tunnel syndromes), very rarely cerebral vasculitis. However, the recognition of CNS lesions in patients with JRA often presents significant difficulties, since the clinical picture, as a rule, is dominated by symptoms of damage to the joints and internal organs.

Key words: Juvenile rheumatoid (ideopathic) arthritis, nervous and immune systems, autonomic dysfunction.

ХАМИДОВА Нодира Абдужаббаровна
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ВЗАИМОСВЯЗЬ МЕЖДУ НЕРВНОЙ И ИММУННОЙ СИСТЕМАМИ ПРИ РЕВМАТОИДНЫХ АРТРИТАХ У ДЕТЕЙ (Литературный обзор)

АННОТАЦИЯ

Ювенильный ревматоидный (идеопатический) артрит относится к ревматическим заболеваниям, которые могут привести к неврологическим осложнениям, а также нарушениям психо-эмоциональной и когнитивной сферы. Поражение нервной системы при ЮРА включает головные боли различного генеза, вегетативную дисфункцию, астено-невротические проявления, нарушения когнитивных функций, реже нейропатии, компрессионные поражения спинного мозга и периферических нервов (туннельные синдромы), крайне редко церебральные васкулиты. Однако распознавание поражения ЦНС у больных ЮРА часто представляет значительные трудности, так как в клинической картине, как правило, превалируют симптомы поражения суставов и внутренних органов.

Ключевые слова: Ювенильный ревматоидный (идеопатический) артрит, нервная и иммунная система, вегетативная дисфункция.

ХАМИДОВА Нодира Абдужаббаровна
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БОЛАЛАРДА РЕВМАТОИД АРТРИТЛАРДА НЕРВ ВА ИММУН ТИЗИМЛАРИ ОРАСИДАГИ БОҒЛИҚЛИК

АННОТАЦИЯ

Ювенил ревматоид (идеопатик) артрит неврологик асоратларга олиб келиши мумкин бўлган ревматик касалликлар гуруҳига киради, шунингдек, психо-эмоционал ва когнитив доира бузилишларига олиб келади. ЮРАдаги асаб тизимининг шикастланишига турли хил сабабли келиб чиққан бош оғриқлари, вегетатив дисфункция, астено-невротик кўринишлар, когнитив функциянинг бузилиши, кам ҳолларда нейропатиялар, орқа мия ва периферик нервларнинг сиқилиши(туннел синдромлар) ҳамда жуда кам ҳолларда мия васкулитларига олиб келади. Бироқ МНСининг бузилиши белгиларини аниқлаш ЮРА билан оғриган беморларда қийин кечади, чунки касалликнинг клиникасида бўғим ва ички органлар фоалияти бузилиши белгилари устунлик қилади.

Калит сўзлари: Ювенил ревматоид (идеопатик) артрит, нерв (асаб) ва иммун тизими, вегетатив дисфункция.

Recently, a lot of research has accumulated showing that the nervous, immune and endocrine systems do not work completely autonomously, but in close cooperation, forming a single system for responding to environmental changes. Understanding the important role of the interaction between these systems of the body contributed to the rethinking of the idea of homeostatic equilibrium, which was proposed in 1932 by Walter Cannon in the book "The Wisdom of the Body". According to her, all physiological processes in the body work in a coordinated manner. And thus, if there are changes in one of the components of this equilibrium, then this must inevitably be reflected in the other. As it turned out, the nervous and immune systems, interacting with each other, are a mechanism that maintains homeostasis in the human body, the violation of which leads to disease [45]. In this regard, clinicians and researchers face new questions regarding the search for the mechanisms of neurological diseases and methods for their treatment.

Modern pediatric rheumatology has achieved indisputable success in studying the problem of juvenile arthritis (JA), however, when considering this complex and multifaceted pathology, debatable and unresolved issues remain. These include terminological aspects, issues of nosology, etiology and immunopathogenesis, clinical polymorphism of the onset and course of JA, and its outcomes. To date, the problems associated with the imperfection of the criteria for diagnosing this disease are coming to the fore, as a result, they use such an important indicator as ACCP - antibodies to cyclic citrullinated peptide, include an assessment of the nature of joint damage (number and localization), allow to fix the presence of active inflammation and adverse prognostic factors [31]. However, their use in pediatric practice is limited due to the variability of the clinical manifestations of the disease in childhood, as well as a significant difference from the symptoms in adults [25]. In the modern classification developed by ILAR, the former division of juvenile arthritis into 3 variants is preserved: systemic, polyarticular and oligoarticular. RF-positive and RF-negative arthritis are allocated to special rubrics. The nature of oligoarthritis is specified (persistent, aggravating) [7, 17]. The proposed classification makes it possible to unite under the general term "juvenile idiopathic arthritis" both various variants of JRA and a number of individual nosological forms of chronic arthritis in children - juvenile spondyloarthritis and even juvenile psoriatic arthritis. This allows for early diagnosis of JRA with the least number of errors [7, 13, 17]. The ILAR classification is used today almost all over the world. [7].

In practical healthcare, the diagnosis of RD and the statistical processing of the incidence structure are carried out in accordance with the International Classification of Diseases (ICD-10) [13,

17, 26, 30]. Given the absence of the term "juvenile idiopathic arthritis" in the ICD-10, its widespread use should be refrained. [13, 26, 27].

According to ICD-10, there are:

— M08 — juvenile (juvenile) arthritis;
— M08.0 — juvenile (juvenile) rheumatoid arthritis;
— M08.1 — juvenile spondylitis;
— M08.2 — juvenile arthritis with systemic onset;
— M08.3 — juvenile rheumatoid arthritis, polyarthritis;
— M08.4 — juvenile rheumatoid arthritis, pauciarthritis;
— M08.8 — juvenile chronic arthritis;
— M08.9 — juvenile chronic arthritis, unspecified;
— M09.0 — psoriatic arthritis.

Despite the abolition of the term "juvenile rheumatoid arthritis" in the international classification of arthritis in children, the allocation of JRA as an independent nosological form is dictated by time and clinical experience, since it is practically the only well-defined nosology in childhood that is present in the ICD-10 and the practice of a pediatric rheumatologist [27].

Etiology. Despite significant advances in the diagnosis and treatment of JRA, the etiology and pathogenesis of this disease remain largely unclear [4, 7, 13, 17, 18]. Allocate factors predisposing to the development of JRA, and factors contributing to the implementation of JRA [3, 4, 18]. Predisposing factors that have a tropism for the tissues of the joints are able to persist in them for a long time, causing immune inflammation. These include arthrotropic persistent viruses (retroviruses, oncornaviruses, parvoviruses) that are capable of “inactive” for a long time and only if they are initiated by any provoking factors can cause damage at the level of the cell genome [3, 4, 17, 18]. Coxsackie, Epstein-Barr viruses, cytomegalovirus, herpes viruses, parvoviruses can cause chronic viral infection against the background of immunological defects [3, 13, 18, 20]. The role of infection in the development of JRA has not yet been definitively proven [7, 8, 13, 17]. The role of intestinal infection, hemolytic streptococcus in the development of JRA is not recognized by a number of rheumatologists [13, 17].

There are data in the literature on the association of JRA with infection caused by Mycoplasma pneumoniae. Thus, IgG antibodies to mycoplasma in diagnostic titers in patients with JRA are detected more often (53%) than in the population [13]. The role of chlamydial infection in the development of chronic joint inflammation in children is not fully understood. About 80% of children with JRA are infected with Chlamydophila pneumoniae [13, 17]. Initiators of the development of inflammation can be frequent acute respiratory viral infections, hypothermia, insolation, preventive vaccinations, hormonal imbalance, joint injuries, adverse environmental factors, chronic psycho-emotional stress [3, 4, 13, 18]. Recently, post-covid complications of JRA in children have become more frequent ...

Hereditary predisposition. A number of authors suggest that an important role in the occurrence and development of JRA is played by genetic predisposition and features of the immune system [4, 7, 8, 13, 17]. Immunogenetic studies have confirmed fundamental differences between JRA and adult RA, which may be associated with histocompatibility antigens — DR4 и DRB1-04 [3, 7, 12, 13, 17]. As risk markers for the development of JRA are called A2, B27, A28, B35, DR5, DR8, DR1 [3, 13, 17]. According to the literature [13, 17], a protective (protective) effect is exerted by DR2 and DR7, which are significantly less common in patients with JRA. In addition, there is information about the association of HLA histocompatibility genes with JRA in general and with individual forms and variants of the disease [3, 13, 17]. So, as HLA A2, DR5, DR8 are markers of oligoarthritis in girls with uveitis, with antinuclear factor seropositivity [3, 6, 7, 13], HLA B27 is a marker of the risk of developing JRA in boys with oligoarthritis or limited polyarthritis, with a predominant damage to the joints of the lower extremities, with the presence of enthesopathy at school or adolescence [6–8, 13, 30], HLA DR4, DR5, DRB1-04 are markers of JRA in seropositive (RF+) girls with lesions of small symmetrical hand joints, with the onset of the disease at senior school age [6, 7, 13]. Many people are carriers of a genetic predisposition to RD, but do not suffer

from them. Viruses and bacteria are considered trigger factors that trigger the pathological process. Due to an inadequate response of the immune system to these pathogens, an inflammatory process develops in the joints, and sometimes in the internal organs. The so-called autoimmune diseases develop, which arise as a result of the aggressive effect of the immune system on its own organs due to its loss of the ability to distinguish between “own” and “foreign” cells and tissues. [3, 8, 13]. Thus, JRA is a multifactorial disease that develops as a result of a combination of genetic predisposition, immune system characteristics, and environmental factors [3, 4, 8, 12].

Immunopathogenesis of JRA. In the pathogenesis of RD, a key role is played by the processes of autoimmunity and autoinflammation associated with genetically determined and induced external factors, which is accompanied by a large percentage of diagnostic errors [2, 25, 27]. The high prevalence of JA in the population, the difficulty of early diagnosis, the frequent involvement of internal organs in the pathological process, the rapid development of disability and poor prognosis determine the relevance of the JA problem [2, 3, 18–20]. JRA (ICD-10: M08.0) refers to systemic inflammatory diseases of the connective tissue with a predominant localization of the process in the musculoskeletal system, which is based on dysfunction of the immune system, pronounced autoaggression, which leads to the development of pathological immune reactions. JRA develops before the age of 16, has a chronic severe progressive course and, as a rule, an unfavorable prognosis [2, 15, 17, 18].

One of the features of rheumatic diseases in children is the early development of disability, the degree of which, as well as the quality of life of the child, as well as the possibility of his social, psychological and professional adaptation in the future determine precisely the timeliness of the start and the adequacy of the treatment.

Juvenile idiopathic (rheumatoid) arthritis is the most severe and disabling form of chronic pathology in children and adolescents. Early diagnosis and treatment of idiopathic arthritis in children is one of the most pressing problems in pediatrics[1].

Considering the importance of this problem, the World Health Organization declared 2000-2010 "Decade (decade) of the fight against diseases of the bones and joints." In addition to the WHO, the initiator of the announcement of the Decade was the UN and more than 700 public organizations.

The purpose of the "Decade" is to change the current situation, draw the attention of the general public of all countries of the world to patients suffering from rheumatic diseases, and improve their quality of life (Sharapova O.V., Korsunsky A.A., 2004).

The use of existing methods of treatment of juvenile idiopathic arthritis does not exclude recurrence and progression of the disease and often does not prevent disability in children. Conducting immunodiagnostics allows you to control the immune status of a sick child, differentiate the approach to prescribing basic drugs and their effectiveness.

Most authors note an increase in the prevalence of diseases of the musculoskeletal system and connective tissue among children and adolescents. JRA remains the most common among childhood rheumatic diseases [3,4]. The incidence of JA ranges from 2 to 16 per 100,000 children under the age of 16. The prevalence of JA in different countries ranges from 0.05 to 0.6%. On the territory of the Russian Federation, the prevalence of JA in children under 18 years of age reaches 62.3, the primary incidence is 16.2 per 100 thousand, including in adolescents, respectively, 116.4 and 28.3, in children under 14 years of age - 45 .8 and 12.6. Arthritis (JA) is more common in girls. Mortality - within 0.5-1% [5]. According to foreign researchers, the prevalence of juvenile arthritis ranges from 3.8 to 165.1 per 100,000 children aged 0–16 years [6, 7]. 40 years have passed since the 1st Conference of the American Rheumatology Association on the problems of childhood rheumatic diseases, at which it was proposed to identify a new nosological unit - juvenile rheumatoid arthritis (JRA). During this time, ideas about the pathophysiological mechanisms of the disease have significantly expanded, new approaches to therapy have appeared. At the same time, the etiology of the disease remains not fully understood, which is mainly pathogenetic and symptomatic treatment.

Classification and terminology.

According to the modern classification of the World Antirheumatic League (ILAR), in 1997 the term "juvenile idiopathic arthritis" (JIA) was introduced. At the same time, the terms "JRA" and

"JXA" are excluded, and all chronic inflammatory diseases of the joints in children are combined under the term "JIA" [7, 27, 42]. JIA is a heterogeneous group of diseases that began before the age of sixteen, of unclear etiology, the leading manifestation of which is a chronic, predominantly progressive articular syndrome lasting more than 6 weeks [7, 25, 27]. At the heart of any classification are classification diagnostic criteria. In fact, a set of criteria is a description of the picture of a classic disease. In the USA, in the countries of the American continent, Japan, the North American JRA diagnostic criteria are widely used (Brewer E.J., Bass J., Baum J., Cassidy J.T., 1977; Cassidy J., Petty R., 1990) [25, 32, 42]. These include: 1) the onset of the disease before the age of 16; 2) arthritis of one or more joints, defined as swelling or effusion; in addition, it is necessary to take into account the presence of two or more of the following signs: - limited range of motion, - sensitivity or pain when moving, - increased local temperature; 3) the duration of the illness is at least 6 weeks; 4) the type of onset of the disease during the first 3–6 months is classified as: - polyarthritis of 5 or more joints, - oligoarthritis of 4 or less joints, - systemic onset (intermittent fever, rheumatoid rash, arthritis, visceral pathology); 5) other RH are excluded. A number of scientific centers of the USSR and Eastern European countries in 1979 developed JRA diagnostic criteria, called East European [13, 25, 26]. In contrast to the North American criteria, these criteria included characteristic radiological signs, biopsy data of the synovial membrane, and the presence of RF in the blood serum. However, the criteria developed have also been subject to continuous improvement. In 2008 S.O. Salugina et al [25–27] published the results of a study of the reliability and specificity of certain JRA criteria. The authors came to the conclusion that to differentiate JRA from JCA, at least 8 signs of the Eastern European criteria must be present, with the presence of the first sign obligatory and the exclusion of RD of another nosological affiliation. These criteria are in demand and are used by pediatric rheumatologists in some countries. In world practice, the diagnostic criteria for RA of the American College of Rheumatology (ACR/EULAR, 1987), improved in 2010, are generally accepted [25, 31]. They are designed specifically for early diagnosis, based on a combination of statistical calculations and expert assessment, environment, defects in the activation of the acquired and innate immune response [12, 22–24]. With active inflammation in children with different types of JRA, involvement of almost all parts of the immune system, activation of the cellular and humoral parts of immunity are characteristic [3, 4, 13, 17, 24]. The pathogenesis of JRA, especially sJA, is dominated by autoinflammatory mechanisms due to innate immune reactions, while in adults with RA, autoimmune processes predominate [10, 23, 28, 35, 41].

The immune system is a unique self-regulating organization consisting of various populations and subpopulations of lymphoid cells, constantly interacting with each other. However, their vital activity, activation, proliferation and differentiation largely depend on other systems of the body, primarily on the nervous system. Between the immune and nervous systems, an interaction has developed and is constantly being carried out, with the help of which they mutually control their functions. Their integration with all other functions ensures the existence of the organism as a whole. Particular attention of researchers is attracted by the participation of immune mediators in neuroimmune interaction. It is believed that in addition to performing their specific functions within the immune system, immunity mediators can also carry out intersystem communications. This is evidenced by the presence of receptors for immunocytokines in the nervous system. The largest number of studies is devoted to the participation of IL-1, which is not only a key element of immunoregulation at the level of immunocompetent cells, but also plays a significant role in the regulation of CNS function [7, 8].

There are data on the production by cells of the central nervous system (microglia and astrocytes) of such cytokines as IL-1, IL-6 and TNF-alpha. The production of TNFalpha directly in the brain tissue is specific for a typical neuroimmunological disease - multiple sclerosis (MS). An increase in the production of TNF-alpha in a culture of isolated LPS-stimulated monocytes/macrophages is most clearly detected in patients with an active course of the disease[8]. The possibility of participation in the production of interferons of brain cells, in particular neuroglia or ependyma, as well as lymphoid elements of the vascular plexuses, has been established. In the process of formation of the immune response, the nerve endings in the corresponding lymphoid

organs are activated. Initiating signals can be transmitted from the immune system to the nervous system in a humoral way, including when cytokines produced by immunocompetent cells directly penetrate into the nervous tissue and change the functional state of certain structures, and the penetration of immunocompetent cells themselves through the intact BBB(blood-brain barrier) with subsequent modulation of the functional state of nerve structures is described.

The influence of the immune and nervous systems on each other is realized through the receptor structures of cells, the interaction of which creates “receptor-receptor” bonds and thus organizes the molecular mechanism for the joint operation of both systems [7,8]. Cell functioning and signaling information are provided by mediators and neurotransmitters in both systems, information is exchanged between the nervous and immune systems using cytokines, steroids and neuropeptides [9] .

Thus, the commonality and interconnection of the nervous and immune systems, the similarity between their structures and functions, and the development of a new direction in modern immunology - neuroimmunology [7,8] have been proved. A wide range of neurological symptoms in autoimmune systemic diseases allows us to consider them as model systems for studying the pathogenetic role of immune mechanisms of damage to the central and peripheral nervous system [10].

The pathogenesis is based on defects in T- and B-cell immune responses, leading to hyperproduction of pro-inflammatory cytokines and a wide range of organ-specific autoantibodies that induce inflammation and destruction of joints and other tissues of the body [17, 22–24, 30]. According to modern concepts, various cells and effector molecules of the immune system are involved in the pathogenesis, however, activated CD4+ T-helper (Th) cells play a key role in the development of synovial inflammation and joint destruction, causing activation of B-lymphocytes and macrophages, as well as increased production of pro-inflammatory cytokines and the development of chronic inflammation [1, 12, 17, 23, 24, 37]. An important feature of the activation of CD4+ T cells is the polarization of the immune response according to the Th1 type, with the predominance of the synthesis of pro-inflammatory cytokines over anti-inflammatory cytokines [19, 22, 24, 30, 37, 38]. Defects in T-regulatory cells play an important role in the violation of immune tolerance to self-proteins in RD [12,22–24]. Cytokines, being low molecular weight protein molecules, provide the process of intercellular communications during inflammation, immune response and intersystem interactions, participate in the regulation of normal biological processes in the body [12, 17, 19, 29, 37]. Conventionally, cytokines are divided into several groups, among which are pro-inflammatory (interleukins (IL)-1, -6, -8, -17, tumor necrosis factor α (TNF-α), interferon-γ, chemokines) and anti-inflammatory cytokines (IL- 4, -10, -13, growth factor) [1, 17, 19, 37]. Hyperproduction of pro-inflammatory cytokines underlies damage to the synovial membrane of the joint, cartilage, as well as the development of systemic manifestations of the disease. Among a large number of pro-inflammatory cytokines, TNF-α, IL-6, IL-1β occupy a central place in the development of rheumatoid synovitis [4, 12–14, 19, 23]. TNF-α is a typical pro-inflammatory cytokine leading to the development of chronic inflammation, destruction of cartilage and bone, and loss of bone tissue [2, 7, 12, 19, 32]. This is an "early" cytokine that appears at the onset of the development of an inflammatory response. [29]. TNF-α can directly cause an inflammatory effect, as well as induce the induction of other pro-inflammatory cytokines (IL-1, -6, -8) [2, 12, 19, 29]. In addition, TNF-α promotes the production of metalloproteinases (especially stromelysin and collagenases), which play a significant role in the destruction of bone and cartilage tissue [4, 12, 17, 29]. From a morphological point of view, JRA marker is cartilage erosion, and the number and quality of erosions correspond to the severity of the process. The key cytokine in the immunopathogenesis of sJA is IL-6 [5, 7, 10, 16, 28, 35]. Its hyperproduction is associated with such extra-articular manifestations of the disease as fever, hypochromic anemia, thrombocytosis. IL-6 stimulates the production of acute phase proteins (C-reactive protein (CRP), fibrinogen, amyloid A) by hepatocytes, the secretion of hepcidin, which reduces the absorption of iron and inhibits its release from macrophages, which leads to iron deficiency and the development of anemia [5, 7, 16, 22, 28, 39]. Such manifestations of the systemic action of IL-6, such as fever and morning stiffness, are associated with the daily rhythm of the

secretion of this cytokine [10, 16, 22, 28, 29]. IL-6 stimulates the differentiation of osteoclasts, activates them, enhances bone resorption and, as a result, promotes the development of generalized osteoporosis, erosive changes in the joints [5, 12, 22, 29, 35]. IL-6 promotes the proliferation and differentiation of B-lymphocytes into mature plasma cells that secrete autoantibodies (RF, antibodies to citrullinated proteins) [12, 22, 29]. IL-6 blocks the production of adrenocorticotropic hormone, cortisol, growth hormone, which leads to the development of fatigue, drowsiness, depression and stunting. The development of amyloidosis in this disease is also associated with the activity of this cytokine [12, 16, 22, 28, 29, 35]. Stimulation of the production of leptin, a hormone that contributes to the formation of anorexia, has also been noted [22]. IL-1 also has a pro-inflammatory effect. IL-1β causes an increase in the proliferation of fibroblasts, an increase in the production of collagenases, metalloproteinases, stimulation of the penetration of synovial fibroblasts into the cartilage in the pannus area, induction of the synthesis of IL-6, -8, IFN-γ [12, 29]. Plays the role of IL-1 in the genesis of sJA [7, 17, 29, 32, 41]. At the same time, the high failure rate in the treatment of patients with sJA with anti-TNF drugs indicates that the role of the cytokine TNF-α in sJA is not decisive in the development of the pathological process [29, 35]. The state of the cytokine network in various JRA variants has not been fully studied. Some authors point to the maximum increase in IL-6 and -1 in sJA compared with other JRA variants [29, 32, 35, 41]. A significant increase in serum TNF-α was found in patients with polyarticular JRA [29, 43, 44]. TNF-α plays a role in the chronization of the process [4]. The content of TNF-α is significantly higher in patients with high RF values [12]. A high level of TNF-α was also found in sJA [4, 29, 44]. TNF-α is important in the pathogenesis of joint damage in all forms of JRA, but is not directly related to the systemic manifestations of the disease [5, 29, 32, 41, 43]. Some authors [29, 40] point out that the concentration of TNF-α in the blood depends more on the activity than on the form of the disease. There is also a point of view that such a severe complication of sJA as macrophage activation syndrome is associated with a significant increase in the level of TNF-α, which is confirmed by the successful use of monoclonal antibodies to TNF-α in the treatment of this condition. However, the development of macrophage activation syndrome as a complication of anti-TNF therapy has been described [29, 35]. The level of pro-inflammatory cytokines correlates with the activity of inflammation and reflects the severity of the disease, and also determines the further prognosis [1, 10, 29, 40]. The relationship between the level of pro-inflammatory cytokines (IL-1β, -6), chemokines (IP-10) and clinical and laboratory indicators of disease activity (erythrocyte sedimentation rate, CRP, number of affected joints) was revealed [1, 10, 14, 29, 40]. A higher level of IL-6 and IP-10 is determined in the group of patients with high activity of the pathological process and the group of patients seropositive for IgM RF, antibodies to citrullinated proteins [1, 29]. Some authors consider the presence of CRP and a high level of IL-6 as a prognostic marker of the progressive course of the disease and the early development of systemic osteoporosis [3, 29]. In patients with oligoarticular JRA, elevated levels of IL-4, -10 are detected, which is associated with the absence of significant erosive changes in the joints and a more favorable course [17, 26]. Due to the fact that oligoarticular JRA is a rather limited inflammatory process with the development of inflammation in a small number of joints, the levels of pro-inflammatory cytokines in it are lower than in systemic and polyarticular JRA [29, 43]. In children with RD, a significant role is played not by the absolute amount of production of certain cytokines, but by an imbalance of pro- and anti-inflammatory cytokines [17, 19, 29], which can occur under the influence of a damaging factor, such as a viral infection. In most children, after the elimination of the damaging factor, the normal ratio of cytokines is restored, and in children with a genetic predisposition, the imbalance persists, which leads to the development of RD [1, 17, 19, 29]. Thus, the development of chronic inflammation in RD is mediated by a variety of disorders in the immune system, inflammation activity correlates with changes in the synthesis of a wide range of immune mediators. According to modern concepts, the pathogenesis of immunoinflammatory RD is based on a combination of genetically determined (HLA system, polymorphism of cytokine genes) and acquired defects (imbalance) of immunoregulatory mechanisms that limit the pathological activation of the immune system in response to potentially pathogenic environmental factors, such as infections, microbiota disturbance. intestines, hypothermia, insolation [12, 22, 23, 38]. Terminology and modern

classification are still the subject of constant debate among both scientists and practicing rheumatologists [25–27].

The pathology of the nervous system in rheumatic diseases (RD) often determines the prognosis, the clinical picture of the disease and the quality of life of patients, and also requires the mandatory combined use of basic anti-inflammatory therapy, angio- and neuroprotectors. In rheumatoid arthritis, the most threatening central neurological complications in the form of cervical myelopathy, hydrocephalus, and vertebrobasilar occlusion with impaired function of stem structures occur as a result of atlantoaxial displacement of the arthritically affected joint of the same name, and the degree of subluxation of the atlantoaxial joints is more pronounced in patients with RA receiving corticosteroids [6].

Damage to the nervous system in rheumatoid arthritis also manifests itself in the form of peripheral polyneuropathy. Patients develop paresthesia, a burning sensation in the region of the lower and upper extremities, tactile and pain sensitivity decreases, movement disorders appear. With the active course of rheumatoid arthritis, symptoms of polyneuritis are sometimes observed with severe pain in the limbs, sensory or motor disorders, and muscle atrophy. Possible disorders of the autonomic nervous system, manifested by hyper- or hypothermia, increased sweating, trophic disorders.

Authors E.V. Baranov, O.V. Paramonova, I.P. Gontar, L.A. Maslakova, I.A. Zborovskaya from the Federal State Budgetary Institution of the Russian Academy of Medical Sciences "Research Institute of Clinical and Experimental Rheumatology", Volgograd, 2GBOU VPO "Volgograd State Medical University" myelin basic protein (MBP); and protein S-100. Elevated levels of antibodies (AB) to MBP were detected in 39.4% of patients with rheumatoid arthritis (RA), and antibodies to the S-100 protein in 32.4% of RA patients. In all cases, the studied indicator correlated with the degree of activity of the pathological process. High levels of antibodies to MBP and S-100 protein in RA were associated with damage to the central nervous system (CNS) and peripheral nervous system (PNS). A decrease in the content of serum antibodies to MBP and to the S-100 protein during treatment allows using this indicator as an additional criterion for evaluating its effectiveness.

Outcomes and forecast

1. All children with an early onset of RF-negative polyarthritis have an unfavorable prognosis. Adolescents with RF-positive polyarthritis have a high risk of developing severe destructive arthritis, disability due to the state of the musculoskeletal system.
2. In 40% of patients with early-onset oligoarthritis, destructive symmetrical polyarthritis develops. In patients with a late onset, the disease can transform into ankylosing spondylitis. 15% of patients with uveitis may develop blindness.
3. A wide range of neurological symptoms in autoimmune systemic diseases allows us to consider them as model systems for studying the pathogenetic role of immune mechanisms of damage to the central and peripheral nervous system.

SUMMARY: In all forms of JIA, there is a change in the cytokine and cellular status in the blood serum. The severity of these changes depends on the variant and the degree of activity of the inflammatory process.

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