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Evaluation of central sensitization and presence of neuropathic pain in patients with rheumatoid arthritis and its relationship with quality of life

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Abstract

Central sensitization and neuropathic pain may develop in rheumatological diseases. This study aimed to investigate the presence of central sensitization and neuropathic pain in patients with rheumatoid arthritis (RA). We used the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire to evaluate neuropathic pain (NP) in patients with RA. The presence of central sensitization in patients was evaluated using the central sensitization inventory (CSI). Demographic and clinical data were obtained from patients and interviews. Beck Depression Scale (BDS) was used to evaluate the mood of the patients, and the Short Form-36 (SF-36) quality of life scale was used to evaluate the quality of life. A total of 104 patients participated in our study, and 33 (31.7%) of them were found to be NP. CSI scores indicated central sensitization in 41 (39.4%) of the patients. A positive significant relationship was detected between LANSS and Visual Analog Scale (VAS), BDI, and Disease Activity Score 28 (DAS28). Central sensitization (CS) and neuropathic pain (NP) significantly contribute to functional disability in RA patients. Central sensitization and neuropathic pain significantly contribute to functional disability in patients experiencing neuropathic pain, with CS having a detrimental impact on their quality of life. Thus, it is imperative to consider neuropathic pain and CS during disease monitoring and follow-up.

Keywords: Neuropathic pain, central sensitization, rheumatoid arthritis, disability

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting nearly 0.5%-1% of adults, leading to increased disability, joint damage, reduced quality of life, and premature mortality compared to the general population [1]. Early identification of RA and prompt initiation of treatment can influence disease progression, prevent joint erosions, or slow down erosive disease progression [2]. Despite apparent control of inflammation, pain management often remains insufficient, with a significant number of patients experiencing persistent pain [3]. Pain is a common complaint among individuals with rheumatic diseases [4,5], and neuropathic pain (NP) in these conditions is associated with varying disease burdens [6,7].

However, research on the neuropathic aspect of pain in the general population is scarce, and indications point to a prevalence spanning from 7 to 10%. [8,9]. Pain in RA can arise from nociceptive and non-nociceptive sources, resulting in distinct pain characteristics discernible through different assessment tools [5,10].

Even though RA patients may attain clinical remission, certain individuals still experience surprisingly elevated levels of pain. [3,11-13]. In 2011, the International Association for the Study of Pain defined NP as 'pain resulting from damage or disease affecting the somatosensory nervous system' [13]. Common conditions leading to NP include nerve damage-related ailments such as postherpetic neuralgia, diabetic neuropathy, and central pain following spinal cord injury or stroke [14]. NP is characterized by sensations such as burning, stinging, tingling, sudden pain attacks, numbness, pain triggered by light touch, and allodynia. [15]. In our study, we aimed to explore the presence of central sensitization and neuropathic pain in patients with rheumatoid arthritis and assess the impact of neuropathic pain on their quality of life.

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Material and Methods

Patient

A total of 104 patients (77 females, 27 males) between the ages of 18-65 were diagnosed with RA according to the 2010 ACR/EULAR ('American College of Rheumatology'/'European League Against Rheumatism') diagnostic criteria in our outpatient clinic were included in the study. The study's sample size was determined based on similar studies in the literature to ensure statistical reliability and generalizability of the findings. However, the specific calculation method was not detailed. The patients were recruited between May 2022 to November 2023. Inclusion criteria were an RA diagnosis according to the American College of Rheumatology (ACR) criteria ages from 18 to 65 [16]. Exclusion criteria of the study were determined as having aphasia, other rheumatic diseases, and patients with neuropathy diagnosed for any reason (for example, diabetic neuropathy, cancer-related neuropathy, carpal tunnel syndrome, postherpetic neuralgia, spinal cord compression), and patients using medication for neuropathic pain. In addition, those taking antidepressants (i.e., duloxetine) and anticonvulsants (gabapentin and pregabalin) were also excluded from the study. Additionally, patients previously diagnosed with fibromyalgia syndrome and neuropathic pain were excluded. In our study, no patients were using targeted synthetic disease-modifying antirheumatic drugs (DMARDs).

Data Collection

Patient demographics; age, gender, body mass index (BMI), marital status, presence of additional disease, education status, medications used, occupational information, cigarette-alcohol use, illness duration, and clinical features were recorded from patient files and through face-to-face interviews.

The study protocol was approved by the local Ethics Committee of Batman Training and Research Hospital (Date: October 8, 2021, decision no:283). The study was organized by the Declaration of Helsinki. Written and verbal consent were obtained from the patients participating in the study.

Visual Analog Scale (VAS) (0–100 mm) was used to evaluate the pain, the Self-Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire and the presence of central sensitization were evaluated with the Central Sensitization Inventory (CSI), Beck Depression Inventory (BDI) was used to assess mood, Short Form-36 (Short Form-36=SF-36) was used to measure the quality of life.

Measurement

Disease activity was assessed using the Disease Activity Score (DAS) based on the evaluation of 28 joints (DAS28), which calculates scores based on the number of tender and swollen joints, erythrocyte sedimentation rate (ESR), and patient's global assessment of disease activity on the VAS [17].

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) was employed to evaluate patients' neuropathic pain symptoms. Bennett introduced this scale as a tool to differentiate neuropathic pain from nociceptive pain. LANSS offers advantages such as rapid administration and ease of evaluation. The total LANSS score is 24, with a score equal to or greater than 12 indicating involvement of neuropathic mechanisms in pain [18].

The CSI comprises two parts: part A assesses symptoms associated with central sensitization syndromes (CSS), while part B quickly queries whether the patient has received a specific diagnosis previously. Part A consists of 25 items rating the frequency of symptoms associated with CSS on a scale of 0-100 points. Part B asks whether the patient has ever been diagnosed with any of the diseases encompassed in CSS by any healthcare provider. This inventory serves as a screening tool and is recognized for its specificity and sensitivity in chronic pain patients [19,20].

Quality of life was evaluated using the Short Form-36 (SF-36), a generic scale comprising eight subscales and a total of 36 items through which patients self-assess their conditions. Subscale scores range from 0 to 100, with lower scores indicating poorer quality of life [21].

The Beck Depression Scale, developed by Beck et al., measures the level of depression by assessing physical, emotional, cognitive, and motivational symptoms of depression in patients [22]. Its validity and reliability in our country were established by Hisli et al. [23] in 1988.

Statistic

Statistical analysis in the study was conducted using IBM SPSS Statistics software, version 25.0 (IBM Corp., Armonk, NY, USA). Normality assumptions for continuous variables were assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics are presented as mean±standard deviation for continuous variables and frequencies (n, %) for categorical variables. Univariate analyses of study variables were performed using Chi-Square tests, Fisher's Exact Test, Fisher-Freeman-Halton exact test, and Independent t-tests. Correlation analysis was employed to explore relationships between variables. Statistical significance was interpreted for cases with a p-value below 0.05 in all analyses.

Results

In the study, a total of 104 participants, comprising 27 males and 77 females, were included. The demographic characteristics of the patients, along with comparisons between the LANSS groups are presented in Table 1 and Table 2. The analysis revealed that there was no statistically significant relationship between gender, the type of medication utilized by the patients, and the LANSS groups ($p>0.05$). However, a statistically significant relationship was observed between smoking status and the LANSS groups ($p<0.05$). The average age of the patients is 55.86±7.51 years. The average BMI is 31.26±4.33.

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There was no statistically significant difference between LANSS ≥12 and LANSS<12 groups in terms of age, BMI, Erythrocyte Sedimentation Rate (ESR), DAS 28, duration of disease, and SF-36 quality of life scale sub-scores related to fatigue (p>0.05). However, differences between LANSS groups were statistically significant regarding CRP, Beck Depression Inventory, SF-36 quality of life scale sub-scores, physical functioning, role limitations due to physical health, bodily pain, social functioning, emotional role limitations, general health perceptions, health compared to last year, and CSI-A values (p<0.05). The CSI-A values of the LANS≥12 groups were found to be higher than those of the LANSS<12 groups.

Table 1. Comparison of patients with (LANSS≥12) and without neuropathic pain according to numeric variables

	Total n=104 (100.0%)	LANSS≥12 n=33 (31.7%)	LANSS<12 n=71 (68.3%)	p	t
Age, mean±sd	55.86±7.51	55.66±8.19	55.95±7.23	0.856	-0.181
BMI, mean±sd	31.26±4.33	31.00±3.75	31.38±4.59	0.678	-0.416
VAS, mean±sd	40.09±26.08	61.21±25.09	30.28±20.14	**<0.001**	6.729
CRP, mean±sd	6.71±3.51	7.71±5.04	6.25±2.41	**0.048**	2.001
ESR, mean±sd	31.36±12.33	33.51±16.42	30.36±9.86	0.227	1.215
DAS 28, mean±sd	3.13±0.78	3.25±0.77	3.06±0.79	0.256	1.142
Duration of disease (month),mean±sd	79.28±49.05	76.27±51.19	80.69±48.33	0.671	0.426
PR, mean±sd	75.36±19.34	67.12±20.65	79.19±17.57	**0.003**	3.082
RR, mean±sd	38.46±46.85	15.15±36.41	49.29±47.42	**<0.001**	3.661
BP,mean±sd	42.45±15.00	36.89±16.02	45.03±13.88	**0.009**	2.649
SF, mean±sd	54.08±21.85	62.50±19.26	50.17±22.00	**0.007**	2.761
MH, mean±sd	53.23±14.77	53.45±14.06	53.12±15.19	0.917	0.105
ER, mean±sd	41.34±48.82	15.15±36.41	53.51±49.27	**<0.001**	3.991
T, mean±sd	39.95±17.05	37.42±14.14	41.12±18.22	0.305	1.030
GH, mean±sd	47.59±15.78	34.09±14.70	53.87±11.89	**<0.001**	7.309
Health compared to last year, mean±sd	37.98±16.33	25.75±14.63	43.66±13.83	**<0.001**	6.031
BD, mean±sd	14.04±6.88	20.51±5.75	11.04±5.08	**<0.001**	8.481
CSI- A, mean±sd	33.84±14.63	47.84±9.68	27.33±11.70	**<0.001**	8.761

BMI: body mass index, VAS: visual analog scale, BP: bodily pain, CRP: C-reactive protein, DAS: disease activity score, ER: emotional role, ESR: erythrocyte sedimentation rate, GH: general health, LANNS: leeds assessment of neuropathic symptoms and signs, MH: mental health, SD: standard deviation, PR: physical role, SF: social function, CSI-A: central sensitization inventory, BD: Beck depression: RR: role restriction, T: tiredness, GH: general health

Table 2. Comparison of patients with (LANSS≥12) and without neuropathic pain

	Total n=104 (100.0%)	LANSS≥12 n=33 (31.7%)	LANSS<12 n=71 (68.3%)	p
Gender, n (%)				
Male	27 (26.0)	5 (15.2)	22 (31.0)	0.140
Female	77 (74.0)	28 (84.8)	49 (69.0)	
Smoking status, n (%)				
Yes	18 (17.3)	12 (36.4)	6 (8.5)	<0.001
No	86 (82.7)	21 (63.6)	65 (91.5)	
Biologic use, n (%)				
Yes	29 (27.9)	7 (21.2)	22 (31.0)	0.301
No	75 (72.1)	26 (78.8)	49 (69.0)	
Dmard use, n (%)				
Yes	69 (66.3)	23 (69.7)	46 (64.8)	0.787
No	35 (33.7)	10 (30.3)	25 (35.2)	
No drugs, n (%)				
Yes	4 (3.8)	1 (3.0)	3 (4.2)	0.768
No	100 (96.2)	32 (97.0)	68 (95.8)	

Dmard: disease-modifying antirheumatic drug

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Central sensitization syndromes are frequently observed in patients. Among these patients, Irritable Bowel Syndrome (25.21%) was found to be the most common. The frequency of Migraine/Tension-type Headaches is 19.3% (Table 3).

Table 3. Rates of central sensitization syndromes occurrence

	n	%
Restless leg syndrome	21	17.65
Chronic fatigue syndrome	6	5.04
Fibromyalgia syndrome	6	5.04
Temporomandibular joint disorder	7	5.88
Migraine/tension type headache	23	19.33
Irritable bowel syndrome	30	25.21
Multiple chemical sensitivity	None	0.0
Whiplash trauma to the neck	4	3.36
Anxiety/panic attack	18	15.13
Depression	4	3.36

Among the patients, 63 (60.6%) were in the CSI<40 group, while 41 (39.4%) were in the CSI≥40 group. There was no statistically significant difference between CSI groups in terms of age means and BMI (p>0.05). However, differences between CSI groups were statistically significant in terms of VAS, CRP, DAS 28, duration of disease, physical function, role limitations, bodily pain, emotional role limitations, fatigue, and general health (Table 4).

Table 4. Comparison of patients with (CSI≥40) and without central sensitization

	Total n=104 (100.0%)	CSI<40 n=63 (60.6%)	CSI≥40 n=41 (39.4%)	P
Gender, n (%)				
Male	27 (26.0)	19 (30.2)	8 (19.5)	0.326
Female	77 (74.0)	44 (69.8)	33 (80.5)	
Smoking status, n (%)				
Yes	18 (17.3)	5 (7.9)	13 (31.7)	0.002
No	86 (82.7)	58 (92.1)	28 (68.3)	
Biologic use, n (%)				
Yes	29 (27.9)	20 (31.7)	9 (22.0)	0.276
No	75 (72.1)	43 (68.3)	32 (78.0)	
Dmard use, n (%)				
Yes	69 (66.3)	39 (61.9)	30 (73.2)	0.235
No	35 (33.7)	24 (38.1)	11 (26.8)	
No drugs, n (%)				
Yes	4 (3.8)	4 (6.3)	0 (0.0)	0.152
Noe	100 (96.2)	59 (93.7)	41 (100.0)	

Dmard: disease-modifying antirheumatic drug

The relationship between gender and CSI groups is not statistically significant (p>0.05). However, the relationship between smoking and CSI groups is statistically significant (p<0.001). Among patients in the CSI<40 group, 7.9% smoke, while in the CSI≥40 group, 31.7% smoke.

The correlation analysis presented in Table 5 utilized Pearson correlation coefficients. The correlation coefficients indicating the relationship between variables are presented. The relationship between LANSS and CSI-A, VAS, BDI, and DAS 28 is positive and significant (respectively r=0.812**, p<0.001, r=0.693**, p<0.001, r=0.711**, p<0.001, r=0.402**, p<0.001). A positive and significant relationship was found between CSI-A and BMI, VAS, BDI, and DAS 28 (respectively r=0.252**, p<0.001, r=0.793**, p<0.001, r=0.709**, p<0.001, r=0.578**, p<0.001). VAS shows a positive and significant relationship with BDI and DAS 28 (respectively r=0.611**, p<0.001, r=0.614**, p<0.001). There is a positive and significant relationship between BDI and DAS 28 (r=0.377**, p<0.001).

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Table 5. Correlation analysis

	LANSS	CSI-A	BMI	VAS	BDI	DAS28
LANSS	1					
CSI-A	0.812** p<0.001	1				
BMI	0.013NS P=0.893	0.252** p<0.001	1			
VAS	0.693** p<0.001	0.793** p<0.001	0.197* P=0.045	1		
BDI	0.711** p<0.001	0.709** p<0.001	0.055NS P=0.582	0.611** p<0.001	1	
DAS 28	0.402** p<0.001	0.578** p<0.001	0.214* P=0.030	0.614** p<0.001	0.377** p<0.001	1

NS: non-significance, LANNS: leeds assessment of neuropathic symptoms and signs, CSI-A: Central Sensitization Inventory, BMI: body mass index, VAS: Visual analog Scale, DAS: disease activity score

Discussion

The main finding of this study is that the development of central sensitization and neuropathic pain in patients diagnosed with RA may lead to deterioration in their quality of life and an increase in depressive feelings.

From a clinical perspective, RA is characterized by synovitis, which is traditionally associated with pain driven by inflammation. Research indicates that synovial inflammation triggers increased production of prostaglandins and bradykinin, activating thin unmyelinated sensory nerves (C fibers) within the synovium [24]. Inflammation plays a critical role in the perception of pain in RA. However, multiple studies, including the findings presented here, suggest that despite adequate inflammation suppression through anti-inflammatory treatment, persistent pain persists, indicating the involvement of other factors in pain perception in RA [25]. It has been proposed that over time, arthritic joints expand their total receptive field to encompass surrounding non-inflamed tissue. The heightened response to joint stimulation in inflamed joints may be mediated by peripheral sensitization [26].

In our study, disease activity was well controlled in patients with RA measured by DAS28. However, when pain levels were assessed by VAS, they were found to be high. This indicates the presence of specific pain components that are not fully detected by VAS in RA patients. Data obtained from LANNS scores indicate that a significant proportion of RA patients have neuropathic pain features. Neuropathic pain typically refers to pain originating from the central nervous system, and as our study demonstrates, individuals with RA may become sensitive to pain in the very early stages of their disease.

Further elevation in pain responses to non-inflamed tissues may arise within the spinal cord, leading to central sensitization. Central sensitization occurs when normal inputs provoke abnormal feedback due to neuronal excitation within the central nervous system [27]. Recent studies in RA have underscored the significance of psychological factors such as anxiety, mood disturbances, and depression in clinical pain perception. Moreover, these factors have been shown to potentially affect brain activation in frontal regions, as demonstrated by functional neuroimaging studies of the brain [28]. Moreover, Rech et al. [29] demonstrated that individuals with RA receiving treatment with biologic therapies may experience early improvements in brain pain sensitization, as observed through brain functional imaging utilizing blood oxygen level-dependent signals, within days of initiating biologic agent therapy such as certolizumab pegol, even before noticeable clinical improvements in joint symptoms are observed.

While we utilized a questionnaire to evaluate NP, a more comprehensive assessment involving electrodiagnostic studies, autonomic studies, and physical examinations could have been employed for NP patients; nevertheless, there exists no definitive standard test for NP among those with RA. The LANSS score utilized in our research represents a straightforward and validated approach to NP assessment. In a study conducted by Yeşil et al., investigating the correlation between vitamin D levels and neuropathic pain in RA patients, they utilized the LANSS score and observed significant declines in quality of life indicators in the presence of neuropathic pain, findings consistent with our study results [30]

It has been reported that 19% of patients with RA have a possible prevalence of neuropathic pain [31]. It has been shown that the majority of cases with rheumatoid arthritis have neuropathic pain characteristics based on pain DETECT scores [32]. Koop et al. [7] obtained similar findings in RA patients, revealing a 17% likelihood and 24% probability of NP based on their survey results. Consistent with our findings, they observed elevated VAS scores (>4) despite the majority of patients being in remission according to the DAS28.

Rifbjerg-Madsen et al. [33] noted the prevalence of non-nociceptive pain as highly common in RA and linked it to higher disease activity scores. A recently published study

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investigating the neuropathic pain component in RA using the PainDetect questionnaire indicated that moderate to severe levels of neuropathic pain had detrimental effects on depression, anxiety, fatigue, overall pain, and the mental component of Health-Related Quality of Life (HRQoL). Furthermore, these patients exhibited elevated disease activity scores independent of inflammatory etiology but associated with non-nociceptive pain [34]. Conversely, higher pain levels were reported to be unrelated to disease activity as assessed by the Disease Activity Score 28 (DAS28) [32].

In a study investigating the presence of central sensitization and neuropathic pain in knee osteoarthritis, they assessed the presence of neuropathic pain using LANNS and the presence of central sensitization using CSI and found that the presence of these two conditions negatively affected the quality of life. Similarly, we found similar results in our study [35].

In a study investigating central sensitization in chronic inflammatory diseases, patients with psoriatic arthritis and rheumatoid arthritis were evaluated. The prevalence of central sensitization was observed to be 35.3% in patients (29% in rheumatoid arthritis, and 42.9% in psoriatic arthritis). A strong, independent, and linear relationship between functional disability and central sensitization was found in both psoriatic arthritis and rheumatoid arthritis patients. The strength of this relationship was greater in psoriatic arthritis compared to rheumatoid arthritis [36]. The results obtained in our study are similar. The main finding of this study is that the development of central sensitization and neuropathic pain in patients diagnosed with RA may lead to deterioration in their quality of life and an increase in depressive feelings.

Recent studies have highlighted the significant impact of central sensitization on functionality and disease activity interpretation in rheumatic diseases. For instance, central sensitization has been shown to significantly impair functionality and the interpretation of self-reported disease activity in primary Sjögren's syndrome [37]. Similar findings have been reported in psoriatic arthritis, where central sensitization was closely related to disease activity, functional disability, and quality of life [38]. Furthermore, the biopsychosocial factors contributing to central sensitization in axial spondyloarthritis should be considered, as they play a crucial role in patient outcomes [39]. Additionally, central sensitization significantly affects clinical and functional outcomes in patients with familial Mediterranean fever [40].

Limitations of the study include an inadequate sample size, the predominance of female gender in the group, the lack of consideration for antiepileptic drugs used in the statistical analysis, and the data being derived from a single center. However, this study's strengths lie in its comprehensive evaluation of central sensitization and neuropathic pain in RA patients, providing novel insights into their impact on quality of life and functionality. The inclusion of well-established assessment tools and a robust methodological approach enhances the validity and reliability of the findings.

Conclusion

In summary, this study holds notable clinical implications. While pain in RA patients has traditionally been linked to peripheral inflammation, our research reveals that central nervous system abnormalities contribute to heightened pain intensity regardless of inflammatory activity. In an era where targeted treatment strategies are increasingly favored, these findings should prompt physicians to thoroughly assess factors influencing pain in patients with active RA before considering adjustments to DMARDs. Given the significant role pain plays in the subjective components of various composite measures of disease activity, patients experiencing central pain in the absence of substantial inflammation may erroneously exhibit elevated composite disease activity scores, potentially leading to unwarranted DMARD adjustments that could negatively impact the patient and expose them to unnecessary DMARD-related toxicities. These findings underscore the importance of further research into tools for identifying pain mechanisms that can inform treatment decisions.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study protocol was approved by the local Ethics Committee of Batman Training and Research Hospital (Date: October 8, 2021, decision no:283).

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