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The relationship between rheumatoid arthritis (RA) and psychiatric disorders

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease that has a destructive effect on the joints, but also leads to many systemic complications, including mental disorders. This review will present the co-occurrence of mood disorders, such as depression, anxiety and cognitive disorders, in patients with RA and analyze the potential pathophysiological mechanisms. The impact of chronic inflammation and proinflammatory cytokines (IL-6, IL-1β, TNF-α) on the central nervous system and the hypothalamic-pituitary-adrenal axis (HPA) will be discussed. When rheumatoid arthritis (RA) is accompanied by mental health disorders, treatment methods used for RA may be less effective. This can make the condition harder to manage, increasing pain and reducing the quality of life. Additionally, the paper will present the impact of pain, fatigue and reduced physical fitness on the deterioration of the mental health of patients. In addition to the pharmacological treatment used for RA, which is also not neutral to patient's

health, additional therapeutic options such as psychological interventions will be discussed. Considering both somatic and psychological aspects, an interdisciplinary approach to the treatment of patients with RA is very important.

KEYWORDS

rheumatoid arthritis, psychiatric disorders, depression, anxiety, cognitive disorders

1. INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune connective tissue disease characterized by chronic inflammation of the synovial membrane of the joints [1]. It is estimated that RA affects approximately 0.3–1.2% of the general population, and women are 2–3 times more likely to develop RA than men [2][3]. As a systemic disease, it causes damage not only to the joints but also to other tissues and organs, such as the heart, lungs, kidneys, digestive system, eyes, skin and nervous system [4]. Despite the well-documented somatic symptoms of RA, which are the main goal of treatment, the psychological aspects of this disease unfortunately remain insufficiently recognized and treated. In the course of this disease, patients are often accompanied by recurrent pain, weakness and deterioration of physical fitness, which can significantly affect the quality of life, increasing the risk of mental disorders. Despite significant progress in pharmacological treatment, including the use of disease-modifying antirheumatic drugs (DMARDs) and biological therapies, studies show a significantly higher risk of developing psychiatric disorders compared to the general population [5]. Recent studies indicate that the most common psychiatric symptoms observed in individuals with rheumatoid arthritis are depression and anxiety [6]. Many studies have presented a common pathophysiological background for rheumatoid arthritis and psychiatric disorders, most often depression. These studies show that proinflammatory cytokines in RA, such as interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 1β (IL-1β), and TNF-α, play important roles in the disease's impact on the hypothalamic-pituitary-adrenal axis [7,8]. The aim of this review is to analyze the current research on the correlation between RA and psychiatric disorders such as

depression, anxiety and cognitive disorders. This work aims to present the scale of these disorders in patients with rheumatoid arthritis, discuss potential pathophysiological mechanisms and emphasize the importance of an appropriate approach to the treatment of patients, taking into account both somatic and psychological aspects**.**

2. CHARACTERISTICS OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive inflammation of the synovial membrane in joints, leading to joint destruction and a range of systemic complications. This disease is significantly associated with a decrease in the quality of life of patients, and in many cases may lead to premature death [2].

2.1 Epidemiology and pathophysiology

RA affects approximately 0.3–1.2% of the world's general population, with women falling ill 2–3 times more often than men. Studies show that the lifetime risk of developing the disease is 3.6% for women and 1.7% for men [2][3].

The pathogenesis of rheumatoid arthritis is based on complex immunological mechanisms, involving the activation of autoreactive CD4+ T lymphocytes, B cells, macrophages and the production of autoantibodies: rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). These processes lead to the proliferation of the synovial membrane, the formation of the so-called pannus and the destruction of cartilage and bone [2].

2.2 Clinical symptoms and impact on quality of life

The characteristic symptoms of rheumatoid arthritis are pain, morning stiffness, swelling and symmetric inflammation of the joints, mainly small joints of the hands and feet. In the course of the disease and with its progression, joint deformation and limitation of their function occur, and consequently, the quality of life of patients is reduced and daily activities are difficult to perform. Additionally, patients with RA often experience chronic fatigue, which may be the result of both the disease itself and the accompanying sleep disorders, anxiety, or depression [9].

2.3 Systemic burden and multi-organ effects of RA

RA is a systemic disease that can lead to many complications in various organs. The most common are cardiovascular, pulmonary and skin diseases, as well as osteoporosis. In the course of this disease, chronic inflammation in the body can contribute to endothelial dysfunction and accelerated development of atherosclerotic plaque, increasing the risk of atherosclerosis, hypertension, stroke, and ischemic heart disease [4]. Studies show that cardiovascular diseases are the main cause of mortality in RA, with a 1.5- to 3-fold higher risk of death compared to the general population [10]. Some patients experience pulmonary complications such as interstitial lung disease, pulmonary hypertension or pleurisy, which significantly worsen the prognosis of patients [4].

2.4 Course and pharmacological treatment

Rheumatoid arthritis is a progressive disease and its course is characterized by periods of exacerbations and remissions. In patients, early diagnosis and aggressive treatment are key to preventing irreversible joint damage. Treatment in RA involves the use of disease-modifying antirheumatic drugs (DMARDs), including methotrexate as the first-line drug. In the absence of response to treatment, biologic drugs such as TNF-α, IL-6 or JAK inhibitors are used. In the case of systemic complications, an interdisciplinary approach to the patient is necessary, including cooperation between rheumatologists, cardiologists, pulmonologists or neurologists. RA is a multi-organ disease, and its systemic complications can significantly affect patients' quality of life and mortality, therefore individualization of therapy and monitoring of disease activity are important for effective disease management [4].

3.NEUROPSYCHIATRIC MECHANISMS IN RA

3.1. Chronic inflammation and the central nervous system

Rheumatoid arthritis is characterized by chronic inflammation in the body, affecting not only the joints but also the central nervous system (CNS). Studies have shown that proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-a) can penetrate the blood-brain barrier and interfere with it indirectly, leading to the stimulation of microglia

and astrocytes, which can affect the functioning of neurons and neurotransmitters [11]. In the event of microglia activation, there may be an increased production of proinflammatory cytokines in the brain and, as a consequence, the occurrence of symptoms of depression and mood disorders.

3.2. The role of proinflammatory cytokines in depression and mood disorders

Proinflammatory cytokines play an important role in the pathogenesis of psychiatric disorders in patients with RA. Increased levels of IL-6 and TNF-α often correlate with the severity of depressive symptoms in patients [8]. A possible cause of depression is the effect of IL-6 on serotonin metabolism through activation of the kynurenine pathway. This leads to a reduction in the availability of tryptophan, which is a precursor of serotonin, and consequently causes a decrease in its synthesis and an increase in the production of neurotoxic metabolites. In the case of TNF-α, it can affect glutamatergic neurotransmission, causing an increase in glutamate and exerting excitotoxic effects, which is associated with symptoms of depression and anxiety [12]. Another important role in initiating and maintaining inflammation in RA is IL-1β. This cytokine is expressed in the central nervous system, including the hippocampus, hypothalamus and cerebral cortex. Studies have shown that elevated levels of IL-1β in blood serum and cerebrospinal fluid occur in patients with depression and those exposed to chronic stress. Correlations have also been observed between the expression of this cytokine and the intensity and duration of depressive symptoms. Macrophages, lymphocytes, monocytes and transformed fibroblasts are responsible for its excessive production. IL-1β is responsible for the expression of other pro-inflammatory mediators such as IL-6 and TNF-a, which results in the migration of inflammatory cells to the joints and increased inflammation. Additionally, IL-1β also stimulates the production of proteoglycans and proteases, which lead to the erosion of joint tissues. The consequence of this process is the degradation of cartilage and bone, and consequently the loss of joint function [8].

3.3 Mental state and the hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal (HPA) axis plays a key role in regulating the body's response to stress, exerting a significant influence on emotional functioning and the development of mood disorders. In RA, chronic inflammation can lead to disruption of the HPA axis through the action of proinflammatory cytokines. IL-6, TNF-α, and IL-1β can stimulate

the HPA axis, leading to increased cortisol secretion. Of these, IL-6 plays the most important role in stimulating the HPA axis, particularly during chronic inflammatory stress, such as in RA. Physical or psychological stress initiates a signal in the hypothalamus, leading to the production of corticotropin-releasing hormone (CRH), which then stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH), stimulating the adrenal glands to secrete cortisol. However, patients with RA often have inappropriately low cortisol levels relative to the severity of inflammation, which may contribute to chronic fatigue. Disturbances in this axis indicate possible dysregulation of the stress response by IL-6 [13].

4. MENTAL DISORDERS CO-EXISTING MOST COMMONLY IN RA

4.1 Depression

Patients with RA often have serious extra-articular systemic symptoms that reduce life expectancy by 5–10 years. One of the contributing factors may be the presence of mental disorders. Depression most often co-occurs with RA, which significantly worsens the quality of life of patients, constituting a serious health problem [14]. In patients with RA, diagnosing depression is a challenge, because distinguishing it from a natural emotional reaction to a chronic, painful and very burdensome disease is very difficult. Patients with RA show systemic symptoms that may also occur in depression, such as: fatigue, insomnia, weight loss or lack of appetite. Studies show that the incidence of depression in the general population is approximately 6%, it is significantly higher in RA patients, reaching 16.8% [15]. This mental disorder in patients with RA can have a significant impact on the course and activity of the disease, contributing to higher levels of pain, greater fatigue, disability, more comorbidities, higher mortality and generally reduced quality of life [16]. Additionally, depression can affect the patient's perception of health, as even mild pain is perceived as more intense, which consequently translates into higher rates of disease activity and complications in treatment [17].

Studies have shown that in the course of early RA, the greater the number of affected joints, the more frequent the occurrence of depression after 6 months [15]. In 2011, Kekow et al. presented that clinical remission reduces symptoms of depression in patients with active and severe RA [18].

4.2 Anxiety disorders

Anxiety disorders are common among patients with RA, often as a response to chronic pain, functional limitations and concerns about treatment. In 2019, a meta-analysis was conducted on 139,875 participants, of whom 6,201 developed an anxiety disorder. These studies showed that patients with RA have a 20% increased risk of developing anxiety compared to the general population (OR 1.20; 95% CI: 1.03–1.39) [19]. The analysis showed strong associations between anxiety symptoms and factors such as depression, pain, disease activity, physical disability and reduced quality of life. Anxiety in patients can worsen RA symptoms, negatively affect treatment outcomes, and increase the psychological burden of patients [20].

4.3 Cognitive disorders

Cognitive disorders are an increasingly common disorder diagnosed in patients with rheumatoid arthritis. Patients, especially those with high inflammatory activity, may experience difficulties with memory, attention, executive functions, or emotion recognition [21][22]. In a study by Gwinnutt et al., the cognitive abilities of people with RA were compared with an age-matched control group. Compared to healthy participants, people with RA had lower scores on tests assessing memory, verbal fluency, executive functions, and emotion recognition in. Additionally, based on the results of the Addenbrooke's Cognitive Examination III, 60.5% of RA patients were classified as having mild cognitive impairment [22].

4.4 Pain and Fatigue in RA

Pain in RA is not only a result of joint inflammation and autoimmune activity but may also stem from non-inflammatory sources such as anxiety, depression, sleep disorders, or psychosocial situations. According to a 2014 study by the National Rheumatoid Arthritis Society (NRAS), The Invisible Disease: Rheumatoid Arthritis and Chronic Fatigue Survey showed that 90% of RA patients reported fatigue as a major factor causing low mood and depression, 89% experienced chronic fatigue, and 79% had never been assessed for fatigue. Fatigue can substantially affect mood, reduce physical activity and increase the severity of morning stiffness (EMS), edema and inflammatory markers such as ESR and IL-6. Due to the difficult course of the disease, tearfulness, irritability and frustration are frequently reported symptoms by RA patients [23].

5. The impact of RA treatment on the mental state

5.1 Disease-modifying antirheumatic drugs (DMARDs)

The basis of RA treatment is disease-modifying antirheumatic drugs. They reduce inflammation and prevent or delay the occurrence of destructive changes in the joints. This group of drugs is divided into synthetic and biological. The drug of first choice in rheumatoid arthritis is methotrexate. Studies show that its use increases the severity of anxiety and depression symptoms compared to patients treated with leflunomide, used in the case of contraindications to methotrexate treatment or in a more advanced stage of the disease[24]. A significant difference is at what stage of the disease the drug is introduced. In the case of methotrexate treatment, patients are newly diagnosed, and the disease is theoretically not yet that advanced. Another drug presented in the studies is hydroxychloroquine, which obtained intermediate results - medium risk of anxiety, a result below the depression threshold, but a very high result of suicidal thoughts [24].

The next group are biological therapies such as TNF-α inhibitors, IL-6. Inhibitors of tumor necrosis factor alpha (TNF-α), used in the treatment of RA, show not only anti-inflammatory effects, but can also have a beneficial effect on the mental state of patients. A study conducted on 4222 patients with RA showed that in patients with a positive response to therapy with TNF-α inhibitors, a 20% lower risk of depression was observed compared to patients who did not achieve clinical improvement after the treatment [25].

Another biological drug used in the treatment of rheumatoid arthritis are IL-6 inhibitors. Interleukin-6 (IL-6) plays an important role in the pathogenesis of RA, but also in depression. Studies on IL-6 blockers, such as sirukumab and siltuximab, have shown that RA patients experienced improvement in depressive symptoms, regardless of the improvement in somatic symptoms. This suggests that these drugs may have a direct antidepressant effect by modulating inflammatory pathways [26].

5.2 Glucocorticosteroids and their effect on mood

Commonly used drugs in RA are glucocorticosteroids (GCs), which are not indifferent to the mental state of patients. Their use in patients significantly reduces inflammation in the body,

but their long-term administration is associated with the risk of mood disorders such as depression or anxiety. Studies show that patients using GCs may experience changes in mood, insomnia, and other mental symptoms. The GCs used affect the hypothalamic-pituitary-adrenal (HPA) axis, leading to its dysregulation. This results in changes in the levels of neurotransmitters such as dopamine, serotonin and glutamate, leading to mood and cognitive disorders. Unfortunately, chronic use of corticosteroids can contribute to structural changes in the brain, leading to hippocampal atrophy and hyperactivity of the amygdala, which is associated with symptoms of depression and anxiety. An important factor increasing the risk of mental disorders is the dose and duration of glucocorticosteroid therapy. When using higher doses (e.g. >40 mg of prednisolone per day), it can result in the occurrence of mania and psychosis, while at lower and chronically used doses of GCs it can lead to depression and anxiety. In more difficult situations, it may be necessary to introduce antipsychotic drugs, especially atypical ones, due to their more favorable side effect profile. The treatment used should be short-term, with monitoring of the patient's condition and gradual discontinuation of the drugs after the symptoms have subsided [27].

6. The impact of mental disorders on the treatment and course of RA

More than 60% of patients with rheumatoid arthritis achieve a good response after 12 months of treatment if patients follow the European League Against Rheumatism (EULAR) treatment guidelines during therapy. Despite this, almost half of patients have moderate or severe RA. Additionally, psychiatric disorders may persist despite reduced markers of inflammation in the system and joints. RA patients are at higher risk of anxiety, depression and cognitive impairment compared to the general healthy population. These mental disorders resulting from fatigue and body pain, among other things, may contribute to a poorer response to treatment and increase disease activity in RA. Medications may alleviate anxiety and depression to some extent, but unfortunately not completely [23].

6.1 Poorer persistence in therapy

Patients with depression or anxiety have been identified as risk factors for discontinuing biological disease-modifying antirheumatic drugs (DMARDs) in a large North American

registry of patients with RA [28]. Additionally, depression can lead to irregular medication use and reduced motivation for active treatment, which in turn reduces the effectiveness of therapy and increases the risk of disease exacerbations.

6.2 Increased pain and reduced effectiveness of therapy

Depression and anxiety are potential factors for the occurrence of periods of RA flares in patients and affect the way patients perceive their current health. The presence of mental disorders significantly affects the intensity of pain, which leads to a subjective deterioration of health. Treatment of these mood disorders can lead to higher pain thresholds and improved quality of life for patients [14].

7. Psychological treatment in RA

Psychological treatment in RA aims to achieve a good quality of life, including increased self-efficacy, mood, emotional and cognitive state, adaptive coping style, active lifestyle, and work capacity [29]. An important assumption of psychological intervention is to reduce the helplessness, catastrophizing, pain, stress, difficulties in daily activities, fatigue, functional and psychological disability and psychological stress experienced by patients [30,31]. In the course of this therapy, an individual approach to the patient is key, based on the biopsychosocial diagnosis and the patient's motivation in the treatment process.The main psychological interventions used in the treatment of RA in patients with concomitant mental health disorders are as follows:

Patient education (PE) - teaches self-control, coping with the disease, includes modular behavioral education and patient education. The importance of lifestyle modification is discussed during the course. Patient education in RA has shown that effective interventions significantly impact health outcomes [32][33][34].

Stress management, relaxation and psychotherapy (R) – this method is based on the use of relaxation techniques, mindfulness, counseling. The main goal is to modify stress appraisal and reduce subjective perceptions of anxiety, which can change autonomic arousal and affect

neuroendocrine activity. Developing methods for coping with the physiological response to stressors may be beneficial in patients with immunological diseases such as RA [35][36].

Cognitive behavioral therapy (CBT) – helps patients improve problem-solving skills, presents the relationship between beliefs, thoughts and feelings and behaviors resulting from these factors [29].

Emotional disclosure (ED) – patients are asked to analyze and describe their deepest thoughts and feelings about the most emotional events they have experienced [29].

Hypnotherapy (HY) – reduces stress and pain, is less researched and rarely used. [29].

Mindfulness (M) – affects the stimulation of internal concentration and improves self-regulation, relieving the psychological pressure of patients, reducing the reaction to pain [29].

Group therapy (GT) – uses group support, although it may limit individual attention [29].

The above-mentioned psychological interventions can significantly improve the mental and physical health of patients with RA. Studies have shown that various methods of psychotherapy can reduce pain, anxiety, depression and physical disability in patients [30,37,38]. Therefore, a multidisciplinary approach to the treatment of patients with RA may be an important element of complementary therapy in RA [29].

CONCLUSIONS

Rheumatoid arthritis (RA) is a chronic autoimmune, systemic connective tissue disease that not only leads to joint inflammation, extra-articular changes or systemic symptoms, but can also significantly affect the mental functioning of patients. Studies show that patients with rheumatoid arthritis are more susceptible to psychiatric disorders. The most common comorbidities are depression, anxiety and cognitive deficits. This paper presents complex neuropsychiatric mechanisms that correlate with RA and psychiatric disorders. In the course of psychiatric disorders in patients, proinflammatory cytokines such as TNF-α, IL-1β and IL-6 play an important role, which cross the blood-brain barrier, negatively affecting neurons and neurotransmitters. Another key element is the impact of ongoing chronic inflammation on the

central nervous system. The result of this process is dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which consequently contributes to the development of mood disorders, chronic fatigue and dysregulation of the stress response.

The treatment modalities used in RA can significantly influence patients 'mental health. Glucocorticosteroids used in RA therapy can affect mood changes, insomnia and increase the risk of depression, anxiety and even mania or psychosis. On the other hand, some therapies such as biological treatment, especially with the use of TNF-α and IL-6 inhibitors, may have a potential antidepressant effect.

Chronic pain, fatigue, stress and difficulties in performing daily activities experienced by RA patients can increase the occurrence of psychiatric disorders. They can negatively affect patients' persistence in therapy, and even intensify pain and reduce the response to treatment. Therefore, in addition to the pharmacological therapy, a significant element in the course of treatment of patients is the use of psychological interventions. Rheumatoid arthritis is a multi-organ disease contributing to cardiovascular, pulmonary, skin and psychiatric diseases. Therefore, a multidisciplinary approach is crucial in treating patients.

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