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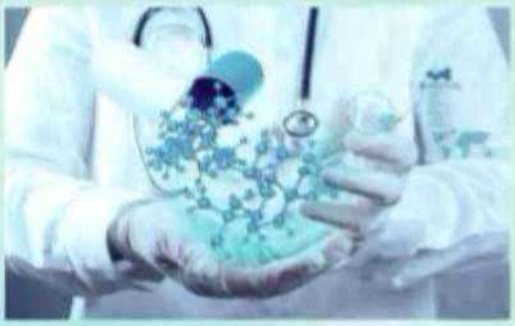

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USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) IN ENTEROPATHIES IN PATIENTS WITH RHEUMATOID ARTHRITIS

(Review article)

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✓ ***Resume***

Enteropathy is a common condition in patients with rheumatic diseases, which can develop secondarily due to the disease itself or drugs used in treatment. Patients with rheumatoid arthritis are one of the pressing problems of modern medicine. The prevalence and frequency of gastrointestinal inflammation in rheumatoid arthritis risk factors for chronic gastrointestinal disease (GIT) are more common than in diagnosed rheumatoid arthritis. As a result, early diagnosis of gastrointestinal inflammation in patients with rheumatoid arthritis has important clinical and prognostic significance. Also, the occurrence of chronic inflammation in rheumatoid arthritis primarily depends on the duration of the disease and the nature of the inflammation

Key words: Enteropathy, rheumatoid arthritis, dyspepsia, gastrointestinal tract, chronic enteritis

ПРИМЕНЕНИЕ НЕСТЕРОИДНЫХ ПРОТИВОВОСПАЛИТЕЛЬНЫХ СРЕДСТВ ПРИ ЭНТЕРОПАТИЯХ У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ

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✓ ***Резюме***

Энтеропатия - распространённое состояние у пациентов с ревматическими заболеваниями, которое может развиваться вторично из-за самого заболевания или лекарственных препаратов, используемых в лечении. Пациенты с ревматоидным артритом являются одной из актуальных проблем современной медицины. Распространенность и частота воспаления желудочно-кишечного тракта при ревматоидном артрите факторы риска хронического заболевания желудочно-кишечного тракта (ЖКТ) встречаются чаще, чем при диагностированном ревматоидном артрите. В результате ранняя диагностика воспаления желудочно-кишечного тракта у больных ревматоидным артритом имеет важное клиническое и прогностическое значение. Также возникновение хронического воспаления при ревматоидном артрите в первую очередь зависит от длительности заболевания и характера воспаления

Ключевые слова: Энтеропатия, ревматоидный артрит, диспепсия, желудочно-кишечный тракт, хронический энтерит

REVMATOID ARTRITLI BEMORLARDA ENTEROPATIYADA NOSTEROID YALLIG'LANISHGA QARSHI PREPARATLARNI QO'LLASH

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✓ ***Rezyume***

Enteropatiya kasalligi revmatik kasalliklar bilan og'rigan bemorlarda ko'p uchraydigan holat bo'lib, kasallikning o'zi yoki davolashda ishlatiladigan dorilar tufayli ikkilamchi rivojlanishi mumkin. Revmatoid artrit bilan og'rigan bemorlar zamonaviy tibbiyotning dolzarb muammolaridan biri bo'lib hisoblanadi. Revmatoid artritda oshqozon-ichak traktining yallig'lanishi tarqalganlik va oshqozon-ichak trakti (OIT) surunkali kasalligining xavf omillari revmatoid artrit tashxislangandan ko'ra ko'proq uchraydi. Natijada erta tashxis qo'yish revmatoid artrit bilan kasallangan bemorlarda oshqozon-ichak traktining yallig'lanishi muhim klinik va prognostik ahamiyatga ega. Shuningdek, revmatoid artritda surunkali yallig'lanishning paydo bo'lishi birinchi navbatda, kasallikning davomiyligi va yallig'lanish xususiyatiga bog'liq jarayon

Kalit so'zlar: Enteropatiya, revmatoid artrit, dispepsiya, oshqozon ichak trakti, surunkali enterit

Relevance

Rheumatoid arthritis (RA) is the most common inflammatory joint disease with a prevalence of about 1% in the population, the etiology and pathogenesis of which have not yet been definitively established. Repeated attempts to find the infectious cause of RA have been unsuccessful; however, the possible trigger role of various infectious agents in the development of this nosology continues to be studied. Due to the similarity of a number of clinical manifestations of RA exacerbation with the symptoms of infectious diseases, infectious agents have been attracting the attention of rheumatologists for many years. [2].

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the development of chronic destructive polyarthritis with frequent involvement of other systems in the pathological process. Extraarticular systemic lesions in RA can have a serious impact on the prognosis of the disease [4]. Pathology of the intestinal organs is detected in 13-62% of rheumatoid arthritis patients and occupies an important place among the extra-articular manifestations of this disease. Most researchers consider microbial translocation as a pathological process that develops as a result of severe organ damage or the development of multiple organ failure. RA and Gut Microbiota: Recent studies suggest a potential link between gut dysbiosis (altered gut microbiota) and RA development, supporting the "gut-joint axis" hypothesis. Bacterial Translocation in RA: Increased intestinal permeability ("leaky gut") in RA patients may facilitate bacterial translocation, contributing to systemic inflammation. Therapeutic Implications: Probiotics, dietary modifications, and gut-targeted therapies are being explored as potential adjunct treatments for RA. At the same time, a number of authors believe that translocation of bacteria from the gastrointestinal tract can occur even in the normal physiological state of the macroorganism. In this case, on the way to the mesenteric lymph nodes, extracellular or intracellular bacteria can be neutralized by the host's defense system.

Materials and methods

Although the lymphatic system is an important obstacle, some bacteria can also reach the portal system and enter various organs through it [17]. NSAIDs are convenient and affordable, but unsafe. NSAIDs can cause various adverse reactions, among which the most common is the development of pathology of the gastrointestinal tract [6, 9].Given the widespread use of NSAIDs, these complications pose a serious medical and social problem [6, 9, 16]. So, in 2008-2011, 133,210 cases of serious adverse reactions related to NSAIDs were recorded in the USA [11]. Taking these drugs increases the risk of gastrointestinal bleeding by more than 4 times (0.5-1.5 episodes per 100 patients per year) and doubles the risk of death from this cause among "users" of NSAIDs in comparison with the general population [6, 9]. In particular, R. Thomsen et al. It has been shown that gastrointestinal bleeding caused by NSAID use is fatal in one in ten patients, and gastrointestinal perforation in one in three patients [12, 13]. Long-term NSAID use significantly increases GI risks, even in patients without prior symptoms. COX-2 selective inhibitors (e.g., celecoxib) were developed to reduce GI toxicity but may still pose risks, especially in high-risk patients. Proton pump inhibitors (PPIs**)** and misoprostol are often co-prescribed to mitigate NSAID-induced GI damage. Chronic enteritis in rheumatoid arthritis (RA) patients primarily develops due to systemic immune and vascular disturbances characteristic of RA, including microcirculatory damage and lymphoplasmacytic infiltration. The disease progresses through stages typical of enteritis (e.g., superficial and chronic phases). Additionally, NSAIDs and glucocorticosteroids

exacerbate mucosal damage in the upper intestinal tract. Histologically, active enteritis in RA is marked by: Severe inflammatory infiltration (lymphocytes, plasma cells, and neutrophils in the epithelium). Neutrophil accumulation, indicating acute-on-chronic inflammation. NSAID use in RA frequently leads to gastrointestinal (GI) adverse effects**,** ranging from mild dyspepsia to life-threatening complications (bleeding, perforation). NSAIDs disrupt mucosal defense mechanisms by: Inhibiting prostaglandin synthesis**,** reducing mucus and bicarbonate secretion. Increasing intestinal permeability, facilitating bacterial translocation. A distinctive feature of NSAID enteropathy is the formation of thin (2–7 mm) circular strictures ("diaphragms"), primarily in the ileum.

Results and discussions

NSAIDs have a negative effect on all parts of the gastrointestinal tract, causing dysfunction and damage to the mucous membrane (CO) with the development of erosions and ulcers, and they can cause bleeding and perforation. These complications are most well-known for the stomach and duodenum, however, lesions of the underlying gastrointestinal tract – the small and large intestine – also occur quite often and have serious clinical significance, although they are much worse diagnosed [7, 9]. Chronic enteritis in patients with rheumatoid arthritis develops primarily as a manifestation of systemic disorders characteristic of RA (damage to the microcirculatory system, lymphoplasmocyte cell reactions), and stages occur that are characteristic of enteritis of any origin, namely– superficial, chronic enteritis. On the other hand, damage to the mucous membrane of the upper intestine is aggravated by taking nonsteroidal anti-inflammatory drugs and glucocorticosteroids.

Morphological manifestations of active enteritis were characterized by the fact that against the background of pronounced inflammatory infiltration of the enteritis mucosa by lymphocytes and plasmocytes, a large number of neutrophils appeared in the infiltrate and in the integumentary epithelium. Most often, when taking medications of this class, undesirable reactions from the gastrointestinal tract occur. Adverse events range from moderate symptoms such as dyspepsia, heartburn, and abdominal discomfort, to more serious events involving life-threatening complications. The mucous membrane (CO) has certain protective mechanisms; when taking NSAIDs, the functioning of most of these mechanisms is disrupted [13]. Intestinal pathology in RA is considered in the literature in terms of side effects of basic therapy [7,9]. Functional and structural features with different disease activity remain less studied, and their role in maintaining autoimmune systemic inflammation has not been established. The role of biogenic amines and peptide hormones produced by the diffuse endocrine system in the regulation of motility, absorption into the small intestine, nociception, tissue trophism, and induction of the inflammatory process is widely discussed. Some studies have been devoted to the study of the concentration of neuropeptides in RA in the synovial membrane and blood plasma, the quantitative density of the components of the intestinal mucosa in RA and the relationship with the activity of the autoimmune process have not been studied. The role of intestinal pathology in rheumatoid arthritis remains unexplored. Changes in the intestine may be a consequence of the development and manifestation of immune inflammation and may be an inducer of a pathological process during which the body is sensitized to the components of the autoflora. Intestinal microecology has a significant impact on homeostasis, taking a direct part in the formation of the immune response. It is possible that deregulatory and dysbiosis intestinal disorders can lead to impaired immune tolerance, being one of the triggers of the systemic response.

The only pathology specific to NSAID enteropathy should be considered the formation of thin, 2 to 7 mm thick circular strictures, mainly occurring in the ileum ("diaphragm"). As a result of chronic inflammation with pronounced lymphohistiocytic infiltration and fibrosis, they are rarely diagnosed. Circular strictures can cause intestinal obstruction or capsule retention during VCE [15, 18]. NSAID-induced erosions and ulcers of the jejunum and ileum usually do not show any subjective symptoms. This was shown in a series of studies that examined the development of NSAID enteropathy in healthy volunteers [19]. Sometimes the first manifestation of NSAID enteropathy is intestinal bleeding or intestinal perforation clinic. However, in most cases, the diagnosis of NSAID enteropathy may be suspected when a patient develops gastrointestinal bleeding of unknown origin (when esophagogastroduodenoscopy and colonoscopy do not allow its source to be determined) or when IDA and hypoalbuminemia are detected against the background of long-term NSAID use [9, 14, 15,6].

The prognosis is especially unfavorable in patients with rheumatoid arthritis with systemic manifestations: generalized vasculitis, rheumatoid nodules, lymphadenopathy, damage to the lungs, heart, liver, kidneys and other organs and systems. Intestinal lesions are the least studied among the extraarticular manifestations of RA, although the most severe process is intestinal amyloidosis, which occurs in 11% of patients and is usually combined with amyloidosis of other internal organs [3]. Disorders of intestinal motility and secretory function were noted in RA patients, the development of chronic enteritis exceeding three times its occurrence in the general population, as well as the frequent occurrence of mucosal ulcers [2,8]. A number of researchers have considered the nature of these changes in the context of the systemic nature of rheumatoid inflammation, believing that enteritis is based on immune disorders. Nevertheless, the question of the proportion of immune disorders in the intestine caused by the underlying disease, on the one hand, and the damaging effect of drugs on the mucous membrane, which patients are forced to take constantly, is still debatable. In recent years, the main focus in the development of intestinal disorders has been on medicinal enteropathies. The pathogenesis of these enteropathies has not been fully deciphered and probably should not be considered outside of the processes that may be caused by general immunopathological patterns characteristic of RA as a systemic disease. Moreover, a position is currently being postulated that represents any chronic enteritis as an immune pathology proceeding according to the standard scheme [1]. In order to achieve remission and a relapse-free course of RA, as well as to prevent the development of irreversible joint deformities, patients are forced to constantly take basic medications. In combination with it, nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed to suppress inflammation in the joints, eliminate pain in them, morning stiffness, and poor general well-being. Such therapy, initiated from the moment of diagnosis of RA, can create prerequisites for the correction of immunoregulatory disorders, affect the course of the disease, slow down its progression, and provide symptomatic treatment [1]. However, the constant intake of NSAIDs, immunosuppressants and HA causes a high level of intestinal damage. It is well known from the literature that NSAIDs, by inhibiting the production of prostaglandins, burn the resistance of the intestinal mucosa to the aggressive effects of hydrochloric acid and pepsin, leading to the development of enteropathy, which, in some cases, may endanger the lives of patients. Reducing joint pain and inflammation in RA patients with NSAID treatment is often achieved at the cost of significant side effects from the digestive tract. Thus, erosive and ulcerative lesions develop more often than in the general population. The risk of NSAID enteropathy increases with concomitant HC therapy. The use of synthetic GHG analogues did not lead to complete elimination, although it reduced the frequency of intestinal lesions. Many risk factors for NSAID enteropathy are similar to similar factors well known for NSAID gastropathy [20,21]. It is important to note that the use of proton pump inhibitors, currently the main class of drugs for the prevention of NSAID gastropathy, not only does not reduce, but significantly increases the risk of developing NSAID enteropathy. This is due to microbiome disorders and bacterial overgrowth syndrome, which can occur against the background of prolonged use of proton pump inhibitors [22,24].

The role of intestinal pathology in RA remains unexplored. Changes in the intestine may be a consequence of the development and manifestation of immune inflammation and may be an inducer of a pathological process during which the body is sensitized to the components of the autoflora. Intestinal microecology has a significant impact on homeostasis, taking a direct part in the formation of the immune response. Data has been published that patient with RA have defective circulating T cells (Tges) [14], with an increased titer of Th17 cells in plasma and synovial fluid [10], the role and significance of which is being studied. It is possible that deregulatory and dysbiosis intestinal disorders can lead to impaired immune tolerance, being one of the triggers of the systemic response. The following approach was used to diagnose gastroduodenal disorders in RA patients. Purposefully clarified gastroenterological history, in order to identify patients at risk of developing gastroduodenal complications, the nature and duration of previous antirheumatic treatment (especially NSAID intake) were clarified in detail, its effectiveness was determined, and the timing of dyspeptic disorders, allergic and other adverse reactions during treatment was established. Since in the vast majority of cases NSAID enteropathy is manifested by a superficial lesion of the small intestine, accurate diagnosis is possible only with the help of endoscopic imaging of the jejunum and ileum. The gold standard here should be considered VCE– a relatively safe and minimally invasive method that allows for the successful diagnosis of pathological changes throughout the small intestine. Unfortunately, the VCE is not without certain drawbacks. This is an expensive technique that requires a long time to perform the procedure itself and view the resulting video by a well-trained specialist. However, in rare cases (approximately 1%), VCE may be complicated by capsule retention caused by the presence of a tumor or stricture of the small intestine. Capsule extraction in such situations may require emergency surgery. [9, 15, 23, 25].

During an objective examination, attention was paid to the condition of the oral cavity, as well as the temporomandibular joints, the damage to which may be accompanied by difficulty chewing food and, as a

result, impaired digestive processes. The presence of sensitive and painful areas in the epigastrium, right and left hypochondrium was determined, and one of the most common symptoms of stomach damage in this category of patients was taken into account – a feeling of fullness after eating. Palpatory symptoms of pancreatic lesion were determined: symptoms of Mayo-Robson, Kacha, Desjardins. In patients with antrum gastritis, constant dull aching pains in the epigastrium came to the fore, which were indicated by all patients. Of the signs of dyspepsia, they had only heartburn, belching, and lack of appetite. With fundal gastritis, the pain was also persistent, but there was a wider range of dyspeptic disorders: heartburn, belching, nausea, vomiting, and a feeling of fullness in the epigastrium. Pangastritis was accompanied by intense pain and the most pronounced dyspeptic disorders. [5] Currently, it is difficult to say which is primary – RA or intestinal changes. Obviously, there is a combination of a violation of the structural and functional characteristics of joints and intestines against the background of a systemic imbalance of the components of DES.

Conclusion

Against the background of an imbalance of hormones and neurotransmitters, inflammatory and dystrophic mucous membranes develop, which facilitate the penetration of antibodies. Microbial and viral antigens of the intestinal ecosystem, in turn, cause endogenous intoxication, initiate immune inflammation, and worsen the course of RA. In addition to antibiotics, probiotic preparations containing lacto and bifidobacteria can improve the condition of the intestinal microflora.

Several clinical studies have been conducted that have shown the effectiveness of probiotics for the treatment and prevention of small intestine damage caused by NSAIDs or low doses of acetylsalicylic acid [26,27]. The pathology that occurs against the background of NSAIDs and low doses of acetylsalicylic acid, even with relatively short-term use of these drugs.

The pathogenesis of NSAID enteropathy is complex and is determined by a decrease in the resistance of CO to aggressive components of intestinal contents and bacteria. In the vast majority of cases, NSAID-induced erosions and ulcers from the small intestine do not manifest themselves as any subjective symptoms, and the main sign of NSAID enteropathy is the development of chronic IDA.

However, in some cases, there are manifest forms of this pathology – bleeding, perforation and intestinal obstruction associated with the formation of thin circular strictures, the so-called diaphragms. The main methods of prevention of NSAID enteropathy should be considered the consideration and correction of risk factors.

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