Review

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Relationship Between Bipolar Disorder and Rheumatoid Arthritis

Bipolar Bozukluk ve Romatoid Artrit İlişkisi

Melike Mandacı[1], Aslı Sarandöl[1], Cengiz Akkaya[1]

[1]Bursa Uludağ University, Bursa, Turkey

ABSTRACT

Rheumatoid arthritis is a chronic autoimmune disease that is characterized by synovitis, systemic inflammation, arthritis and vasculitis, anemia, mononeuritis, pulmonary fibrosis, and can cause joint destruction, limitation of joint movements and impairment of the patient's quality of life if not treated in right time and adequate manner. In addition to joint symptoms, neuropsychiatric symptoms such as cognitive dysfunction, behavioral changes, and mood changes may accompany rheumatoid arthritis patients. It is thought that neuroinflammatory process in rheumatoid arthritis patients, increase in proinflammatory cytokine levels in plasma; side effects of drugs used for a long time, disability that occurs with the disease, and possible common gene regions may cause these symptoms. An increasing number of studies are being published on psychiatric symptoms and disorders in patients with rheumatoid arthritis. There are many studies focusing especially on its relationship with anxiety disorders and major depressive disorder. There are increasing numbers of studies showing that the impairment of immune functions is involved in the etiology of bipolar disorder. The changes in cytokine levels in the plasma of bipolar disorder patients supports this argument. The relationship between various autoimmune diseases and bipolar disorder continues to be examined. In people with rheumatological diseases, it is important to be careful in psychiatric comorbidities in terms of patient compliance and clinical course.

Keywords: Bipolar disorder, rheumatoid arthritis, inflammation, psychoneuroimmunology

ÖZ

Romatoid artrit, sinovit, sistemik inflamasyon, artrit ve vaskülit, anemi, mononörit, pulmoner fibrozis gibi eklem dışı sistem tutulumu ile karakterize olan zamanında ve yeterli tedavi edilmezse eklem destruksiyonuna, eklem hareketlerinin kısıtlanmasına, hastanın yaşam kalitesinin bozulmasına neden olabilecek kronik bir otoimmün hastalıktır. Romatoid artrit hastalarında eklem bulgularının yanı sıra klinik tabloya bilişsel işlev bozukluğu, davranış değişiklikleri ve duygudurum değişiklikleri gibi nöropsikiyatrik belirtiler de eşlik edebilir. Romatoid artrit hastalarında nöroinflamatuar sürecin, plazmadaki proinflamatuar sitokin düzeylerinde artışın, uzun süre kullanılan ilaçların yan etkilerinin, hastalıkla birlikte oluşan yeti yitiminin ve olası ortak gen bölgelerinin bu belirtilere neden olabileceği düşünülmektedir. Romatoid artrit hastalarında psikiyatrik semptom ve bozukluklarla ilgili giderek artan sayıda çalışmalar yayınlanmaktadır. Özellikle anksiyete bozuklukları ve major depresif bozukluk ile ilişkisine odaklanan birçok çalışma mevcuttur. Bipolar bozukluk etiyolojisinde immün fonksiyonlarda bozulmanın yer aldığına ilişkin giderek artan sayıda çalışma bulunmaktadır. Bipolar bozukluk hastalarının plazmalarında sitokin düzeylerinde değişiklikler görülmesi bu görüşü destekler niteliktedir. Çeşitli otoimmün hastalıklarla bipolar bozukluk arasındaki ilişki baraştırılmaya devam edilmektedir. Romatolojik hastalığı olan bireylerde, psikiyatrik eş tanılar açısından dikkatli olunması hastaların tedaviye uyumu ve klinik seyir açısından önemlidir.

Anahtar sözcükler: Bipolar bozukluk, romatoid artrit, inflamasyon, psikonöroimmünoloji

Introduction

Rheumatoid Arthritis (RA) is a common inflammatory disease that primarily affects the synovial joints and is associated with progressive musculoskeletal damage (Uhlig et al. 2014). Although the incidence of RA is 40/100000 person/year, the highest incidence is at the ages of 50 to 60 (Cross et al. 2010, Scott et al. 2010). Extra-articular effects of RA include cardiovascular system diseases such as ischemic heart diseases and heart failure, pulmonary diseases, and skeletal system diseases such as osteoporosis. RA has been associated with increased mortality and morbidity.

RA is a progressive disease that has physical effects as well as other effects in all aspects of the patient's life, causing dysfunctioning of the patient in family, work, social relationships, and psychological domains. Being an autoimmune disease,

Address for Correspondence: Melike Mandacı, Bursa Uludağ University Faculty of Medicine, Department of Psychiatry, Bursa, Turkey
E-mail: melikemandaci@uludag.edu.tr **Received:** 19.04.2021 **Accepted:** 27.08.2021
ORCID ID: orcid.org/0000-0002-1333-3475

the pathogenesis of RA includes increased proinflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and deterioration in innate and acquired immune system functions (Szekanecz et al. 2010, Firestein and McInnes 2017). Autoimmune diseases like RA are characterized by chronic inflammation that may cause neurotransmitter abnormalities and neuroinflammation.

Following the demonstration that neuroinflammation and neurotransmitter abnormalities are associated with psychiatric diseases, studies on a possible relationship between autoimmune diseases with chronic inflammation and psychiatric diseases have increased. The relationship between autoimmune diseases and Major Depressive Disorder (MDD), Schizophrenia and BD has been shown by many studies (Najjar et al. 2013). Although there are many studies emphasizing the relationship between RA and particularly Schizophrenia and MDD, studies on its relationship with BD are relatively few (Torrey and Yolken 2001, Dickens et al. 2002). Data on BD-RA comorbidity are very limited in the literature. This article aims to focus on the relationship between RA and BD and the possible etiopathogenesis of this relationship. It can be suggested that these possible mechanisms will provide a basis for pharmacological research and insight into the pathogenesis of the disease.

Comorbidity of Rheumatoid Arthritis and Psychiatric Diseases

More than one-third of patients showed high emotional stress when diagnosed with RA (Persson et al. 2005). In addition, it was reported that 80% of the patients had a depressive disorder in the following 5 years (Wang et al. 2014). A large-scale study using health data in Denmark showed that the risk of BD increased in the first 4 years after the diagnosis of thyrotoxicosis, RA, Multiple Sclerosis, psoriasis and Inflammatory Bowel Disease, and 5 years after the diagnosis of autoimmune hepatitis (Eaton et al. 2010). Considering the studies dating back to the pre-diagnosis, the incidence of BD in RA patients was found higher even 2-3 years before the diagnosis, compared to healthy controls (Marrie et al. 2019).

Among all mental illnesses, depression has the strongest link with RA (Covic et al. 2012). Studies investigating the relationship between depression and RA defined the prevalence of depression in RA patients in a wide range from 14% to 48% (Waraich et al. 2004, Matcham et al. 2013). A meta-analysis published by Matcham et al. (2013), which included 13189 patients, obtained a more consistent result and found that the prevalence of depression in RA patients was 18.8%, therefore, the risk of depression increased in RA patients compared to the general population.

The incidence of anxiety was determined to be higher in RA patients than in the general population (Ho et al. 2011). Anxiety has been associated with age, gender, marital status, the intensity of pain sensation, disease activity, and the socio-economic status of the patient (Kojima et al. 2009, Ho et al. 2011, İmran et al. 2015). A meta-analysis of 139875 patients, including 10 cohort studies published by Qiu et al. concluded that the prevalence of anxiety was increased in RA patients compared to non-patients (Qiu et al. 2019). In addition, it was observed that patients with RA accompanied by anxiety had lower adherence to treatment (Kekow et al. 2011).

In people with a recent diagnosis of RA, the initial psychiatric comorbidity, particularly depression, was associated with more pain and worse functionality at baseline, as well as a 40% lower probability of clinical remission at 1 year (Hitchon et al. 2016).

Recent genome-wide association studies suggest that some genetic loci associated with psychiatric disorders have pleiotropic effects and may be associated with depression, bipolar disorder, and schizophrenia. Some genetic loci are associated with RA and other immune-mediated disorders, as well as the risk of bipolar disorder and schizophrenia (Wang et al. 2003). Common environmental factors such as chronic stress secondary to chronic disease may also play a role (Cohen et al. 2012, Pervanidou and Chrousos 2012, Winkel et al. 2013, Schmeer and Yoon 2016, Calcia et al. 2016,).

Although there are studies showing an increased risk of BD in RA patients among the studies investigating the relationship between RA and BD in recent years, there are also studies that are not statistically significant. A longitudinal study reported that people with arthritis have a higher risk of mood and anxiety disorders simultaneously compared to healthy controls and there is evidence that arthritis contributes to the development of mood disorders over time (Van't et al. 2010). The underlying mechanism of the relationship found in the studies has not yet been fully elucidated.

There are some possible mechanisms to explain the higher prevalence of psychiatric disorders before or during the diagnosis. It can be argued that autoimmune diseases do not initially become manifest clinically but the chronic inflammatory process has progressed to such an extent that psychiatric symptoms occur. The data show that the risks of depression, anxiety, and bipolar disorder are affected by inflammation and the cell-mediated immune system (Vieira et al. 2010, Berk et al. 2013, Rosenblat and McIntyre 2015). Second, autoimmune diseases like RA and psychiatric disorders may have common etiologies. For example, social difficulties and chronic stress may cause some neurobiological changes, and as a result, the risk of one or more chronic diseases may increase (Cohen et al. 2012). In autoimmune diseases, common etiological factors with different local pathogenetic effects may occur as chronic immune disorders in one or more organ systems. In addition, there may be a surveillance bias that the people with chronic diseases like RA have an increased number of applications to the health system, thus increasing the probability of being diagnosed with other conditions. One of the possible mechanisms emphasized is that various cytokines in plasma cause deterioration in blood-brain barrier function and peripheral inflammation increases inflammation in the central nervous system (Abbott et al. 2006).

Bipolar Disorder and Peripheral Inflammation

A study on patients with schizophrenia and BD found increased levels of autoantibodies, cytokines, and acute phase reactants indicating an innate or acquired immune system response (Miller et al. 2011, Modabbernia et al. 2013, İsgren et al. 2015), increases in endothelial cell and glial activation markers (Jakobsson et al. 2015), glutamatergic system disorders (Sasayama et al. 2013, Pålsson et al. 2015), and increased oxidative stress and blood-brain barrier dysfunctions (Najjar et al. 2013, Zetterberg et al. 2014). Brietzke et al. (2009) observed a proinflammatory condition in euthymic and symptomatic phases in BD patients and suggested that immune signaling was activated in BD patients independently of mood. With increasing studies in the field of immunology, chronic neuroinflammation has been shown to play a role in the pathogenesis of BD. (Rege and Hodgkinson 2013). Postmortem studies have shown increased excitotoxicity and neuroinflammatory markers in the frontal cortex in BD patients (Rao et al. 2010).

Epidemiological studies claim that psychiatric disorders can be linked to autoimmunity, inflammation, and infections that may induce autoimmune diseases. (Arias et al. 2012, Benros et al. 2013). Danish population-based studies have reported a 29-45% higher risk of schizophrenia and a 20-70% higher risk of BD in people with a personal or family history of autoimmune diseases. (Eaton et al. 2006, 2010).

Levels of interleukin-4 (IL-4), IL-6, interleukin-10 (IL-10), soluble interleukin-2 receptor sIL-2R), soluble interleukin-6 receptor (sIL-6R), TNF -a, soluble tumor necrosis factor receptor-1 (sTNFR-1), which are peripheral inflammatory markers, were found to be increased in BD patients (Modabbernia et al. 2013, Munkholm et al. 2013). Proinflammatory cytokines such as TNF-a and IL-6, and antiinflammatory cytokines such as IL-4 was found to increase during manic episodes compared to healthy controls, and another study found that IL-1 β levels and attacks of microglial activation increased in cerebrospinal fluid (CSF) and serum during manic and hypomanic episodes (Söderlund et al. 2011), which supports the effects of immune system disorders on mood. A meta-analysis published by Goldsmith et al. (2016) found an increase in the serum levels of IL-6, TNF-a, sIL-2R, and interleukin-1 receptor antagonist (IL-1RA) during an acute attack and concluded that IL-6 and IL-1RA levels decreased with treatment.

Many inflammatory diseases such as RA and Systemic Lupus Erythematosus have neuropsychiatric components. The effects of peripheral inflammation on the central nervous system are investigated. Studies conducted on this purpose in mice and humans found that, as a result of cytokine-induced neurotransmitter changes of RA-induced peripheral inflammation and increased microglial activation (Miller and Raison 2016, Rosenblat and McIntyre 2017) the neuroinflammation increases (Lampa et al. 2012). Cytokines play a role in regulating the neuroendocrine system, which affects the brain pathways that regulate mood in humans (Brietzke and Kapczinski 2008). One of the possible mechanisms is that proinflammatory cytokines increase the activation of the Hypothalamic-pituitary-adrenal (HPA) axis. Meta-analyses have shown that cortisol and Adrenocorticotropic Hormone levels are higher in BD patients than in healthy controls. High levels of cortisol are also associated with manic episodes. (Belvederi et al. 2016).

Chronic HPA activation may lead to abnormal glucocorticoid signaling in BD patients (Spiliotaki et al. 2006). Decreased cortisol responses have been reported in BD patients (Daban et al. 2005). Glucocorticoid receptor (GR) activation has anti-inflammatory effects. Chronic stress causes GR resistance and prevents the negative feedback loop of the immune response (Cohen et al. 2012). In addition, inflammatory cytokines such as IL-1, IL-6, TNF-a, and IFN-a cause chronic hypercortisolemia, reducing HPA activity and preventing the immune response from limiting itself (Pace and Miller 2009). Hypercortisolemia leads to endocrine changes associated with BD, such as weight gain, insulin resistance, and hypothyroidism. (Cole et al. 2002)

The immune system and the brain are not fully developed in the early stages of life and can therefore be affected by psychological stress. Damages in neuroplasticity, which plays an important role in the activation of inflammatory changes (Pace et al. 2007, Miller et al. 2009, Zunszain et al. 2011), occur as a result of epigenetic modifications (McGowan et al. 2009, Perroud et al. 2011, Labonte et al. 2012, Tyrka et al. 2012, Mehta et al. 2013, Klengel et al. 2013). Childhood traumas have been associated with an increased inflammatory response, whether or not resulted in psychiatric disorders, compared with people that have not had any traumas (Pace et al. 2006, Carpenter et al. 2010). Childhood traumas may also lead to deterioration of GR signaling and hyperactivation of the HPA axis. As a result, cortisol level, which limits inflammation, decreases (Weaver et al. 2004, Pervanidou 2008, Trickett et al. 2010, Klengel et al. 2013). In addition, childhood traumas have been associated with factors such as gut microbiota disorders that aggravate inflammation, sleep disorders, alcohol/drug abuse (Danese and Lewis 2017), autoimmune diseases (Dube et al. 2009), and metabolic syndrome (Pervanidou and Chrousos, 2012).

Besides their immunological roles, cytokines also have roles in sleep regulation in the central nervous system (Opp 2005). The mechanism of these regulations is complex and has not yet been fully elucidated. While IL-1 and TNF-a support NREM sleep in animal models, their antagonists have been shown to increase the REM period (Obal and Krueger 2003). Excessive concentrations of these proinflammatory cytokines have been found to cause sleep disruption and more frequent awakenings (Imeri and Opp 2009) and IL-6 level has been associated with an increase in REM sleep, REM intensity, and suppression of NREM sleep in humans (Irwin et al. 2004, Thomas et al., 2011). High levels of IL-6 are subjectively associated with reduced sleep quality (Thomas et al. 2011).

The assumption that sleep disorders are secondary to the upregulation of IL-6 and that this upregulation is associated with high levels of mRNA coding for IL-6 in monocytes may pave the

way for the use of immunomodulatory drugs for the treatment of dysregulated sleep in patients with bipolar disorder. IL-6 has an important role in the treatment of RA patients. Significant improvement in sleep quality has been shown in RA patients who received tocilizumab, an IL-6 antagonist (Fragiadaki et al. 2012). It is thought that increased oxygen radicals and oxidative stress due to inflammation may also cause neurological damage, and mood and cognition changes. (Berk et al. 2011).

Bipolar Disorder and Genetics

In recent years, the relationship between BD and autoimmune diseases has gained the focus of researchers. Clinical studies have shown that RA, thyroid diseases, Type 1 Diabetes, and similar immune system-related diseases occur more commonly in BD patients compared to the general population (Forty et al. 2014). The interaction between immune system diseases and BD is not unidirectional. In their study on schizophrenia and BD patients, Cremaschi et al. (2017) found that RA, rheumatoid myalgia, and autoimmune thyroid diseases increased in bipolar patients.

The term pleiotropy is used in genetics to describe the relationships between gene mutations and phenotype (Paaby and Rockman 2013). In genetic studies, pleiotropy can help to understand the correlations between diseases and find their genetic relations (Li et al. 2014). A study investigating nucleotide polymorphisms and specific gene regions showed that the MHC region contributes to the pleiotropy between psychiatric diseases and immune system diseases. (Tylee et al. 2018)

Some studies investigated genetic alterations in BD and inflammation-related comorbidities, in which the preliminary data suggested that BD patients may carry genes that cause predisposition to inflammation. Compared to healthy individuals, BD patients were found to have more genetic alterations directly related to IL-6, IL-8, and IFN pathways (Drago et al. 2015). Among the 13 genes associated with BD, CASP1 and STAT are notable. CASP1 is responsible for the production of IL1-β (Vasilakos and Shivers 1996), while STAT encodes transcriptional factors involved in inflammatory responses (Brierley and Fish 2005). Genetic variations have been identified in genes encoding receptors responsible for the innate immune response in BD patients. For instance, TLR-4 rs1927914 A and TLR-4 rs11536891 T alleles were found to be often homozygous in BD patients, this difference may be associated with decreased defense against pathogens (Oliveira et al. 2014).

The 17q12 locus and the identified ERBD2 gene were found to be associated with BD in genetic association studies (Hou et al. 2016). ERBD2 and related genes encode growth factors such as receptor tyrosine kinases and neuregulin, which act on neural circuits, myelination, neurotransmission, and synaptic plasticity. There is increasing evidence that these ligands and receptors cause predisposition to BD and schizophrenia (Mei and Nave, 2014). In addition, genetic studies have found remarkable results that the ERBD2 gene may cause predisposition to many autoimmune diseases (Tylee et al, 2018). In conclusion, RA and BD are both diseases known to have strong hereditary characteristics and although it is thought that these diseases may have similar genetic susceptibility loci, a similar locus has not yet been identified for these diseases. Comprehensive studies are needed in this field.

Bipolar Disorder-Rheumatoid Arthritis Comorbidity

BD patients with autoimmune disease comorbidities have a lower average life expectancy, higher risk of self-harm, lower treatment success, and higher risk of in-hospital mortality compared to BD patients without autoimmune disease comorbidities (Dickerson et al. 2016; Singhal et al. 2014, Thomsen et al. 2005, Chebli et al. 2020). As a result, the risks in the treatment and management of those patients are more serious. Comorbidity of BD and autoimmune diseases may provide a ground for future research and guide the treatment and management of the disease. Firstly, there are various abnormalities in non-specific antibody titers in patients with BD and most of these abnormalities occur before the onset of the disease (Benedetti et al. 2020).

Therefore, measured results of immunological parameters contribute to early warnings of the onset of BD in high-risk groups. Secondly, due to the variety of changes in the immunological index during the onset of bipolar disorder, such as a higher proportion of regulatory T cells (Drexahge et al. 2011, Kuwabara et al. 2018), changes occur in concentrations of various cytokines such as IL-6, IL -8, IL-1β, TNF-α, and TNF-β1, and brain-derived neurotrophic factor (BDNF) (Luo et al. 2016, Rosenblat and McIntyre 2017, Chen et al. 2020). Both the concentration changes and the extent of these changes are associated with the severity of mood disorders. Therefore, there are many studies about the use of these immunological indicators as a reference for the clinical treatment and outcomes of BD. Thirdly, studies have shown that some non-specific immunological indicators (such as the central granulocyte/lymphocyte ratio) can predict suicide risk and cognitive levels of patients with BD, which is of practical importance for public health management and social life (Ivkovic et al. 2016, Sağlam et al. 2018). As a result of investigations on the pathogenesis of autoimmune diseases, researchers hypothesized about cytokine-induced monoamine level changes, increased oxidative stress, abnormally increased microglial activation, and increased HPA axis activity in the pathogenesis of BD (Rosenblat and McIntyre 2017). Today, the inflammation-mood pathway has become a target area for the treatment of bipolar disorder (Sayuri Yagamata et al. 2017) and anti-inflammatory drugs and immunosuppressive drugs have begun to be included in clinical trials. Based on the result of these studies, it can be suggested that important progress can be made in the treatment of the comorbidity of BD and autoimmune diseases like RA.

Drugs Used in Rheumatoid Arthritis Treatment and Their Mental Effects

It is thought that prolonged use of drugs in autoimmune diseases may be among the causes of psychiatric symptoms and disorders. Psychiatric symptoms are common during systemic therapy with

corticosteroids, which are widely used in the treatment of RA. These symptoms include mood changes, cognitive disorders, sleep and behavior changes, and delirium and psychosis (Warrington and Bostwick 2006). Bolanos et al. (2004) have found a 60% risk of mood or anxiety disorders due to corticosteroid use. The neuropsychiatric effects of corticosteroids have often been associated with dysregulation of the HPA axis and impaired immune response.

Although there are case reports in the literature that monoclonal antibodies such as TNF-a antagonists contribute to improvements in cognition and mood, there are also reports of manic episodes associated with various monoclonal antibodies (Kaufman 2005, Brietzke and Lafer 2010, Ceïde and Rosenberg 2011, Austen and Tan 2012). The data on the relationship between monoclonal antibodies and triggered mood attacks is limited to the case reports. More studies are needed in this area.

Antimalarial drugs may cause clinical conditions such as central nervous system symptoms, irritability, nervousness, mood changes, sleep disorders, and psychosis (Hsu et al. 2011). It is thought that the ability of hydroxychloroquine to cross the blood-brain barrier and reach concentrations much higher than plasma levels facilitates the occurrence of possible side effects on the central nervous system (Kelley et al. 2001, Manzo et al. 2017). Chloroquine has been shown to increase dopamine neurotransmission and decrease the downregulation of dopamine receptors by binding directly to dopamine receptors (Bogaczewicz et al. 2013). Considering the known neurotransmitter interactions in the brain, it can be assumed that the dopaminergic properties of chloroquine will be further increased by its antagonistic effects on muscarinic acetylcholine receptors and by the indirect negative modulation of glutamate signaling (Kanju et al. 2007, Schatzberg and Nemeroff 2009). Previous findings suggest that conventional anti-inflammatory drugs such as celecoxib and infliximab may be suitable for use as a potential antidepressant in populations with mood disorders (Raison et al. 2013, Fond et al. 2014, Weinberger et al. 2015).

The recent development of new anti-inflammatory and immunomodulatory drugs has accelerated the development and implementation of immune-based interventions for the treatment of mood disorders (Rosenblat et al. 2016). Genome-wide association studies have shown that interactions with immune/inflammatory cytokine receptors have important roles in the development and progression of immunological diseases (e.g. T-cell-mediated diseases) via Janus kinase/signal transducers and activators of transcription (JAK/STAT) and mediated mechanisms (O'Shea and Robert Plenge 2012; Seif et al. 2017).

In recent years, significant progress has been made in the development of specific JAK inhibitors. Currently, there are 25 JAKinibs under development (at different stages of development) for the treatment of myelofibrosis, ulcerative colitis, psoriasis, RA, spondyloarthropathy, systemic lupus erythematosus, and various cancers, which are used as therapeutic agents in clinical trials. Only two JAKinibs have been approved for human use by the US Food and Drug Administration (FDA): ruxolitinib, a JAK1/JAK2 inhibitor, and tofacitinib, a JAK3/JAK1 inhibitor. Ruxolitinib was approved for the treatment of myelofibrosis and polycythemia in 2011 (Deisseroth et al. 2012) and tofacitinib was approved for the treatment of RA in 2012 (Traynor 2012). The significant second-generation JAKinibs are currently under development and considered to be potential disease-modified anti-inflammatory drugs for the treatment of autoimmune conditions, particularly RA (Banerjee et al. 2017). Current JAKinibs differ mainly in their selectivity for different JAK receptors; however, the selectivity that provides the greatest therapeutic effect with the lowest level of toxicity has not yet been determined. Although there are no clinical studies that specifically evaluated the therapeutic efficacy of JAKinibs for the treatment of depressive disorders, there are some indirect data suggesting that JAKinibs may have clinically significant antidepressant effects. For example, the use of JAKinibs has been associated with improvements in health-related quality of life measurements in individuals with inflammatory diseases (Panés et al. 2018). Particularly one study has shown that treatment of patients with inflammatory bowel disease (IBD) with tofacitinib resulted in significant improvement in mental health and quality of life. This improvement is probably associated with the improvement of depressive symptoms (Panés et al. 2015). Similar results were observed in another study involving JAKinib treatment in patients with RA (Schiff et al. 2017).

Physical Symptoms and Mental Health Effects of Rheumatoid Arthritis

One of the important physical symptoms of RA is fatigue. Approximately 80% of the patients clinically describe complaints of fatigue, which significantly affects their quality of life and physical capabilities (Rupp et al. 2004, Mok et al. 2012, Öncü et al. 2013, Nikolaus et al. 2013). The etiology of this symptom in RA patients is more complex than it seems. The etiology of fatigue includes pain intensity (Pollard et al. 2006), RA disease activity (Cutolo et al. 2014), inflammatory processes (Joharatnam et al. 2015), stress (Fifield et al. 2001), and the presence of concurrent mood disorders such as depression (Belt et al. 2009, Kekow et al. 2011). However, there have been important debates continuing about the mechanisms leading to fatigue in RA; the results of some studies suggest that fatigue occurs independently of RA disease activity (Nikolaus et al. 2013, Matcham et al. 2013). Some observations suggest that fatigue may mediate inflammation and therefore be treated with Disease-Modifying Drugs (DMDs) (Pollard et al. 2006). However, several studies have clearly shown that there are close relationships between fatigue, anxiety (Mok et al. 2012), and depression (Işık et al. 2007, Bruce 2008, Wolfe and Michaud 2009). The relationship between depression and fatigue is not limited to this. Fatigue is a common symptom of depression even among individuals without rheumatic disorders (Corfield et al. 2016).

Pain management is of great importance in RA patients. Antidepressants are used clinically by rheumatologists for pain and sleep disorders, added to the existing treatment. For this

purpose, tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and noradrenaline reuptake inhibitors are usually preferred, although not included in the guidelines. However, evidence-based data on this subject are not yet sufficient.

During the inflammation process, major plasticity changes occur in the peripheral and central nervous systems, resulting in lower pain threshold, allodynia, and hyperalgesia (Woolf and Salter 2000). Several mechanisms have been described including increased primary afferent excitability (Julius and Basbaum 2001), changes in gene expression (Woolf and Costigan 1999), abnormal neuron-glia interactions (Marchand et al. 2005), increased neurotransmission in the dorsal horn (Woolf and Salter 2000), and neuronal apoptosis (Scholz et al. 2005). But these mechanisms constitute only a small part of a complex puzzle yet known. Studies in this area may contribute to the development of new treatment approaches to pain management in the future. Depressed mood increases pain perception. The fact that pain perception and depression share similar neurochemical mechanisms supports the relationship between RA and BD (Blackburn-Munro 2001).

Antidepressants have been used for pain management, sleep disorders, and possible depressive complaints of RA patients for nearly half a century (Kuipers 1962). For this purpose, tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), and noradrenaline reuptake inhibitors (NRI) are usually preferred, although not included in the guidelines. TCAs block noradrenaline (NA) and serotonin (5HT) transporters, increasing the amount of these neurotransmitters in the intercellular space and expanding neurotransmission. The most significant condition limiting the use of TCAs is the common adverse event profile including dry mouth, urinary retention, cardiac conduction problems, orthostatic hypotension, and constipation. MAOIs act by increasing monoamine levels in the central nervous system. They may cause adverse events such as orthostatic hypotension, reflex tachycardia, weight gain, and sedation. SSRIs increase 5HT levels by inhibiting 5HT reuptake from presynaptic cells. They have also been reported to have an immunomodulatory and anti-inflammatory effect (Kubera et al. 2001). Adverse effects of SSRIs include insomnia, loss of appetite, sexual dysfunction, and drowsiness.

Selective serotonin-noradrenaline reuptake inhibitors (SNRI) increase both NA and 5HT levels. Their adverse effect profiles are similar to SSRI. NRIs, on the other hand, increase adrenergic transmission by blocking noradrenaline transporter activity. They may cause dry mouth, nausea, tremor, hypertension, and headache. Antidepressants are increasingly prescribed for conditions such as fibromyalgia, spondyloarthropathies, low back pain, and osteoarthritis (Lynch 2001, Hauser et al. 2009). In addition to such mechanisms observed with antidepressants, some studies have reported that antidepressants show anti-inflammatory activity by increasing the local synthesis of nitric oxide and Prostaglandin E2 in the joints (Yaron et al. 1999). These data support that antidepressants given for analgesic purposes provide pain relief independently of mood and also provide efficacy at lower doses than the antidepressant efficacy doses in less time (Lynch 2001). However, their analgesic role in patients with RA is unclear and their use is controversial. It may be recommended that antidepressants should be included in treatment regimens after considering their adverse event profiles and the risk-benefit ratio and after discussing them with the patient.

Physical symptoms of RA, such as fatigue and pain, significantly affect patients' mental health. Deteriorations in such chronic physical conditions may cause alterations in neural mechanisms, resulting in various effects on mental health. When we look at the literature, there are studies showing that there is an abnormality in the HPA axis response in RA patients (Straub and Cutolo 2001). In RA patients, changes in plasma hormone levels (such as testosterone), decreased cortisol release in response to stress, desynchronization of signals that coordinate the HPA axis and the autonomic nervous system, and increased levels of proinflammatory cytokines in plasma causes changes in immune system functions, which affect the mental state of the person (Straub 2014).

Stress-Cognition in Rheumatoid Arthritis Patients

Stress is the main link between HPA axis abnormalities and mental health in RA patients. Some studies have suggested that the decrease in the signal that manages the cooperation between the HPA axis and the sympathetic nervous system may result from chronic sympathetic nervous system activation and dysregulation of the acute physiological stress response (Nikolaus et al. 2013). Stress alone has also been identified as a factor that triggers RA attacks.

The individual's reaction to having a rheumatological disease is effective on his/her mood, physical and psychosocial functions (Evers et al. 2011). Perception of pain more than usual/exaggerated pain is more common in individuals with RA than in healthy individuals, which predicts increases in pain severity, inflammatory activity, and disability levels (Edwards et al. 2011).

Behaviors of the person to adapt to living with RA are effective on RA symptoms and the problems caused by the symptoms. Passive coping methods, such as self-isolation or adjusting behaviors to avoid the experience of pain, increase the likelihood of future functional impairment in RA patients (Englbrecht et al. 2012). Behavioral coping responses of patients with RA are closely related to how they view the disease; As noted earlier, individuals who view their pain and disease as uncontrollable or catastrophic are less likely to cope effectively with their physical symptoms than patients with optimistic views (Nakajima et al. 2006, Englbrecht et al. 2012).

Case Samples

Case 1

B.E. is a 28-year-old female patient, married, has one child, a university graduate, not working. She presented to our outpatient clinic with the symptoms of talking too much and too fast, jumping from one topic to another, increased energy, nervousness, insomnia, and increased self-confidence, which had been going on for three months.

The patient had presented to a physician with complaints of morning stiffness, swelling in the left ankle, and joint pain, and had been diagnosed with RA in 2011, then started treatment with methylprednisolone at 15 mg/day. The patient's complaints had regressed with this treatment, then methylprednisolone had been discontinued in 2013 due to drug incompatibility, and 15 mg/week methotrexate treatment started. She had achieved remission with this treatment, and due to the planned pregnancy, discontinued the drug in March 2018 under the supervision of a doctor. Due to the recurrence of joint tenderness, pain, and morning stiffness, she had started treatment with salicylazosulfapyridine at 3 g/day and hydroxychloroquine at 400 mg/day in June 2018. She had received this treatment for 3 months, then her first psychiatric symptoms had started in September 2018 with a manic episode accompanied by psychotic symptoms of persecutory delusions. During this period, she had been hospitalized to receive treatment with lithium, quetiapine, olanzapine, biperiden, and diazepam, and then discharged. After 2 weeks of discharge, she had discontinued lithium under the supervision of a doctor. Other drugs had also been gradually reduced and she had completely discontinued them in December 2018 due to a planned pregnancy. Her pregnancy had started in January 2019, and she had not been check by a psychiatrist or used psychotropic drugs. 2 months after giving birth, she had developed an elevation with nervousness, insomnia, talking a lot, and increased energy, and started to receive olanzapine 5 mg, which had been increased within a week to 15 mg/day. Since her complaints did not regress, she presented to our outpatient clinic with these complaints. In the psychiatric examination of the patient, it was observed that she was oriented and cooperative and had a euphoric affect, enhanced involuntary attention, increased volume and speed of talking, disorganized associations, dominance of grandiose themes in the thought content, and increased psychomotor activity. The duration of sleep was reduced. No pathological perceptions were found within the limits of the examination. Consequently, the patient was hospitalized in the psychiatry clinic of B.U.Ü.T.F Hospital with the preliminary diagnosis of a manic episode without psychotic symptoms.

She had no history of disease other than RA. r cousin was under monitoring for BD due to the family history. She did not use alcohol-cigarettes-drugs.

She was treated with haloperidol 5 mg+biperiden 5 mg+chlorpromazine 25 mg 2x1 intramuscular (IM) for 1 week followed by orally administered haloperidol 5 mg/day, biperiden 4 mg/day, chlorpromazine 300 mg/day, and lithium 300 mg as a mood stabilizer. Her elevated mood symptoms regressed and the lithium dose was increased to 600 mg/day when the plasma lithium level was measured 0.5 mmol/L. The plasma lithium level was measured as 0.8 mol/L with this treatment. She had a normal psychomotor activation, but following the development of sub-threshold depressive symptoms, antipsychotic treatment was gradually discontinued and she was discharged in remission with lithium 600 mg/day. The patient was euthymic when this article was prepared.

Case 2

S.B. is a 37-year-old female patient and married. She has two children and she is a university graduate but not working. She

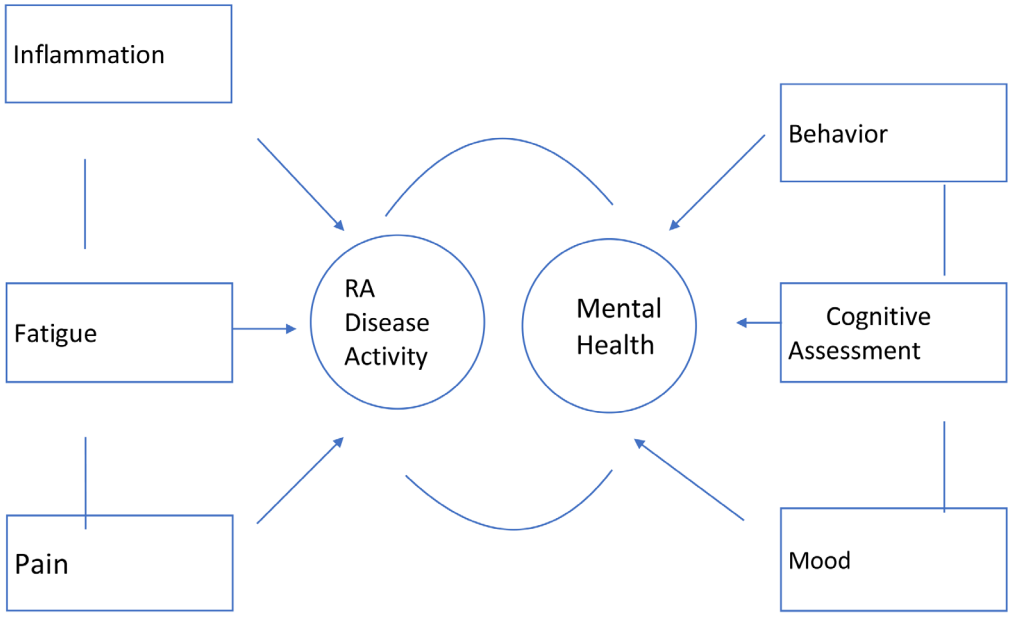

Figure 1. Relationship between mental health and rheumatoid arthritis (RA) disease activity

presented to our outpatient clinic due to nervousness, insomnia, and increased self-confidence she had for 10 days.

She had been diagnosed with RA in 2009 due to the complaints of swelling in the hand and knee joints during the second trimester of her second pregnancy. Her rheumatological complaints had regressed with 15 mg/day methylprednisolone treatment after giving birth. Three months after the initiation of methylprednisolone treatment, complaints of persecutory delusions, reference delusions, and increased irritability had started. She had presented to a psychiatrist with these complaints and started risperidone 2 mg/day. The treatment had been revised by the rheumatologist as leflunomide 10 mg/day. Her psychiatric and rheumatological complaints had regressed.

After 6 months, she had discontinued the psychiatric treatment on her own decision without the approval of the physician. Following discontinuation of the drug, her complaints of increased irritability, talking too much, and grandiose delusions had recurred, then her treatment had been revised as quetiapine 25 mg/day, olanzapine 5 mg/day, and lamotrigine 50 mg/day. She had continued with this treatment until 2015, with a total of nine attacks in similar characteristics, simultaneous with the periods of drug discontinuation. She had been hospitalized in B.U.Ü.T.F. psychiatry clinic in 2017 due to persecutory and grandiose delusions, increased irritability, and suicidal thoughts. She had been discharged in remission on treatment with haloperidol 5 mg/day, biperiden 4 mg/day, olanzapine 20 mg/day, and zuclopenthixol 200 mg/every 3 weeks. Following her non-compliance with the medication, she presented to our outpatient clinic in January 2019 with complaints of insomnia, increased energy, irritability, and talking too much. Her psychiatric examination revealed that she had full orientation and cooperation, irritable affect, increased volume and speed of talking, dominance of grandiose themes in thoughts, increased psychomotor activity, and reduced sleep. No pathological perceptions were detected within the limits of the psychiatric examination; therefore, the patient was hospitalized in the psychiatry clinic of B.U.Ü.T.F Hospital with the preliminary diagnosis of a manic episode.

She had no history of disease other than RA. She had no relevant family history. She did not use alcohol-cigarettes-drugs.

She was treated with haloperidol 5 mg+biperiden 5 mg+chlorpromazine 25 mg 2x1 IM for 3 days followed by orally administered haloperidol 5 mg/day, biperiden 4 mg/day, and chlorpromazine 100 mg/day. Considering that the patient had seasonal manic episodes with psychotic characteristics, she was discharged in remission on treatment with lithium 600 mg/day, haloperidol 5 mg/day, and biperiden 4 mg/day. The last treatment she received during the monitoring period was lithium 600 mg/day and aripiprazole 400 mg/once a month by intramuscular injection, and the patient was euthymic when this article was prepared.

Conclusion

With the cases presented in this context, it should be noted that there may be an increased risk in terms of BD spectrum and other psychiatric comorbidities in RA patients with various mental and physical disorders. Clinicians should keep the psychiatric disorders in mind in association with the patient's compliance with treatment, the course of the disease, and the quality of life.

It should be taken into account that this process may cause neuroinflammation and, as a result, psychiatric disorders in chronic inflammatory diseases. In the light of the information obtained, it was aimed to draw attention to psychiatric comorbidities in systemic diseases with these two cases, although RA could not be regarded as a definite risk factor for BD. More controlled studies are needed in this area. Both the stress caused by the disability resulting from the general deteriorating course of the disease and the effects of the drugs used in the treatment of RA may trigger several types of mood disorders. It is noteworthy that steroids, which are commonly used in the treatment of many patients, can cause psychiatric symptoms such as mood attacks. It can be recommended that especially people with a family history of BD should be carefully monitored for psychiatric symptoms that may occur with steroid use. It is a research subject that the inflammatory system diseases impact many systems and whether they play a role in the etiology of many diseases, especially psychiatric diseases, In this regard, it can be suggested that the relationship between RA and BD should be examined in detail since it is partially neglected and needs to be investigated.

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