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RELATION BETWEEN WRIST DEFORMITY AND INFLAMMATORY MARKERS ON PAIN INTENSITY IN RHEUMATOID AARTHRITIS

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ABSTRACT

Objective: To investigate the relationship between the intensity of wrist pain and joint deformity, total number of painful joints (PJC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in patients with RA.

Methods: Cross-sectional study including users of a reference outpatient service diagnosed with RA according to the American College of Rheumatology criteria. This study was authorized by the ethics committee CAAE 51642315.5.0000.5544. We analyzed wrist pain intensity (Visual Analogue Scale), joint deformity (Modified Larsen Score), total number of painful joints (PJC) and inflammatory markers (CRP and ESR). Linear correlation and multiple linear regression with a confidence interval of 95% were performed.

Results: A total of 95 participants with moderate (31.6%) and high (68.4%) level of disease activity were included. The mean intensity of wrist pain was 8.32±1.98 in the VAS. PJC correlated with the intensity of wrist pain (r=0.343; p=0,001) and CRP inversely correlated with the intensity of wrist pain (r=-0.220; p=0.030) in Pearson's correlation test. Multiple linear regression analysis confirmed that the CRP was a factor inversely related (p=0.020) and PJC directly related (p=0,001) to the intensity of wrist pain.

Conclusion: In the present sample we observed that the intensity wrist pain did not correlate with joint deformity, correlated with PJC and that higher intensities of wrist pain were associated with lower CRP levels, which leads us to believe that non-inflammatory mediators of pain and of pain perpetuation may be involved in these clinical presentation and therefore should be investigated in future studies.

KEYWORDS : Inflammation, Joint Deformity, Pain, Rheumatoid Arthritis, Wrist.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease, which causes persistent joint pain that affects functionality of daily and work-related activities [1]. It affects about 1% of the world population and leads to retirement 10 years earlier than expected [2]. Its etiology, although unknown, is related to genetic predisposition, and hormonal, infectious and environmental exposure factors. RA presents slow progression and typically affects the joint capsule and adjacent structures [3]. The main symptoms include edema, increased local temperature, morning stiffness and moderate to extreme pain intensity. Peripheral joints are the most affected, especially involving hands and feet, bilaterally [1].

The joints affected over time suffer permanent deformities which develop progressively, as a result of repeated inflammatory attacks. While many peripheral joints may be affected, the wrist is one of the most affected and this has a significant impact on functional activities of the upper limb [4]. The arthritic wrist can develop significant limitations for manual activities, causing social and economic impact and frequent need of surgery [5]. Recognizing conditions that exacerbate wrist pain can greatly contribute to the identification of more effective therapeutic approaches, with less risk and lower cost.

When monitoring patients with RA, clinicians often assess the development of joint deformities by evaluating X-ray images [6]. X-ray of wrist and hand has been an important marker for monitoring the clinical course of RA, allowing clinicians to measure whether the approaches adopted are effective and decide if adjustments in dosage of anti-inflammatory and immunosuppressive drugs are needed 4, in addition to supporting the choice of physical resources by physical therapy. Wrist deformities are well evaluated by this exam, which demonstrates appropriate confidence level. Ratings deformities helps health professionals stratify clinical outcome in RA [6].

Clinicians also measure plasma inflammatory markers to monitor the evolution of RA patients. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most common inflammatory biomarkers used in clinical practice to stratify the level of disease activity (LDA). CRP and ESR can help adjust doses of medications and parameters of physical therapy procedures. CRP belongs to the pentraxin family of proteins and promotes humoral and cellular interaction. Its function is to join pathogens and damaged cells and/or apoptosis to start their elimination by the complement system or phagocytes 7. CRP represents the extent and intensity of inflammation. Erythrocyte sedimentation rate test (ESR), on the other hand, reflects protein concentration in plasma,

mainly fibrinogen, and is another indicator of inflammatory processes [8]. Both ESR and CRP are nonspecific inflammatory indicators, nonetheless, they are the most recommended for routine clinical practice [9].

Although deformities and inflammation levels are often used to stratify the level of disease activity (LDA) in RA, it is unknown whether these variables may be associated with pain intensity. On one hand, pain is the major complaint of RA patients, and on the other hand, inflammation and deformities are the main markers used to determine treatment strategies. Therefore, the objective of this study is to verify the relationship of deformities and inflammatory markers with the intensity of wrist pain in people with RA.

MATERIAL AND METHODS

Cross-sectional study of patients diagnosed with RA according to the American College of Rheumatology criteria, originated from an outpatient rheumatology service and research center of Bahiana School of Medicine and Public Health (BSMPH) in Brotas, Salvador, Bahia, Brazil. Were included in this study patients of both sexes, aged 18 to 70 who had been diagnosed with RA for at least one year and presented with moderate to high level of disease activity according to DAS-28. Patients were excluded from this study if they had difficulties to understand the instruments used in the data collection or if they had any associated diseases that could present with chronic pain.

The sample size was set up with the help of an online calculator from the Epidemiology and Statistics Laboratory of the University of São Paulo, available onhttp:// www.lee.dante.br/ pesquisa/ amost ragem/di2pro.html. Parameters adopted for calculations were: the ability to detect 30mm differences in the visual pain scale between the groups with major and minor deformities, considering a standard deviation of 50mm, and joint deformity as the main cause of pain intensity in the analysis of this study. The size calculation suggested to include 79 subjects, for a 95% power and 5% alpha. The sample size was calculated using the G * Power calculator available in www. macupdate.com/app/mac/24037/g-power/. We decided increase the sample by 20% (total of 95 individuals) considering the possibility of a non-normal sample distribution A convenience sample among registered patients was contacted by telephone following the numerical order of records (after considering the eligibility criteria based on medical records).

Data collection was conducted from February to August 2012 in a private environment by a trained team. The invitation to participate was based on medical records. Participants who accepted to come to the clinic were read the free and informed consent (FIC) and, after clarification of all doubts, participants who agreed signed the FIT. After this procedure, they were directed to the blood sample collection area. All subjects had fasted for at least 6 hours to perform the measurement of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Participants were then referred to a radiology center where standard anteroposterior X-ray images of both hands and wrists were obtained. The analysis of X-rays was carried out according to the modified Larsen deformity classification 10 by two radiologists independently. The only two differences were solved by consensus. The joints were classified as grade 0 (no joint changes), grade I (osteoporosis and edema), grade II (decreased joint space and erosion), Grade III (severe erosion with moderate destruction), grade IV (loss of joint space and severe destruction) and grade V (ankylosis).

In a private service office, the visual pain scale (VAS) was applied to all patients by the same professional in order to identify the presence of spontaneous pain of the wrists. A 100mm length scale was presented and participants were asked to express the intensity of pain experienced at the time of evaluation, where zero meant no pain and 100 the worst possible pain. The 28 joints recommended by the Disease Activity Score (DAS-28) protocol were evaluated for the presence of pain and edema which, together with the values of CRP or ESR (in our case we used CRP), to determine the LDA (11) in order to exclude patients in remission or with mild LDA. DAS-28 scores range between 0 and 10, with scores below 2.7 indicating remission, scores 2.7 to 3.1 indicating low LDA, scores 3.2 to 5.1 indicating moderate LDA and scores ≥ 5.2 representing high LDA (11). The total number of painful joints (PJC) was later used separately in the analyses. Social class was stratified according to the recommendations of the Brazilian Institute of Geography and Statistics (IBGE in Portuguese) as high (A1, A2 and B1), medium (B2, C1 and C2) and low (D and E). Educational level was considered to be low (up to four years of study), medium (five to eight years of study) and high (9 or more years of schooling or complete high school or college). The subjects were subdivided into young adults (18-34 years), adults (35-60 years) and elderly (over 60). Participants were also classified according to self-declared color of skin. The project was approved by the Ethics Committee of EBMSP under CAAE number 51642315.5.0000.5544 and followed all recommendations of 466/12 Resolution of the National Health Council on ethics in research involving humans.

The study sample was described using mean and standard deviation (numerical variables) and proportions (categorical variables). To test the relationship between the intensity of wrist pain, total number of painful joints, degree of joint deformity and inflammatory markers (CRP and ESR) statistical analysis was performed using the Pearson's correlation and multiple linear regression. Significance level was set at 5% and 95% confidence intervals for all analyses. Statistical analysis was conducted using the SPSS (Statistical Package for Social Sciences) for Windows (version 21.0).

RESULTS

In the present sample, 95 patients were analyzed, 88 (92.6%) were females, mean age was 51.7 ± 11.7 years. The sociodemographic characteristics of the participants are shown in table I. The sample was composed mostly by blacks and mulattos (86.3%), adults (54.7%), belonging to the middle socioeconomic class (81, 1%).

Table I. Sociodemographic characteristics of sample of RA individuals, Salvador, Bahia, Brazil

Variables	n=95	%
Sex		
Female	88	92.6
Age (years old)		
Young Adult (18-34)	17	17.9
Adult (35-59)	52	54.7
Elder (60-65)	26	27.4
Skin Collor (self reported)		
Young Adult (18-34)	17	17.9
Adult (35-59)	52	54.7
Elder (60-65)	26	27.4
White	10	10.5
Red	3	3.2
Black	36	37.9
Mullato	46	48.4
Social Class (IBGE classification)		
High	6	6.3
Midle	77	81.1
Low	12	12.6
Educational Level (IBGE classification)		
Basic	34	35.8
Midle	19	20.0
High	42	44.2

IBGE – Brazilian Institute of Geografy and Stattistic in Portuguese

The level of disease activity classification (DAS-28) divided our sample in moderate and high levels, where 30 (31.6%) patients presented moderate LDA and 65 (68.4%) high LDA. This protocol also revealed that wrists and knees were the most painful joints among our patients. Joint deformity evaluation revealed that 11 (11.6%) subjects had no radiological findings, 45 (47.4%) had osteoporosis and edema or joint space narrowing and erosion, and 16 (16.8%) had signs of wrist ankylosis. Considering pain symptoms, the majority of the sample (81.1%) showed high levels of pain by visual pain scale evaluation (Table II). The mean pain intensity was 8.32 ± 1.98 in the VAS varying in our sample from 3 to 10. The mean painful join count was 15.23 ± 10.81 varying from 1 to 28. Mean VHS values were 34.61 ± 19.71 varying from 2 to 103 mm/sec. Mean CRP values were 16.49 ± 13.03 varying from 6 to 52 mg/dL.

Table II. Clinic data of patients with RA, Salvador, Bahia, Brazil.

Variables	n=95	%
Disease Activity Level		
Moderate Activity	30	31.6
High Activity	65	68.4
Larsen Classification		
Grade 0	11	11.6
Grade I	22	23.2
Grade II	23	24.2
Grade III	14	14.7
Grade IV	9	9.5
Grade V	16	16.8

Pearson's correlation was conducted to determine whether a higher number of painful joints, an increased ESR, CRP and degree of deformity correlated to increased wrist pain intensity. It was noted that painful joint count positively correlated to intensity of wrist pain and a weak negative correlation was observed between wrist pain intensity and CRP levels (Table III).

Table III. Correlation between Wrist Pain Intensity and painful joint count, ESR, CRP and Larsen deformity scores of RA Individuals, Salvador, Bahia

Variables	r	P
C-Reative Protein	-0.209	**0.042**
Erythrocyte Sedimentation Rate	-0.058	0.577
Larsen deformity score	0.060	0.564
Painful joint count	0.343	**0.001**

Pearson Correlation, alfa 5%, CI 95%.

When we performed multiple linear regression to determine which variable (PJC, degree of deformity, CRP or ESR) was more related to wrist pain intensity, it was confirmed that PJC and CRP were the only significant variables both in the primary model and the final model (Table IV).

Table IV. Multiple linear regression to identify the principal variable to determine pain intensity in the present sample RA individuals, Salvador, Bahia.

Variables	Primary Model		Final Model
	p	p	Beta
CRP	0.029	0.021	-0.226
ESR	0.846		
Larsen Score	0.919		
Painful joint coun t	0.002	0.001	0.320

Alfa 5%, CI 95%; CRP=C-Reative Protein; ESR=Erythrocyte Sedimentation Rate; Larsen Score=Larsen's modified deformity score.

DISCUSSION

This study aimed to clarify which diagnostic and prognostic markers of RA are related to exacerbation of the painful phenomenon of the wrist of patients with RA. Our findings revealed that wrist pain intensity negatively correlated to CRP levels and positively correlated to PJC.

Although it was observed that the degree of deformity was distributed homogeneously among patients of our sample, values of inflammatory markers and pain intensity are distributed unevenly. Wrist pain is more intense in patients with deformities between Grade I and III. Similarly, CRP is highest in subjects with moderate pain. This fact may be explained by the joint destruction in the initial phase 4. It is possible that at this stage there is a greater phagocytosis and more free nerve endings leading to faster and more efficient stimulus reception and conduction [13,14]. Unexpe ctedly, however, the degree of joint deformity in these patients was not directly correlated with CRP and ESR. Nevertheless, as the disease progresses, the process is no longer understood as an acute condition, and therefore a more adaptive modulation begins, which is very common in chronic diseases [15].

Assessment of inflammatory markers is a widespread practice in rheumatology clinic. The reactivity of serum inflammatory agents with painful inflammatory responses has been corroborated by previous studies 16. Inflammatory markers can act synergistically with the transduction of nociceptive stimuli, reducing the threshold of perception. However, the negative correlation we observed between wrist pain intensity and CRP levels raises a question regarding the synergy between inflammation and pain in patients with RA. With chronicity of pain symptoms, there is a central sensitization process that reflects the contribution of non-inflammatory factors in the pain of RA patients [11]. Recent studies demonstrated important non-sensory components of pain and revealed that chronic pain is associated with apparent structural changes in the brain, that reinforce the notion of chronic pain as a disease of the nervous system [17]. Central sensitization can be the foundation of the high intensity of pain in this condition, even when inflammatory levels are lower [16]. Pain in RA is perpetuated even when inflammatory levels are controlled, reinforcing the hypothesis that the phenomenon could be related to central sensitization [15]. Also, painful joint count positively correlated to intensity of wrist pain, but not to CRP levels, corroborating with the hypothesis that inflammation is no longer a central player in pain perpetuation.

It has been suggested that a mixed pain concept is applicable in RA, stating that although inflammation contributes to pain in RA, it may not be the only factor and other pain mechanisms such as neuropathic pain may also play a role [16]. In this study, authors consider to have provided "preliminary support of a non-inflammatory pain component in RA" in patients with low LDA and in remission, identifying neuropathic-like pain symptoms in a substantial number of patients [16]. Many advances have been accomplished by recent studies focusing on this paradox, however, whether these non-sensory, non-inflammatory pain symptoms are a result of peripheral or central sensitization has not been clarified [18].

Another interesting finding in this study is that 68% of the population presented high LDA, which raises the question as to why a high number of people in appropriate medical monitoring remain in a critical stage of the disease. Some studies have questioned the lack of adherence of patients to medications and physical therapy, due to lack of educational orientation that should have been provided by health professionals, from the moment of diagnosis [19]. It is possible that the lack of adequate information about the disease, erroneous beliefs and inappropriate behavior hinders the control of the pain process in RA.

This study presents limitations regarding the convenience sample. Even though patients were recruited from a reference service, this service is used mainly by patients who rely on drugs provided by the government. Perhaps for this reason we observed such a high percentage of patients with high and moderate inflammatory levels, which can be related to the vulnerable health conditions of the sample. Fluctuations of the supply of medications by the public

health system may influence these patients' analgesic responses, since they are unable to pay for the required medication when it is not provided. In this study we were not able to assess the adherence to treatment, which leaves us with many questions related to whether participants were properly medicated or not. As supplementary information, the majority of the sample declared resistant to physical therapy and regular exercise. The convenience sample also limits the application of the findings to patients in remission or with mild disease activity, as well as more privileged socioeconomic conditions not present in our sample.

According to our results, and in accordance with previous studies, we can conclude that there is a clear necessity to identify more sensitive and specific indicators of diagnosis and prognosis in RA. Since the intensity of pain is the main responsible for reduced functionality in daily activities from the affected patient's point of view, controlling its intensity is of major importance for a patient-centered treatment approach. Therefore, the follow-up of RA patients should add to the control of inflammatory levels a set of measures to quantify, characterize and control painful phenom enon. This also suggests including pain specialists in the team responsible for monitoring patients with RA. Further studies are needed to clarify the observed negative correlation between wrist pain intensity and CRP levels, which highlights the importance of investigating probable non-inflammatory mediators of pain and of pain perpetuation in RA.

Conflict of Interest: The authors declare that there is no potential conflict of interest and did not receive any funding for the development of this study.

REFERENCES

1. Mota LMH, Cruz BA, Brenol CV, Pereira IA, Fronza LSR, Bertolo MB, et al. Consensus of the Brazilian Society of Rheumatology for diagnosis and early assessment of rheumatoid arthritis. Rev Bras Reumatol. 2011;51:199–219.
2. Laurindo I, Ximenes A, Lima F, Pinheiro G, Batistella L, Bertolo M, et al. Artrite reumatóide: diagnóstico e tratamento. Rev Bras Reumatol. 2004;44:435–42.
3. Pereira IA, Pereira RMR. Osteoporose e erosões osseas focais na artrite reumatóide: da patogênese ao tratamento. Rev Bras Reumatol. 2004;44:347–54.
4. Johnsson PM, Eberhardt K. Hand deformities are important signs of disease severity in patients with early rheumatoid arthritis. Rheumatology. 2009;48:1398–401.
5. Uçan H, Borman P, Keskin D, Barça N. Carpal collapse in patients with rheumatoid arthritis. Clin Rheumatol. 2006;25:845–9.
6. Mota LMH da, Laurindo IMM, Santos Neto LL dos, Lima FAC, Viana SL, Mendlovitz PS, et al. Diagnóstico por imagem da artrite reumatoide inicial. Rev Bras Reumatol. 2012;52:761–6.
7. Kim K-W, Kim B-M, Moon H, Lee S, Kim H. Role of C-reactive protein in osteoclastogenesis in rheumatoid arthritis. Arthritis Res Ther. 2015;17:41.
8. Words EY. Velocidade de sedimentação das hemácias: utilidade e limitações. Rev Bras Reum. 2000;46:232–6.
9. Medeiros MMDC, Oliveira BMGB de, Cerqueira JVM de, Quixadá RTDS, Oliveira ÍMX de. Correlação dos índices de atividade da artrite reumatoide (Disease Activity Score 28 medidos com VHS, PCR, Simplified Disease Activity Index e Clinical Disease Activity Index) e concordância dos estados de atividade da doença com vários pontos de corte numa população do nordeste brasileiro. Rev Bras Reumatol. 2015;55:477-84.
10. Mangnus L, van Steenbergen HW, Lindqvist E, Brouwer E, Reijnierse M, Huizinga TW, et al. Studies on ageing and the severity of radiographic joint damage in rheumatoid arthritis. Arthritis Res Ther. 2015;17:222.
11. Wells G, Becker J, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68:954–60.
12. McWilliams DF, Zhang W, Mansell JS, Kiely PDW, Young A, Walsh DA. Predictors of change in bodily pain in early rheumatoid arthritis: An inception cohort study. Arthritis Care Res. 2012;64:1505–13.
13. Edwards RR, Wasan AD, Bingham CO, Bathon J, Haythornthwaite JA, Smith MT, et al. Enhanced reactivity to pain in patients with rheumatoid arthritis. Arthritis Res Ther. 2009;11:R61.
14. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:581–92.
15. Sofat N, Ahmed S, Magan T, Vargas M, Harrison A. Use of the pain DETECT tool in rheumatoid arthritis suggests neuropathic and sensitization components in pain reporting. J Pain Res. 2014;7:579.
16. Koop SMW, ten Klooster PM, Vonkeman HE, Steunebrink LMM, van de Laar MAFJ. Neuropathic-like pain features and cross-sectional associations in rheumatoid arthritis. Arthritis Res Ther. 2015;17:237.
17. Woolf CJ. What is this thing called pain? J Clin Invest. 2010;120:3742–4.
18. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2011;152:S2–15.
19. International Association for Study of Pain - IASP. Taxonomy. 2012.