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Research Article

The Impact of Depression, Anxiety, and Fatigue on Rheumatoid Arthritis Activity

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Abstract

Rheumatoid arthritis (RA) is a chronic, immune-mediated disease that affects more than 15 million people worldwide. The disease occurs predominantly between the fourth and fifth decades of life.

RA is associated with considerable disability. Anxiodepressive terrain and fatigue are frequent comorbidities in rheumatoid arthritis (RA) and affect up to 66% of sufferers.

In people with RA, depression is associated with lower levels of pain and disability, as well as a lower quality of life.

Symptoms of depression and anxiety are associated with increased disease activity, reduced response to treatment, and decreased likelihood of symptom remission. Their management could be a way to improve the quality of life of patients. However, pharmacological treatments commonly used for depression may be less effective in people with RA who use anti-inflammatory drugs or cause potentially harmful side effects.

However, few studies have evaluated their impact on disease activity as well as on therapeutic response.

The main objective of this study would be to identify the psychological impact on the activity of rheumatoid arthritis.

Keywords: Rheumatoid Arthritis; Depression; Anxiety; Disease Activity

Abbreviations

RA: Rheumatoid Arthritis; VS: Sedimentation Rate; CRP: C-reactive Protein; ANA: Antinuclear Antibodies; FR: Rheumatoid Factors; anti-CCP: Anti-peptide Antibodies Citrullines; HAQ: Health Assessment Questionnaire; MADRS: The Montgomery and Asberg Depression Rating Scale

Introduction

Rheumatoid arthritis (RA) is the most frequent chronic inflammatory rheumatism with a prevalence in Morocco estimated between 0.25 and 0.50% [1]. It generally begins at a relatively young age but can nevertheless appear at any age.

The functional impact caused by disability and pain and chronic as well as the deformities caused by the disease, have a major impact on the quality of life, the progression of the disease relapses, and the undesirable effects of certain drugs justify a long-term and close follow-up, which could prove to have a major impact on the daily lives of patients and thus affect their mental state [2].

Therefore, the anxiety and depression generated can be responsible for an impact that can lead to worsening of the activity of rheumatism, pain, as well as a deterioration in the quality of sleep, and the appearance of chronic fatigue. It is in this perspective that the screening and management of these comorbidities should be early for better control of the pathology.

In our study, depression and anxiety were commonly found in patients with RA and their presence interfered with disease activity.

The objective of this study is to describe the psychological comorbidities associated with RA, which would favor them with an evaluation of their impact on the activity of the latter.

Material and Methods

We conducted a cross-sectional study over a period of eight months (February to September 2021), including consecutively 60 patients with RA, at the rheumatology consultation of the CHU IBN Rochd de Casabalanca. We excluded patients with a psychiatric history or factors that could lead to depressive disorders and those with hearing or comprehension problems that did not allow them to answer questions.

This work required the collection of epidemiological, clinical and para-clinical (biological, immunological and radiological) data, using a survey sheet. All the patients had a systematic sample including an inflammatory work-up (sedimentation rate [VS] and C-reactive protein [CRP]) and an immunological work-up (antinuclear antibodies [ANA], rheumatoid factors [FR] and anti-peptide antibodies.

citrullines [anti-CCP]). The activity of RA was assessed by the disease activity score (DAS) 28-VS and DAS 28-CRP and the quality of life of patients by the validated moroccan version of the health assessment questionnaire (HAQ) [6]. Standard x-rays (front hands and wrists, front forefoots and front pelvis) were taken to assess the condition structural. Depression was assessed by the Montgomery and Asberg depression rating scale (MADRS). The latter is a hetero-assessment scale carried out face to face with the patient, comprising ten psychic and somatic items rated from 0 to 6, the scores of which add up. The depression threshold score is set at 15 [7].

An overall description of the entire sample was made, specifying the simple frequencies and the relative frequencies (percentage) for the qualitative variables. Means, medians, and span-determined standard deviations (outliers) were reported for quantitative variables. Comparisons of means on independent series were performed using the t test of Student for independent series. The correlation study was carried out between the various parameters collected and the psychiatric rating scale by the Pearson correlation coefficient (r). In all statistical tests, the significance level was set at 0.05.

Results

Sixty patients were included. A female predominance was noted with a sex ratio F/M = 4. The mean age of the patients was 59.7 years [26-79 years]. The main characteristics of the study population are summarized in table 1. The mean MADRS score was 13.2% [0-37] with a prevalence of depression at 45%. The factors associated with the occurrence of RA were female sex (p = 0.04), existence of associated diabetes (p = 0.039), lack of professional activity (p = 0.001) and not being affiliated with compulsory health insurance (p = 0.005).

The age of the patients (p = 0.63), their family status (p = 0.7), their level of study (p = 0.12) and their living environment (p = 0.8) did not constitute risk factors for the onset of depression.

Regarding factors related to RA itself, depression was correlated with clinical parameters of RA activity: number of painful (p = 0.03) and swollen (p = 0.023) joints, duration of stiffness morning (p = 0.007), general assessment by the doctor (p = 0.003) and pain intensity assessed by the visual analogue scale (p = 0.013). It was also correlated with the DAS28-VS and DAS28-CRP scores (respectively p = 0.04 and p = 0.002) as well as with the deterioration in the quality of life of the patients (p = 0.001).

Radiographically, depressed patients had more joint destruction (p = 0.028) and had more coxitis (p = 0.039) than non-depressed patients. The other parameters related to RA were not associated with depression, including duration of disease progression (p = 0.29), existence of joint deformities (p = 0.06) and presence of extra-articular manifestations. Biologically, the values of ESR and CRP in depressed patients were comparable to those in non-depressed patients (p = 0.458 and p = 0.07, respectively). RF positivity and the presence of anti-CCP antibodies were significantly comparable in depressed and non-depressed patients.

Depressed (respectively p = 0.6 and p = 0.39). The different treatments administered did not influence the onset of depression either (p = 0.063).

Discussion

Depression is associated with RA, the associated with its occurrence being female sex, lack of social coverage, professional inactivity, high RA activity, impaired quality of life as the existence of structural damage.

Characteristics	Résults
Antecedents médicaux	80.36%
Arterial hypertension	23.3%
Diabetes	11.7%
Dylipemia	6.7%
Others	8.3%
Any Socio-economic characteristics	50.0%
Married	70%
Singles	16.7%
Divorced	1.7%
Widowed	11.7%
Children	80%
Schooled	53.3%
Illiterate	46.7%
Professional activity	16.7%
Manual work	80%
Social Security	78%
Urban living environment	80%
Rural living environment	20%

Table 1: The main characteristics of the study population.

Characteristics of RA	
Duration of development in years	9.91 ans +/-[8 ans]
Treatment: analgesics	91.2%
Treatment: NSAIDs	48.6%
Treatment: low dose corticosteroid therapy	86.5%
Background treatment	83.3%
DAS 28 VS medium	4.92[1.61 - 8.37]
DAS 28 average CRP	4.3[1.61 - 7.82]
Average HAQ	1.29[0-3]
Joint deformities	53.6%
Extra-articular manifestations	51.6%
Positive anti - nuclear antibodies	1.7%
Positive rheumatoid factors	76.4%
Anti-CCP positive bodies	71.5%
Radiological joint destruction	92.5%

Table 2: Characteristics of RA.

The prevalence of depression in RA has been estimated to be 45%; in the literature, the prevalence is 15-66.2% [1.8-10]. The difference in these results could be explained, on the one hand, by the difference between the study populations, and on the other hand, by the use of different diagnostic tools. The prevalence of depression varies among populations.

Margaretten., *et al*. observed that Asian patients perceived RA had a lower prevalence of depression compared to Caucasian patients, African patients, American patients and Hispanic patients [13]. We chose the MADRS scale for its reliability, sensitivity and specificity [6,14]. are directly linked to high disease activity.

Chronic pain can cause depression through a direct effect on the brain. Pain is felt in a specific area of the brain, and if that area is constantly active, as pain messages keep coming in, depression can result. The chemicals in the brain at the pain center are the same chemicals that control mood, so overactivity in the pain center can cause depression.

Thus, the workload, whether at home or in a professional environment, can seem too great with the disease. Stress, shame at not being able to do it and not holding on, demotivation can be felt by the patient. He may become irritable and withdraw into himself.

Intimate life can also be disrupted by rheumatoid arthritis and threaten the balance of the couple.

Thus the symptoms of rheumatoid arthritis have real consequences on the daily life of the patient and also in his social relations. The repercussions of these symptoms are experienced differently by individuals and by their family/social situation. Negative feelings can then develop in some cases and turn into depression.

Epidemiological and social factors

In most studies, the mean ages were not significantly different between the depressed and non-depressed groups [1,4,9,11]. We did not observe a correlation between age and depression in our study (p = 0.63).

Ho., *et al*. observed a significant positive correlation between age and depression in RA. Women are twice as affected by depression as men [16]. Genetic, neuro-hormonal, psycho-biological and social

differences explain this difference [17,18]. During RA, the female predominance of depressed patients could be explained by the greater psychological vulnerability of women to pain as well as to the aesthetic, functional and social repercussions of RA. an increase in the perception of pain with a decrease in the threshold of the latter, thus increasing the functional handicap as well as the repercussions on family, professional and social life, would constitute greater risk factors for the onset of depression, sometimes requiring even recourse to hospitalization. Co-morbidities associated with RA are not always a definite risk factor for depression [12]. In our study, only a history of diabetes was a predictor of the onset of depression. This is explained by the frequency of the association of diabetes and depression, the latter being three times more common in diabetics compared to the general population [12]. The influence of family status would in turn affect the psychological component [8]. Work is a risk factor for the occurrence of anxiety-depressive disorders in the general population [13], but this has not been confirmed during RA [5,8], and moreover in our study, the on the contrary, practicing a professional activity was a protective factor against the onset of depression. This could be explained by the fact that work offers patients with RA other concerns, thus preventing them from focusing too much on their illness while those who are not in a professional activity would be more prone to feelings of Self-deprecation and worthlessness which was linked in our study has a very important activity of rheumatism.

Specific factors of rheumatoid arthritis

The duration of RA does not seem to have a clear influence on the onset of depression [9,11], this finding was found in our study. This has not always been confirmed since in some studies the evaluation score of depression increased significantly over time [15,16]. The results are therefore mixed as to the worsening or improvement of depressive disorders during the course of RA, suggesting that the course of Depression may depend on how well your RA progresses. RA in remission would lead to an improvement in depressive disorders while a more active, more erosive RA, causing more joint deformities and functional disability would induce their persistence, or even their aggravation, itself leading to a increased activity in rheumatoid arthritis.

Certain anti-depressant treatments, specifically imipramine, even induce a significant drop in RF levels from the second week of treatment [17]. These are findings, with no real hypothesis capable of explaining the basis of this association.

In our study, the immunological profile of the patients was not a predictor of the onset of depression. In a ten-year Norwegian cohort study of patients with recent RA, the level of depression was correlated with structural progression [14]. Joint destruction can be a source of deformities which cause significant aesthetic damage, thus suggesting a greater prevalence of depression in these subjects. In our study, depression would be a factor favoring the appearance of joint deformities ($p = 0.022$).

Regarding the relationship between depression and medications used in RA, a Canadian study reported a greater prevalence of depression in RA patients with gastrointestinal disturbances due to nonsteroidal anti-inflammatory drugs. However, the retrospective nature of this study does not allow us to know whether it was dyspeptic disorders caused by NSAIDs that were responsible for the onset of depression, or if depression was a risk factor for the onset of gastrointestinal disorders. induced by nonsteroidal anti-inflammatory drugs [18].

Ho., *et al*. reported an increased risk of depression and anxiety with an increase in the number of treatments received, regardless of type [17]. The more the patients were satisfied with their treatments, the lower the risk of developing depression [7,9]. Depression is a risk factor for non-adherence to treatment, which in turn explains its direct link with disease activity, depressed patients being three times more likely to be non-compliant to treatment compared to non-depressed patients [5]. Essentially corticosteroids, the psychiatric complications of which are well known [4,11].

We did not observe in our study an association between depression and the use of corticosteroids ($p = 0.063$), or with the various DMARDs ($p = 0.73$).

One of the main axes around which the PR-depression relationship revolves is the activity of RA. Contrary to our results, Murphy., *et al*. found no correlation between the number of painful joints and/or the number of swollen joints and the occurrence of depression in RA [9]. El Miedany., *et al*. reported a significant correlation between morning stiffness and depression ($p < 0.009$) [10]. But the most studied clinical endpoint of RA activity is probably pain and this the latter would be a strong provider of depression [10,11] which itself is linked to the increase in the intensity and chronicity of pain phenomena, since it affects the perception and processing of nociceptive data [3,14].

This relationship between depression and pain is believed to be supported by common biological bases mediated by four neurotransmitters involved in both pain and depression: serotonin, norepine phrine, substance P and corticotrophin-releasing factor [16].

The elevation of ESR and CRP reflects the inflammatory phenomena that occur during active RA, these phenomena are mediated by various proinflammatory cytokines. The latter would play a key role in the pathophysiology of depression [1]. This would suggest a greater prevalence of depression in patients with high rates of SV and CRP [11,12]. RA activity scores (DAS 28) are correlated with depression and anxiety [1,11,12], and our results are superimposable on those of the literature (respectively p = 0.004 with DAS28-VS and p = 0.002 with DAS28-CRP). Elevation of serum cytokine levels is positively correlated with symptoms observed during depression (anorexia, decreased libido, weight loss, fatigue, sleep disturbances, cognitive impairment..) [12]. These cytokines are associated with neurochemical and neuroendocrine mechanisms involved in the pathophysiology of depression [1], they are believed to be a key element in the mediation of the behavioral, neuroendocrine and neurochemical characteristics of depressive disorders [8]. Psychological factors are likely to be closely associated with disease activity: psychological factors capable of affecting the immune, endocrine and central nervous system (leading in particular to increased production of pro-inflammatory cytokines). A meta-analysis on the role of cytokines in depression concluded that among the different cytokines involved, only TNFα and IL6 were significantly correlated with depression [2]. These results are all the more interesting as it is now recognized that TNFα and IL6 are key cytokines in the pathophysiology of RA.

The existence of specific therapies directed against these cytokines (anti-TNFa and anti-IL6) suggests a possible effect on depression when using these treatments [7].

Anxiety and depression

Anxiety and depression are very common manifestations in RA Joint involvement is responsible for impaired quality of life, sleep disturbances, fatigue which contribute to psychiatric comorbidities. Depression and suicidal ideation are more common in patients with severe deformities. In a European multicenter study depression, analyzed by the Anxiety and Depression Scale (HAD), was present in 13.8% of patients with RA 4.3% of healthy controls (adjusted OR = 3.02; 95% CI, 1.86-4.90). Suicidal ideation was reported by 17.3% of patients compared to 8.3% of controls (adjusted OR = 1.94; 95% CI, 1.33-2.82). Finally, in the Danish DANBIO registry, anxiety and depression are associated with poorer maintenance of therapy under biological therapy, which would have a direct link with an increase in rheumatism activity [18].

Rhumatoid arthritis and risk suicidary

The prevalence of major depression in RA is estimated at 17% [8]. According to Timonen M., *et al*. [22], the suicide in women with RA is more important compared to the general population (52.6% vs 17.3%). Major depression was present in 90% ofpatients with RA. Before autolysis, 50% of women and 11% of men have tried at least one attempt at suicide.

Management of depression in PR

There are currently no studies evaluating the efficacy of specific treatments for RA in the accompanying depression. However, taking into burden of depression during RA should be multidisciplinary. Indeed, in addition to the usual treatment of RA which allows remission to be achieved or low disease activity, treatment of depression acquires a special dimension and will be based on a pharmacological therapeutic approach and not pharmacological.

Antidepressants

Antidepressants are often prescribed in several rheumatological pathologies for analgesic purposes (fibromyalgia, neuropathic pain, low back pain chronicles...) [27,28]. The dosage and methods of taken in these cases can obey the recommendations ADER (Anti Depressant In Rheumatology) established by the CEDR 2004 (Circle for the Study of Pain in Rheumatology which is a dynamic section of the French Society of Rheumatology). However, depression during RA is attracting particular attention because the problem

spreads over a psychological affection and not only chronic pain.

There is no difference in clinical efficacy demonstrated between different types of antidepressants. In the event of a depressive episode of moderate to severe intensity,it is recommended in first intention to prescribe a selective serotonin reuptake inhibitor (SSRI) or a serotonin reuptake inhibitor and norepinephrine (SNRI) (table 2) [29].

Particular attention should be paid to the xerophthalmia of Gougerot-Sjögren syndrome secondary to RA, since antidepressants tricyclics such as amitriptyline and MAOIs can considerably aggravate this dry eye by their parasympthicolytic effect. The duration of antidepressant treatment is usually 6 to 9 months after symptomatic remission. As part of the prevention of recurrences, the duration of treatment may be extended. Antidepressant treatment should not be discontinued when there are residual symptoms. The psychological assessment should be initiated after the first week of treatment [31].

Benzodiazepines

A concomitant prescription of benzodiazepines (or related) must not be systematic because of the risk of dependency. It can only be justified when there is disabling insomnia and/or anxiety. Bear avoid this risk, it is recommended to use the dose effective minimum and to interrupt the treatment as soon as anxiety and/or insomnia improved thanks to the effect antidepressant [32].

Non-pharmacological management of depression in RA

Patients with RA often tend to consider psychiatric consultations as a treatment maladjusted and to have the feeling of not being recognized in the «reality» of their illness and pain. Referral to a psychiatrist can then be experienced as a «surrender». The reactions of mistrust and denial must be acknowledged and addressed directly by the psychotherapist during the first contact to try to dissipate them later in a climate of trust [33].

Support in practice

It is proposed in inflammatory rheumatism to collect the existence of depression, risk factors, a history of depression or taking antidepressants [12]. Assessment of psychological parameters should include relationships and family environment, impact on social relationships, work, quality of life, sleep, pain, and fatigue [18]. This assessment can be facilitated by multidisciplinary care involving specialist doctors (rheumatologist, dermatologist, psychiatrist) and general practitioner, therapeutic education nurse and/or advanced practice nurse, psychologist, social worker.

Questionnaires can be used to assess quality of life (HAQ-DI, Health Assessment Questionnaire Disability; SF-36, ShortForm-36; EQ-5D, EuroQOL-5D;) anxiety and depression (HADS, Hospital Anxiety and Depression Scale), fatigue (FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue) but are difficult to use in daily practice outside of clinical research [19].

Conclusion

Psychological factors are likely to be closely associated with disease activity: psychological factors capable of affecting the immune, endocrine and central nervous system (leading in particular to increased production of pro-inflammatory cytokines). We can thus imagine that certain psychological factors participate in the increase in the activity of the disease; which can be at the origin of a true vicious circle since the increase in the activity of the disease will itself be likely to generate or exacerbate psychological factors such as anxiety and especially depression [1].

In the end, we note in particular the association between a high Thompson score and at 6 months an increase in psychological symptoms. Conversely, the prospective study shows that the existence of depressive symptoms is significantly associated with greater disease activity at 8 months ($p < 0.04$) [1].

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