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RA and depression

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Abstract

Depression constitutes the most frequent comorbid condition associated with rheumatoid arthritis (RA), with prevalence rates ranging from 14% to 48%. This wide range can be explained by several factors including subtypes of depression considered, instrument of measure (i.e. self-questionnaires versus clinical interview), threshold applied but also the overlap of symptoms between the two conditions. Despite being a frequent comorbid condition in RA, depressive states are repeatedly underdiagnosed and thus, often remain untreated. Consequences are dramatic as conclusive evidence shows that depression deleteriously impacts just about all outcomes of RA, including disease activity, arthritis-related complications, level of pain, chance of remission, quality of life and mortality. Importantly, links between depression and RA appear to be bidirectional as if RA patients show increased prevalence of depression. Conversely, patients with depression compared to the general population have higher risk to develop RA. Among the factors explaining this strong association between depression and RA, recent advances have underlined the putative role of models based on the inflammatory hypothesis. Pro-inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-1, IL-6, and IL-18 are involved in RA pathogenesis, but also in depression. Furthermore, the connections between the central nervous system, the peripheral system and the immune system are now better understood. As a consequence of the strong comorbidity and the aggravated prognosis, the management of patient showing this dual diagnosis should be carefully monitored. The common pathophysiology also opens the path to utilization of RA treatment in severe depression or treatment-resistant depression.

Keywords

Rheumatoid arthritis; depression; common characteristics; inflammation

Recent evidence from last decade has widely reported an association between rheumatoid arthritis (RA) and depression. We therefore review main mechanisms of this association.

RA and depression : prevalence

Depression is the most common comorbid disorder associated with RA, although the exact prevalence rates of depression in RA remains unclear. In 3,920 European RA patients, depression is the most common comorbidity, accounting for approximately 15% [1]. Matcham and colleagues [2] already propose a systematic review and meta-analysis of this prevalence, including 72 reports of a total of 13,189 RA patients. While the prevalence rates of all studies, including the large number of studies using self-questionnaires, range from 14% to 48%, pooled estimates from the limited number of studies using clinical interviews show that 16.8% of RA patient suffered from major depression. A recent systematic review in China [3], which includes 21 studies for a total of 4,447 patients, reports rates of 48% of depression in RA. However, when looking at the different types of depression, the authors find rates of 30% for minor depression and dysthymic disorder, and 18% for moderate or major depression. This high prevalence compared to the general population is similar to that of other chronic diseases such as diabetes [4] or cancer [5]. This suggests a plurality of factors linking depression and RA. Similarly, in population-based cohorts, the incidence rate ratio for depression is significantly higher in patients with RA compared to the general population [IRR 1.46], after adjustment for covariates [6]. Low socioeconomic factors, gender, age (younger), race/ethnicity, functional limitation, pain and unfavorable clinical status and systemic inflammation have all been associated to depression among patients with RA [7]. Low self-esteem is one of the strongest predictors of depression in patients with RA [7]. Furthermore, it appears that comorbid depression is most likely linked to severe forms of RA [8].

Major depressive disorder: diagnostic problems

The wide variance in prevalence rates of depression in RA is mainly due to the disparity in definition of depression, the scale thresholds use to identify depression and the overlap of symptoms between these two conditions [9]. Although depressive disorders are a common comorbidity in RA, they are frequently underdiagnosed. There are several reasons for this, such as the stigma attached to psychiatric illnesses, or the lack of time available to inspect psychological aspects in depth. Also, as with many other chronic diseases, the presence of sleep disturbance, fatigue, loss of appetite or pain may be wrongly attributed to a somatic condition rather than a mood disorder. Conversely, studies

using only a mood questionnaire may overestimate depression for the same reasons. Indeed, screening instruments for depression are validated and used in the general population [10,11] and the items of these scales include somatic symptoms of mood disorders (sleep disorders, fatigue,...) which, as mentioned before, are frequently encountered in RA as consequences of this disease. In order to correctly distinguish the causality of these overlapping symptoms, it is necessary to use instruments that dissociate the emotional, cognitive, and somatic components. It is noteworthy that some questionnaires, such as the Beck Depression Inventory for Primary Care BDI- PC [12] (also known as BDI Fast Screen for Medical Patients [BDI-FS]) or the Hospital Anxiety and Depression Scale (HADS) [13], are specifically designed to identify depression in primary care patients. As a result, these scales place less emphasis on, or even eliminate, the somatic components of depression. A practical review of depression scales used in the clinical setting of rheumatology [14] also highlights the high usefulness of the Patient Health Questionnaire-9 (PHQ-9) [15] and the Geriatric Depression Scale (GDS) in older patients [16].

Another caveat is that most studies reporting rates of depression in RA are based solely on self-administered questionnaires. While these tools can be used to evaluate symptom severity and as screening instruments to detect patients at risk of depression, they are not designed to establish diagnostic status, which must be established by an appropriate interview. Given the reported sensitivity and specificity estimates, these tools may again overestimate the prevalence of depression [17]. A recent study specifically tests the validity and reliability of screening instruments for depression and anxiety in RA, compared to SCID (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders) diagnostic interviews [18]. Among the 150 RA patients assessed, 11.3% has depression diagnosed with SCID interview, a rate that is in the lower range of depression levels typically reported in RA. These figures are then used to measure sensitivity and specificity thresholds of the cut-points in screening tools and show good performance for depression scales, but more variable performance for anxiety scales.

Impact of depression on RA

There is compelling evidence that depression has a negative impact on the course of RA. Depression increases disease activity, worsens arthritis-related complications, intensifies pain levels, and is associated with a decreased chance of remission as well as decline in health-related quality of life [9,19]. Depression is also linked to increased mortality in RA, with an attributable proportion of mortality due to depression of 6.9% [20]. These negative effects of depression can be explained by several factors. Firstly, depression may impair adherence and compliance to treatment. It can also

reduce pain tolerance and physical activity. In addition, the cognitive impairment and negative cognitive perceptions encountered in depression may impact patient reported outcomes. Finally, in line with the inflammatory hypothesis (see below), depression may also increase inflammation, thereby worsening RA disease activity [21].

In line with the latter hypothesis, it should be noted that the link between depression and RA appears to be bidirectional. While about 30% of RA patients develop depression within 5 years of diagnosis [7], conversely, depressed patients, compared to the general population, have an increased risk of developing RA [22]. The National Health Insurance research database shows a higher incidence of RA in depressed than in non-depressed individuals (2.07 vs. 1.21 per 1,000 person-years), with an adjusted hazard ratio of 1.65 (95% CI, 1.41-1.77) [23]. Similarly, in a retrospective study using the British Health Improvement Network (THIN) database, Cox proportional hazards models show a 38% increased risk of developing RA in people with major depressive disorder after adjustment for age, sex, comorbidities, smoking, body mass index, and antidepressant use [24]. Interestingly, this study shows that the use of antidepressants in patients with depression may have a protective effect on the risk of developing RA. The latter result seems to be in line with the possible direct anti-inflammatory effect of antidepressant drugs [25]. The protective and therefore confounding effect of antidepressant drugs on RA is further supported by a recent study. This other retrospective cohort study examines pooled data from the Nurses' Health Study (NHS) [26]. The results confirm higher Cox regression estimated hazard ratios (HRs) in depressed women than in non-depressed women [HR: 1.28 (95% CI 1.10-1.48)] for all subsets of RA. However, further analysis of the depression subgroup reveals that regular antidepressant use is not associated with subsequent seropositive RA (HR 1.21 [95% CI 0.97-1.49]) but is associated with seronegative RA (HR 1.75 [95% CI 1.32-2.32]).

Common risk factors

In general, the associated diseases share some common risk factors. Among risk factors for both diseases, post-traumatic stress disorder (PTSD) is shared by both. The relation is largely described in depression, but has also been reported in RA in recent years [27,28]. However, a chronic disease and handicap are two features of RA and risk factors for depression. The risk of RA in depression does not vary by gender, but the risk of RA is increased after 40 years of age [23]. An effect of the duration of depression is observed, with a higher incidence rate of RA observed in the periods of 3-5 years and more than 5 years after the onset of depression. The postpartum period is a period of increased risk for both depression and RA [29]. Recently, it has been reported that mental disorders such as depression increase the risk of inflammatory diseases such as another inflammatory arthropathy,

psoriatic arthritis [30], as well as other autoimmune diseases including inflammatory bowel disease [31], and others [32]. These reinforce the temporal nature of these inflammatory relationships.

Pathophysiology

The increased frequency of depression in RA can be explained by several factors. Firstly, the overwhelming effect of a chronic disease induces disability and has negative functional consequences. Furthermore, persistent pain, fatigue and low energy can also have an impact on patients' mood. In addition to these psychological causes, recent advances have highlighted possible biological explanations through models based on the inflammatory hypothesis [33]. In recent years, the interactions between the central nervous system (CNS) and the immune system have been described in detail [34]. It is assumed that some of the psychiatric diseases, including depression, are closely associated with systemic inflammation and cytokines [35]. This model proposes that pro-inflammatory cytokines, comprising tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and IL-18, are present at high levels as a result of the inflammatory response to RA. These peripheral cytokines influence brain function in two ways:

- The neural pathway, where peripheral pathogen-associated molecular patterns (PAMPs) and cytokines activate primary afferent nerves, such as the vagal nerves, which then modulate the brain nuclei, including the amygdala, a central actor of the limbic system.
- The humoral pathway. PAMPs reach the brain via direct connections to the choroid plexuses and circumventricular organs, independently to blood-brain barrier. These activated structures promote the discharge of pro-inflammatory cytokines by macrophage-like cells expressing Toll-like receptors (TLRs), which then reach the brain. Circulating mediators can also activate the blood-brain barrier endothelium, which then actively transports molecules such as TNF α into the brain, or lead in microglial activation and subsequent secretion of pro-inflammatory factors.

Once the pro-inflammatory cytokines have entered the CNS, they have multiple effects on the brain tissue. They impact neurotransmission, notably serotonin, a major neurotransmitter involved in depression, due to the decreased availability of tryptophan, resulting from the upregulation of the enzyme indole-amine 2,3-dioxygenase (IDO). In addition, TNF can also increase the expression of the serotonin transporter, which further reduces serotonin levels. Pro-inflammatory cytokines also impact on another neurotransmitter, glutamate, as IDO leads to increase in kynurenine, which upon conversion, leads to an increase in glutamate, with neurotoxic effects [36]. Pro-inflammatory cytokines also impact neurogenesis and neuroplasticity by decreasing both brain-derived neurotrophic factor (BDNF) expression and neurogenesis. Importantly, these changes in brain function and morphology

affect corticolimbic circuits involved in emotion regulation and stress regulation. Finally, the cytokines induce also modification in hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid function, which are widely associated with depression.

Treatment of depression and the impact of rheumatoid arthritis treatments on depression

The treatment for major depressive disorder is multidisciplinary, and pharmacology plays an extremely important role. Although advances have been made in the treatment of major depressive disorder, it is estimated that at least 50% of individuals will not respond to the initially proposed therapeutic regimen, and that 15-30% of depressed individuals will not respond satisfactory to any treatment with pharmacotherapy or psychotherapy [37]. Regarding pharmacological treatments for major depressive disorder, it is estimated that 15-50% of patients do not respond to treatment with traditional antidepressant [38]. It is important to emphasize that untreated depression has important consequences, and could have a substantial impact on clinical outcomes. A shorter duration of untreated depression is associated with better clinical outcomes [39], both in terms of recovery from depression symptoms, and with more pronounced reductions in depression-related disability - including improved work recovery, home management, social activities, and recreation. The term "treatment-resistant depression" (TRD) is used for severe depression when there has been a failure of at least two evidence-based, dose-dependent, time-tailored treatment regimens (>4 weeks) [40].

We describe above that inflammation is fundamental to the course of major depressive disorder [41]. High levels of pro-inflammatory cytokines in patients with major depressive disorder are an important factor in the alterations to their behavior, neuroplasticity, and brain structure [42]. Furthermore, elevated levels of pro-inflammatory cytokines may also be associated with the decreased levels of anti-inflammatory cytokines such as IL-10 [43]. Thus, inhibition of these pro-inflammatory cytokines would improve depressive symptoms, and increases the patient's response to antidepressant effect [44]. Patients with treatment-resistant depression exhibited higher levels of TNF, IL-6, IL-8, C-reactive protein (CRP), and macrophage inflammatory protein-1, which are also associated with poorer treatment outcomes [45].

Some anti-inflammatory drugs such as N-acetylcysteine and minocycline are reported to be effective in treating severe depressive episodes [46]. New therapeutic agents with anti-pro-inflammatory cytokine properties are also being investigated to reverse the symptoms of these psychiatric disorders [47]. Evidence of association between TNF and mood disorders is well established [48]. Infliximab is proposed as a promising adjuvant treatment of antidepressant drugs. Infliximab is delivered at baseline, 2 weeks, and 6 weeks (5 mg/kg) versus placebo [49]. Infliximab demonstrates a 50% reduction in depressive symptoms within the study duration of 12 weeks, but in both groups. However,

lipid markers are related to treatment response to infliximab and only decrease after a single infusion of infliximab only in patients with CRP >5 mg/L. This paper confirms previous result exploring gene expressions related to glucose and lipid metabolism in the peripheral blood mononuclear cells [50]. Altered transcriptional signatures of baseline lipid and glucose metabolism are predictive of the antidepressant response to infliximab. Thus, TRD patients have dysregulation of lipid and glucose metabolisms with a putative clinical beneficial of infliximab. Serum lipid levels are compared between patients major depressive episode or major depressive disorder and healthy controls [51]. Authors observe an important association between serum lipid levels and depression symptoms. Since pro-inflammatory cytokines are elevated in depression, it is not surprising that some targeted anticytokine therapies are investigated to treat major depressive disorder. Furthermore, an increased expression of inflammatory genes -including TNF- is reported in TRD patients compared to those who responded to treatment. A pro-inflammatory imbalance in the TNF system could contribute to the pathogenesis of mood disorders and related comorbidities [52]. There is evidence that TNF plays an important role in autoimmune and inflammatory diseases, and that any disruption of TNF levels in the central nervous system can induce inflammatory responses [53]. Patients with major depressive disorder have higher serum concentrations of TNF receptor subtype 1 than healthy controls [54]. So, targeting TNF can be efficient in depression. Infliximab efficacy is related not only to its TNF-binding neutralization capabilities, but also to its effector functions associated with the Fc domain [55]. In responders, concentrations of TNF and its soluble receptors are significantly higher at baseline versus non-responders to infliximab, as the decreasing of CRP from baseline to week 12 [56]. This is consistent with the idea that increased inflammation prior to treatment predicts non-response to conventional antidepressant therapy, while potentially predicting a successful response to immune-targeted therapy. Furthermore, this elevated TNF level has also been reported as a good predictor in RA [57]. Adjuvant infliximab therapy in adults with bipolar I and bipolar II depression is assessed [58]. This study confirms evidence of pre-treatment inflammatory activation, but fails to demonstrate a reduction of depressive symptoms by infliximab. So, despite several studies confirming involvement of TNF in depression, the use of anti-TNF drugs is not well investigated [59].

IL-6 is the second pro-inflammatory cytokine targeted during depression. Clinicaltrials.gov lists two studies to block IL-6. The first one, NCT02473289 with sirukumab an anti-IL-6 is not effective with no significant variation of HDRS-17 versus placebo. The second is the NCT02660528 with tocilizumab. The trial protocol is already published with only one intravenous infusion of tocilizumab on somatic symptoms score in patients with severe depression [36]. However, No participants are assigned to treatment arms because none of the participants were eligible to continue the study after screening. JAK/STAT modulation is currently used in RA since few years. Since JAK/STAT pathway is involved in neurogenesis, synaptic plasticity, gliogenesis and microglial activation, blocking JAK pathway will have

some antidepressants [60]. However, a clinical trial testing tofacitinib on emotional processing in depression was suspended due to Covid-19 pandemic (Tofacitinib in Depression; TIDE study; NCT04141904). Another study will describe effect of tofacitinib on depression in RA patients (NCT03992781).

To conclude, the link between inflammation and depression is strong explaining in part the association with RA. Despite negative few clinical trials in depression, blocking inflammation could be a new way to improve severe depress patients with resistance to usual treatment. Nether less, in our RA patients, depression tend to be reduced by active treat to target management.

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