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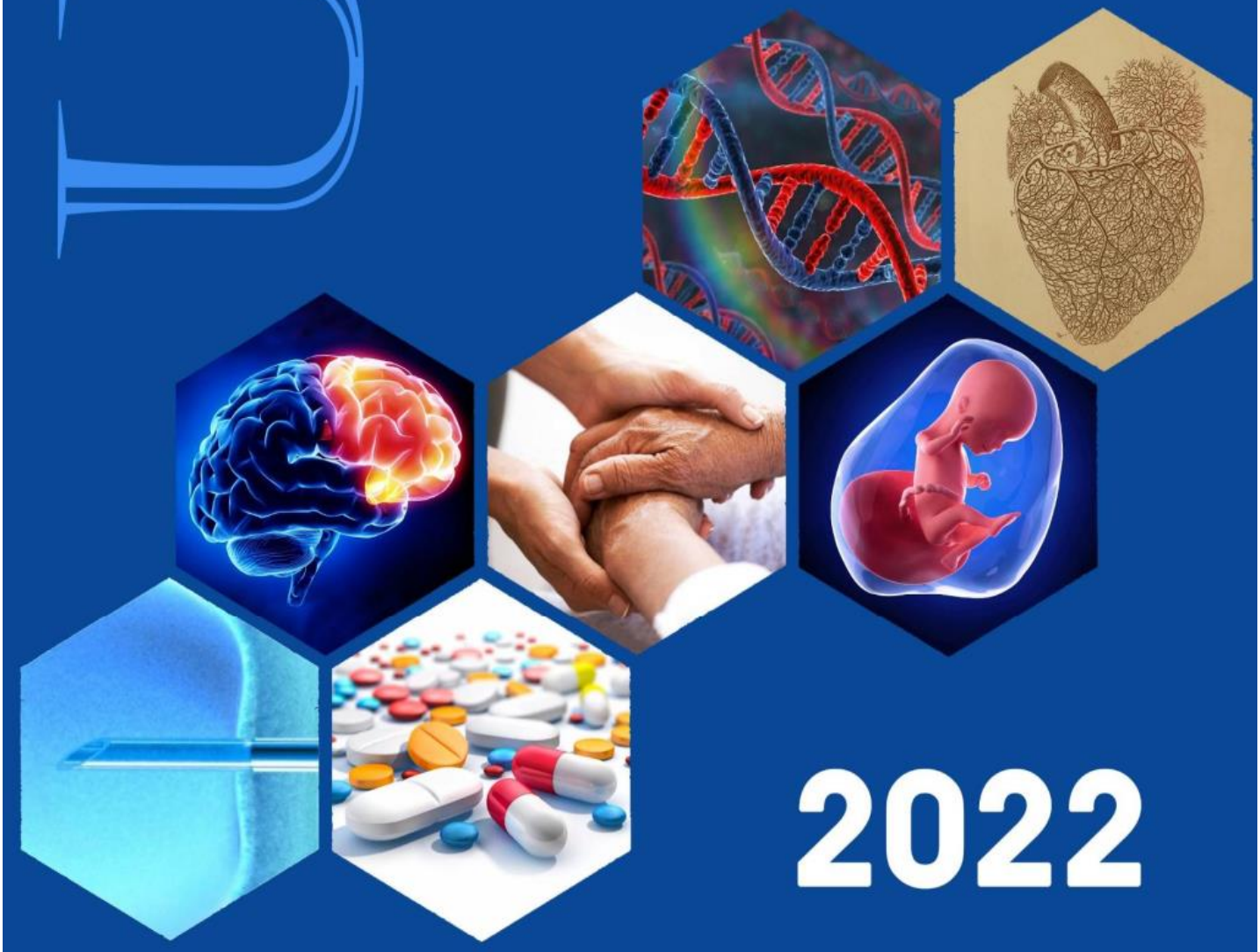

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MODERN DIAGNOSTICS OF JOINT DAMAGE IN PATIENTS WITH REACTIVE ARTHRITIS

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ABSTRACT

In the world, the problem of diagnosing reactive arthritis has not yet been solved, and several studies are being carried out to study the practical significance of an accurate diagnosis of this disease in the early stages. We defined the mechanism of cartilage early destruction in the development of apparent structural alterations in joints in reactive arthritis and its role in the deterioration of articulate syndrome.

Keywords: reactive arthritis, joint syndrome, destruction, structural alterations, Chlamydia trachomatis, cartilage, pro-inflammatory cytokines, synovial liquid, enthesopathy, synovitis

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СОВРЕМЕННАЯ ДИАГНОСТИКА ДЕСТРУКЦИИ СУСТАВА У БОЛЬНЫХ РЕАКТИВНЫМ АРТРИТОМ

АННОТАЦИЯ

В мире до сих пор проблема диагностики реактивного артрита не решена, и проводится ряд исследований для изучения на практической значимости точной диагностики данного заболевания на ранних стадиях. Обоснована роль механизма ранней деструкции сустава в развитии выраженных структурных изменений и при прогрессировании суставного синдрома при реактивном артрите.

Ключевые слова: реактивный артрит, суставной синдром, деструкция, структурные изменения, Chlamydia trachomatis, хрящ, провоспалительные цитокины, синовиальная жидкость, энтезопатия, синовит

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РЕАКТИВ АРТРИТГА ЧАЛИНГАН БЕМОРЛАРДА БЎҒИМ ДЕСТРУКЦИЯСИНИНГ ЗАМОНАВИЙ ТАШХИСОТИ

АННОТАЦИЯ

Дунёда реактив артритни ташхислаш муаммоси ҳозирги давргача тўлиқ ҳал қилинмаган бўлиб, унинг эрта даврида аниқ ташхислашнинг ўзига хос томонларини амалий жиҳатдан ўрганиш мақсадида қатор илмий-тадқиқотлар амалга оширилмоқда. Реактив артритда бўғимлардаги яққол структур ўзгаришларнинг шаклланишида тоғайнинг эрта деструкцияланиш механизми ва унинг бўғим синдромини авжланишидаги ўрни асосланган.

Калит сўзлар: реактив артрит, бўғим синдроми, деструкция, структур ўзгаришлар, Chlamydia trachomatis, тоғай, яллиғланиш олди цитокинлари, синовиал суюқлик, энтезопатия, синовит

Introduction. It is known that reactive arthritis (ReA) is considered an immune-inflammatory articulate pathology, which appears at the same time as an intestinal or urinary infectious process or soon after it [5]. Among rheumatic diseases, ReA occupies one of the leading places according to its prevalence. Prevalence of ReA in the structure of rheumatic diseases in various countries of the world varies from 8 to 41% [10] and in the majority of cases people aged 15-40 years old suffer from it [14]; that reflects the urgency of the problem.

ReA is characterized by a chronologic link with infection: arthritis develops within the convalescence period or soon after recovery (from 1 week to 1 month). When more than a month passed after recovery chronological link is considered to be lost and ReA diagnosis is scarcely probable. Within an acute stage of the infectious process, ReA develops rarely (but in the case of hematogenous infection of joints there can be infectious arthritis) [15].

Based on all aforesaid it can be concluded that the major agent in the development of ReA is an infectious one, causing immune response with the production of antibodies circulating in the blood and synovial liquid. A high level of antibodies preserved for a long time indicates the presence of infectious agents from one side and the persistence of microbe antigens in tissues and synovial liquid on the other. At the same time, the immune response is directed both against the infectious agent and its tissue cells, causing their damage. Cross reacting antibodies decrease the immune response to the infectious agent, by these means preventing complete elimination and promoting its persistence [1,8]. Besides that, multiple references mention the significance of genetic predisposition [2,4,5,6,7]. HLA–B27 association with urogenic arthritis is observed in 80-90%, and its association with post enterocolitic one in 56%. However, the role of HLA –B27 in the development of ReA is not studied well yet. At the same ReA “sterility” is under discussion, as improvement of methods allowed isolation of certain microbe antigens and even micro organisms able to reproduce [6] from articulate tissues and synovial liquid.

The most characteristic feature of ReA is inflammation of peripheral joints (asymmetric mono oligoarthritis) and periarticular soft tissue structures (enthesopathy), in other words, an articulate syndrome in this pathology is the dominant one. Its expression determines the progression and severity of the disease. There are variants of an articulate lesion such as transitory arthralgia, synovitis, erosive arthritis, arthrosoarthritis, joint ankylosis. Arthritis can start acute, be accompanied by strong pain and common manifestations (fever, shivers, feebleness). There are sub-acute variants of articulate syndrome with moderate exudative alterations in joints. Joints of lower limbs (knee, ankle, feet) are damaged in most cases. There are no “exclusion” joints for Reuter’s disease, so any joint can be involved in the pathological process. Damages to sacral-ileac joints (sacroiliitis) and vertebral joints (spondyloarthritis) are possible. Special attention should be paid to a manifestation of articulate syndrome with damage to the synovial membrane of joints, its hyperplasia and fast increase of synovial tissue volume, accompanied by progressing destruction of cartilage and damage of tendon and alteration in muscles, playing a leading part in the change of articulate structures. Consequently, that kind of damage leads to stiffness in joints and, as a result, a decrease in the life quality of the patients.

Nowadays ReA modern laboratory diagnosis includes a definition of a wide range of biomarkers (BM) such as auto antibodies, indicators of acute inflammation, cytokines, endothelial

activation markers, lymphocyte subpopulations and genetic markers in the blood, synovial liquid and synovial tissue [2, 3]. These provide an assessment of common reactions to infection, to a certain degree reflected in the stage of the articulate syndrome. However, there is no possibility of an accurate prognosis, and those markers do not serve as predictors of articulate structures destruction in ReA. That is why, in modern times special attention is paid to the search for early markers of articulate structure damage, revealing signs of articulate tissue damage (synovial membrane, cartilage and underlying bone tissue) at the initial stage of the disease; providing an assessment of the stage of damage and prognosis; serving the basis for the prescription of therapy adequate to the stage of pathological process; and monitoring of the performed therapy [7].

In modern time there is work on BM which allow quantifying joint remodeling and progress of the disease. Molecules and molecular fragments, present in cartilage, bone and synovial membrane, as a rule, are very important. These can be specific for one type of articulate tissue or be common for all. Lots of studied BM are linked with collagen metabolism in cartilage or bone or aggrecan metabolism in cartilage. Another BM is linked with non-collagen proteins, inflammation, and fibrosis. According to the stage of disease BM in ReA can be classified as biomarkers used in tests, prognostic, intervention efficiency markers, diagnostic and safety markers [8].

Among BM a special interest is paid to the study of modern cartilage BM, cartilage oligomeric matrix protein (COPM) in blood serum, as, in our opinion, this protein is the most perspective from the point of view of its diagnostic value as a BM of early cartilage destruction in rheumatic diseases, and particularly ReA. So, due to its great diagnostic value for patients with ReA and OA, there was a lot of research dedicated not only to the study of its specificity and sensitivity, but also dependence of its concentration on the activity and stage of the disease. Nowadays, a direct correlation between disease activity according to DAS 28 in patients with ReA and COMP is proven [10]. Most published works confirm that serum COMP provides important information about metabolic alterations occurring in the cartilage matrix in case of articulate diseases. These studies showed that serum COMP correlates with cartilage degradation and serves to be a potential prognostic marker in inflammatory articulate pathologies, such as OA and ReA. Results also demonstrate a link between elevated serum COMP and progressing joint cartilage destruction, observed using the radiologic method [7, 11].

COMP was first detected in cartilage tissue by Professor Dick Heinegård's research team at Lund University, Sweden, where they described it as a pentamer protein. According to these data [10], that protein consists of five similar subunits linked by disulfide bonds with a common molecular mass equal to 434 kDa. However, recently it was determined that COMP is found in tendon tissues and synovial membranes too. COMP was not found in the culture of connective tissue of the skin and pulmonary tissue cells. It is well known, that during disease protein fragments formed in case of articulate cartilage destruction go-to joint fluid. Some of these proteins, such as COMP, later appear in the blood and can be used for the monitoring of cartilage destruction in inflammatory joint diseases, such as rheumatoid arthritis and osteoarthritis. Quantitative correlation between COMP concentration in blood serum and cartilage degradation stage, determined based on changes on x-ray as a surrogate clinical final point was defined. Later it was confirmed by an experiment with induced arthritis in animal models, where serum COMP had a great correlation with the severity of arthritis and clinical assessment of cartilage damage and histological signs of cartilage erosion. High serum COMP considered together with other laboratory and clinical data is useful for the assessment of the risk of aggressive tissue destruction in the case of pathologies such as rheumatoid arthritis. Indications for blood COMP definition are the following: monitoring of rheumatoid arthritis and osteoarthrosis therapy; differential diagnosis of inflammatory articulate diseases. That protein is also a sensitive marker of age-related change. Its amount in cartilage tissue increases with age. That is why interest in it is growing among scientists, as COMP functions are not clarified completely yet. It is supposed to serve as a linking unit with proteoglycans. Taking into account that at the places where collagen fibrils are formed we can find chondrocalcin, there is a probability that its function is linking collagen fibrils to each other. According to reference data [12], COMP binds collagen I, II and IX types, playing an important role in the maintenance of the properties and integrity of the collagen network.

Thus, COMP molecules connect collagen fibers to each other, by these means stabilizing the collagen network in cartilage tissue. COMP is involved in the development of cartilage, bone metaphysis; its dysfunction leads to the development of OA [10]. Therefore, in cases accompanied by cartilage damage matrix proteins go to synovial liquid and then to blood [12]. Moreover, COMP functions, as a member of the thrombospondin family, are not studied. It is contained in the growth plates proliferation area. So in the study of growth zone using immune cytological chemical methods with polyclonal antibodies, it was registered, that the greatest COMP activity was determined in the zones of growing cartilage proliferation in the cellular local matrix, while the least one was registered in the pericellular and interlocal matrix. A low concentration of the protein is found in resting and hypertrophic chondrocytes. Based on these data we can suppose, that COMP can be considered a marker of normal differentiation of proliferating chondrocytes. In joint cartilage that protein is contained in small amounts. It is proven, that rise of serum COMP can be a biochemical marker of osteoarthrosis complicated by synovitis [11].

Literature data confirm [7], that serum COMP correlates with the presence of OA, age, stage of disease, gender, and the number of involved joints. COMP causes pseudoachondroplasia (PSACH) and multiple epiphysis dysplasia (MED). According to the latest data [8], COMP gene mutations can determine the development of joint hypermobility. That condition is one of the early OA risk factors. COMP gene mutations, besides various chondrodysplasia, cause myopathy and pathologies of ligament apparatus in mice. The most severe phenotypes of PSACH are conditioned not only by COMP gene mutation but also COL9A3 gene defect, leading to more unfavorable clinical progression of the disease; there is also an association with gender. Among the studied patients with PSACH, 81% had COL9A3 and COMP gene mutations, 61% of them combined, and 30% only in the COMP gene [6]. Thus, alterations in COMP structure affect the condition of the human ligamentous apparatus as a whole.

Studies showed that the definition of high COMP concentration is a more sensitive diagnostic method in cases of cartilage destruction, than changes on x-ray images. Excretion of COMP to blood correlates with cartilage tissue exchange. It is probably because the COMP molecule plays a central role in cartilage tissue stability, and, consequently, it goes to blood before morphologically expressed cartilage destruction [7, 11].

The rise of COMP can be observed not only in the case of pathology. For example, marathon runners have risen COMP concentration in blood at increased loads. Despite the actions taken in the field of biochemical markers definition, now there are no markers and their combinations, which indicate reliably strong and consequent correlations with corresponding clinical and structural parameters of OA and RA, to justify biochemically their wide application in studies and clinical practice [3].

Conclusion. An arsenal of clinical strategies for the diagnosis of articulate lesions is wide enough, but not all of these methods are equally descriptive. So, radiological research methods are visual only at RA late stages; radioisotopic ones give a notion of the location of areas with intensive blood flow, but they are not specific. Implementation into clinical practice of magnetic resonance imaging and ultra sound extended capabilities of nosology diagnosis [9]. However, for many years in the literature, there is a discussion on the character of the echographic structure of joint cartilage, interrelations of stages, the activity of the process, and alterations in intra articulate tissues in RA. In the early stages, it is involved in the immune pathological process under the influence of high concentrations of pro-inflammatory cytokines on chondrocytes, promoting enzymatic resorption of the matrix. As a result cartilage counter is not more even; it becomes dentate. There is the formation of destructive loci in the areas between the synovial membrane and hyaline cartilage, covering joint surfaces, and in the area of cartilage and tendon junction [12]. That is why a diagnosis of early RA is based on the complex analysis of clinical (MRI or arthroscopic) and laboratory data, while traditional x-ray imaging of a joint is not applicable for that purpose. Several studied RA biomarkers possess a proven potential to intensify diagnostic capabilities in the perspective, but for now, they still serve to be a subject of scientific studies. Consequently, based on all the aforesaid, it becomes evident, that suppression of inflammation and prevention of articulate structures destruction together with the

decrease of pro-inflammatory cytokines, prostaglandins, synovial membranes enzymes, proteolytic enzymes synthesis, is one of the priority directions in OA therapy. That is why, the study of the role of cartilage oligomeric matrix protein in the mechanisms of joint cartilage degradation, and its correction are of both scientific and practical interest.

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