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Neuropathic Pain-Like Features in Patients With Rheumatoid Arthritis and Spondyloarthritis Receiving Targeted Therapies: Prevalence and Associated Factors

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Abstract

Persistent pain despite targeted therapy remains a major challenge in patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA), and neuropathic pain-like features may contribute to this residual pain. We conducted a cross-sectional study including 155 patients receiving biologic or targeted synthetic disease-modifying antirheumatic drugs (bDMARDs or tsDMARDs; 78 RA and 77 SpA) to determine the prevalence of neuropathic pain-like features and identify associated clinical factors. Neuropathic pain-like features were screened using the Douleur Neuropathique 4 (DN4) and painDETECT questionnaires. Univariable logistic regression analyses were performed separately for each disease group, followed by parsimonious multivariable models including functional impairment, disease activity, and current pain intensity.

Neuropathic pain-like features (DN4 ≥4) were identified in 19 (24.4%) patients with RA and 21 (27.3%) patients with SpA, with no statistically significant between-group difference ($p = 0.679$). Although median painDETECT scores were significantly higher in SpA, the distribution of painDETECT categories did not differ significantly between the two groups. In univariable analyses, Health Assessment Questionnaire (HAQ) and current pain visual analogue scale (VAS) were significantly associated with DN4 positivity in RA, whereas Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP), and current pain VAS were significantly associated with DN4 positivity in SpA. In multivariable analyses, current pain intensity remained significantly associated with DN4 positivity in both disease groups: pain VAS in RA (adjusted OR 2.77, 95% CI 1.54-4.98; $p < 0.001$) and SpA (adjusted OR 1.90, 95% CI 1.26-2.88; $p = 0.002$). The adjusted associations with functional impairment and disease activity did not reach statistical significance in either disease group.

Neuropathic pain-like features were frequently identified in patients with RA and SpA receiving targeted therapies and were significantly associated with greater pain intensity after adjustment. Associations with functional impairment and inflammatory disease activity remained uncertain after adjustment. These findings support a comprehensive assessment of persistent pain in patients receiving targeted therapies.

Categories: Neurology, Pain Management, Rheumatology

Keywords: biologic therapy, disease activity, dn4, neuropathic pain, paindetect, persistent pain, rheumatoid arthritis, spondyloarthritis, targeted therapy

Introduction

Chronic inflammatory rheumatic diseases (CIRDs), particularly rheumatoid arthritis (RA) and spondyloarthritis (SpA), are major causes of chronic pain, disability, and impaired quality of life, imposing a substantial socioeconomic burden worldwide. Pain is a major symptom reported by patients and remains an important determinant of disease impact and treatment satisfaction, even in the era of targeted therapies [1].

Pain in RA and SpA is multifactorial and may arise from inflammatory, mechanical, neuropathic, nociplastic, and structural musculoskeletal contributors [2,3]. The introduction of conventional disease-modifying antirheumatic drugs (DMARDs) and targeted therapies has markedly improved disease control, allowing many patients to achieve low disease activity or sustained remission. However, persistent pain remains common even when inflammation is adequately controlled, indicating that additional mechanisms may contribute to ongoing pain [4,5].

Among these mechanisms, neuropathic pain-like features have received increasing attention. Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system [6]. It may manifest as burning pain, tingling, electric shock-like sensations, hyperalgesia, or allodynia. In clinical

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practice and research, validated screening questionnaires such as the Douleur Neuropathique 4 (DN4) and painDETECT are commonly used to identify neuropathic pain-like features. However, these screening tools do not establish a definitive diagnosis of neuropathic pain [6,7].

Initially investigated mainly in conditions such as osteoarthritis and fibromyalgia, neuropathic pain-like features have increasingly been reported in inflammatory rheumatic diseases [7]. In RA, such features have been observed even in patients with limited inflammatory activity, suggesting that pain severity may not always parallel inflammatory disease activity [8]. Similarly, studies in SpA have reported associations between neuropathic pain-like features and greater pain severity, functional impairment, and poorer quality of life [7,9]. Neurophysiological studies have also reported subclinical peripheral nerve abnormalities in patients with RA [10]. However, the mechanisms underlying neuropathic pain-like features in these diseases remain incompletely understood, and screening questionnaires alone cannot distinguish neuropathic, nociceptive, or other non-inflammatory pain mechanisms.

Despite effective control of inflammation with targeted therapies, neuropathic pain-like features may persist in some patients and potentially contribute to residual pain. Their identification may therefore provide complementary information when evaluating persistent pain and may help support a more individualized assessment of pain mechanisms alongside conventional measures of inflammatory disease activity.

Accordingly, the primary objective of this study was to estimate the prevalence of neuropathic pain-like features, defined by DN4 positivity (DN4 ≥ 4), in patients with RA and SpA receiving biologic or targeted synthetic disease-modifying antirheumatic drugs (bDMARDs or tsDMARDs). Prespecified secondary objectives included comparing DN4 positivity between RA and SpA, describing painDETECT findings, and exploring associations between DN4 positivity and clinical characteristics, particularly disease activity and functional impairment.

Materials And Methods

Study design and patients

We conducted a cross-sectional study at the Department of Rheumatology of Mohammed V Military Teaching Hospital in Rabat, Morocco, between January 1, 2026, and March 1, 2026. The diagnosis of RA or SpA was confirmed by a rheumatologist, with classification based on the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria for RA and the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial and/or peripheral SpA [11,12].

Patients were consecutively recruited during routine intravenous infusions or outpatient visits for prescription renewal. Eligible patients were receiving targeted therapies, including bDMARDs, such as tumor necrosis factor inhibitors (TNFi), interleukin-6 inhibitors, and anti-CD20 agents, or tsDMARDs, including Janus kinase (JAK) inhibitors. Treatments were administered according to standard clinical protocols.

During the study period, 160 patients were assessed for eligibility. Two patients were excluded because of conditions meeting the predefined exclusion criteria: one had diabetic peripheral neuropathy, and one had herpes zoster. Among the remaining 158 eligible patients, three declined to participate. The final study population comprised 155 patients, including 78 with RA and 77 with SpA.

Inclusion and exclusion criteria

Patients were eligible for inclusion if they were 18 years of age or older, had a confirmed diagnosis of RA or SpA according to the ACR/EULAR or ASAS classification criteria, and had received targeted therapy with a bDMARD or tsDMARD for at least six months before inclusion.

Patients with conditions that could interfere with the assessment of neuropathic pain-like features were excluded. Exclusion criteria included previously diagnosed peripheral polyneuropathy of any etiology (including diabetic, alcoholic, toxic, or hereditary neuropathy), active neurological disorders affecting the peripheral nervous system, active infection, fibromyalgia, herpes zoster within the previous six months, severe cognitive impairment precluding questionnaire completion, and refusal to participate in the study.

The presence of a pre-existing peripheral neuropathy was assessed through medical history-taking and clinical examination. Patients with a previously established diagnosis of peripheral polyneuropathy or clinical findings suggestive of an active peripheral neurological disorder were not eligible for inclusion.

Questionnaire and clinical assessment

Sociodemographic data, including age and sex, were collected for all participants. Clinical information comprised disease duration, body mass index (BMI), smoking status, comorbidities (diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, chronic kidney disease, thyroid disorders, inflammatory

bowel disease, psoriasis, and uveitis), current targeted therapy (bDMARDs or tsDMARDs), treatment duration, concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and corticosteroid use.

Pain severity was evaluated using a 10-cm Visual Analogue Scale (VAS), ranging from 0 (no pain) to 10 (worst imaginable pain) [13]. For RA, inflammatory activity was determined using the Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP), and functional impairment was evaluated using the Health Assessment Questionnaire Disability Index (HAQ-DI) [14,15]. For SpA, the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP) was used to evaluate disease activity, while function was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) [16,17].

Neuropathic pain-like features were assessed using the validated Arabic versions of the DN4 questionnaire and the painDETECT questionnaire (PDQ), following prior authorization from the respective copyright holders [18,19].

All clinical assessments and questionnaire administrations were conducted by a single investigator, including the sensory examination components of the DN4. The investigator relied on standard clinical training in rheumatology without additional DN4-specific training. The questionnaires were administered in a consistent order for all participants, with the DN4 assessment performed first, followed by the PDQ. Patients completed the PDQ with assistance from the same investigator.

The DN4 is a validated screening questionnaire consisting of 10 items covering neuropathic pain-related symptoms and findings on clinical examination. Seven items address symptoms, including burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching, while three assess sensory findings during examination, including hypoesthesia to touch and pinprick and pain induced by brushing. Each item is scored as either 0 or 1, yielding an overall score between 0 and 10. The symptom-related questions addressed the painful symptoms reported by participants, whereas the sensory examination was performed on the most painful region identified by each participant. A DN4 score of ≥ 4 was used to indicate neuropathic pain-like features rather than a confirmed diagnosis of neuropathic pain [18].

The PDQ is a patient-reported screening instrument, completed with investigator assistance, for neuropathic pain-like symptoms. It assesses current pain intensity, average pain intensity over the preceding four weeks, pain characteristics, temporal patterns, and pain radiation. The questionnaire referred to pain experienced during the preceding four weeks, with current pain intensity assessed at the time of evaluation. The total PDQ score ranges from -1 to 38. Scores ≥ 19 indicate a high likelihood of neuropathic pain-like features, scores from 13 to 18 represent an uncertain classification, and scores ≤ 12 indicate a low likelihood of neuropathic pain-like features [19]. These categories reflect screening results rather than a confirmed diagnosis of neuropathic pain.

Data analysis

Descriptive statistics were used to summarize the study population. Continuous variables were expressed as mean $\pm$ standard deviation (SD) when normally distributed or as median and interquartile range (IQR) when non-normally distributed. Categorical variables were presented as frequencies and percentages.

Analyses comparing patients according to the presence or absence of neuropathic pain-like features were conducted independently within the RA and SpA groups. Student's t-test was applied to normally distributed continuous variables, whereas non-normally distributed variables were analyzed using the Mann-Whitney U test. Categorical variables were analyzed with the chi-square test or Fisher's exact test, as appropriate.

Continuous variables included age, BMI, disease duration, pain VAS, DAS28-CRP, ASDAS-CRP, BASFI, and HAQ scores. Categorical variables included sex, diabetes mellitus, other relevant comorbidities, type of targeted therapy, and concomitant csDMARD therapy.

Factors associated with DN4 positivity (DN4 ≥ 4) were first examined using separate univariable logistic regression analyses for RA and SpA. Disease-specific multivariable logistic regression models were subsequently fitted, including functional impairment, disease activity, and current pain intensity as covariates. The RA model included HAQ-DI, DAS28-CRP, and pain VAS, whereas the SpA model included BASFI, ASDAS-CRP, and pain VAS. Associations were reported as odds ratios (ORs) for univariable analyses and adjusted odds ratios (aORs) for multivariable analyses, with corresponding 95% confidence intervals (CIs). Statistical significance was defined as a two-sided p-value < 0.05 .

All questionnaires were fully completed, and no missing data were identified. Therefore, no data imputation was required. Statistical analyses were performed using jamovi (version 2.7.4.0; The jamovi project, Sydney, Australia).

Sample size

No formal a priori sample size calculation was performed. The sample size was determined by consecutive recruitment during the predefined study period. A total of 160 patients were assessed for eligibility, of whom two were excluded because of diabetic peripheral neuropathy and recent herpes zoster, respectively. Among the remaining 158 eligible patients, three declined to participate, resulting in a final sample of 155 patients, including 78 with RA and 77 with SpA.

Results

Patient characteristics

A total of 155 patients were included, comprising 78 with RA and 77 with SpA. Compared with patients with SpA, those with RA were significantly older (55.6 ± 13.5 vs. 50.7 ± 12.8 years, $p < 0.001$) and more frequently female (68 (87.2%) vs. 22 (28.6%), $p < 0.001$). Disease duration was comparable between the two groups, with a median of 14 (7.75–20.00) years in RA and 13 (7.00–22.00) years in SpA ($p = 0.644$). BMI distribution differed significantly between the groups ($p = 0.021$). Hypertension was more frequent in patients with RA than in those with SpA (29 (37.2%) vs. 4 (5.2%), $p < 0.001$). Diabetes mellitus (11 (14.1%) vs. 1 (1.3%), $p = 0.005$) and dyslipidemia (11 (14.1%) vs. 2 (2.6%), $p = 0.017$) were also more frequent in patients with RA. No significant differences were observed for chronic kidney disease (10 (12.8%) vs. 3 (3.9%), $p = 0.079$), cardiovascular disease (6 (7.7%) vs. 1 (1.3%), $p = 0.117$), or smoking (6 (7.7%) vs. 11 (14.3%), $p = 0.189$). CRP levels were comparable between the two groups ($p = 0.472$), whereas the duration of targeted therapy was significantly longer in patients with RA, with a median of 6 (4.00–10.00) years versus 4 (2.00–6.00) years in SpA ($p < 0.001$). The distribution of targeted therapies also differed significantly between the two groups ($p < 0.001$) (Table [1](#)). Regarding disease activity, RA patients had a mean DAS28-CRP of 3.13 ± 1.39 and a median HAQ score of 0.65 (0.30–1.32). In patients with SpA, the median ASDAS-CRP was 1.50 (1.10–2.10), and the median BASFI score was 2.20 (1.20–4.00) (Table [1](#)).

Variable	RA (n = 78)	SpA (n = 77)	Test used	Test statistic	p-value
Age ^a (years)	55.60 ± 13.50	50.70 ± 12.80	t-student	5.95	<0.001
Female	68 (87.29)	22 (28.60)	Chi-square	54.7	<0.001
Male	10 (12.80)	55 (71.40)	-	-	-
Disease duration (years) ^b	14 (7.75-20.00)	13 (7.00-22.00)	Mann-Whitney U	2203	0.644
Body mass index (BMI) ^c	-	-	Chi-square	7.77	0.021
Normal weight	30 (38.5)	44 (57.10)	-	-	-
Overweight	30 (38.5)	26 (33.80)	-	-	-
Obesity	18 (23.10)	7 (9.10)	-	-	-
Diabetes	11 (14.10)	1 (1.30)	Fisher	-	0.005
Hypertension	29 (37.20)	4 (5.20)	Fisher	-	<0.001
Dyslipidemia	11 (14.20)	2 (2.60)	Fisher	-	0.017
Chronic kidney disease	10 (12.80)	3 (3.90)	Fisher	-	0.079
Heart disease	6 (7.70)	1 (1.30)	Fisher	-	0.117
Smoking	6 (7.70)	11 (14.30)	Chi-square	1.73	0.189
CRP in mg/L ^b	5.65 (1.75-12.90)	3.90 (2.00-8.00)	Mann-Whitney U	2802	0.472
Duration of targeted therapy (years) ^b	6 (4.00-10.00)	4 (2.00-6.00)	Mann-Whitney U	2009	<0.001
Anti-TNF ^c	-	-	Chi-square	1	<0.001
Etanercept	10 (12.80)	20 (26.00)	-	-	-
Infliximab	6 (7.70)	19 (24.70)	-	-	-
Adalimumab	6 (7.70)	24 (31.20)	-	-	-
Golimumab	0 (0.00)	8 (10.40)	-	-	-
Rituximab ^c	26 (33.30)	-	-	-	-
Tocilizumab ^c	28 (35.90)	-	-	-	-
Secukinumab ^c	-	6 (7.80)	-	-	-
Tofacitinib ^c	2 (2.60)	-	-	-	-
DAS28-CRP	3.13 ± 1.39	-	-	-	-
ASDAS-CRP	-	1.50 (1.10-2.10)	-	-	-
HAQ	0.65 (0.30-1.32)	-	-	-	-
BASFI	-	2.20 (1.20-4.00)	-	-	-

TABLE 1: Patient characteristics

^a Mean ± standard deviation (SD); ^b Median (interquartile range (IQR)); ^c Number (percentage), n (%)

The p-value considered statistically significant is <0.05.

CRP: C-reactive protein; DAS28-CRP: Disease Activity Score in 28 Joints using C-reactive Protein; HAQ: Health Assessment Questionnaire; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive Protein; BASFI: Bath Ankylosing Spondylitis Functional Index; RA: rheumatoid arthritis; SpA: spondyloarthritis; TNF: tumor necrosis factor

Neuropathic pain-like features according to DN4 and painDETECT

According to the DN4 questionnaire, neuropathic pain-like features (DN4 ≥ 4) were identified in 19 (24.4%) patients with RA and 21 (27.3%) patients with SpA, with comparable frequencies between the two groups ($p = 0.679$). The median painDETECT score was higher in the SpA group than in the RA group, at 8.0 (6.0-13.0) and 6.0 (4.3-9.0), respectively ($p = 0.035$). However, no significant between-group difference was found in the distribution of painDETECT categories ($p = 0.305$) (Table 2).

Variable	RA (N = 78)	SpA (N = 77)	Test used	Test statistic	p-value
DN4-positive ^a	19 (24.4)	21 (27.3)	Chi-square	0.172	0.679
PainDETECT score ^b	6 (4.3-9.0)	8 (6.0-13.0)	Mann-Whitney U	2415	0.035
PainDETECT categories ^a	-	-	Chi-square	2.38	0.305
Neuropathic pain unlikely (≤ 12)	61 (78.2)	53 (68.8)	-	-	-
Unclear (13-18)	5 (6.4)	8 (10.4)	-	-	-
Neuropathic pain likely (≥ 19)	12 (15.4)	16 (20.8)	-	-	-

TABLE 2: DN4 and painDETECT findings in patients with RA and SpA

^a Number (percentage), n (%); ^b Median (interquartile range (IQR))

RA: rheumatoid arthritis; SpA: spondyloarthritis; DN4: Douleur Neuropathique 4

Factors associated with DN4-defined neuropathic pain-like features

In patients with SpA, univariable logistic regression analyses showed that higher BASFI scores were associated with greater odds of DN4 positivity (OR 2.12, 95% CI 1.43-3.17; $p < 0.001$). Significant associations were also observed for ASDAS-CRP (OR 3.81, 95% CI 1.80-8.08; $p < 0.001$) and current pain VAS (OR 2.36, 95% CI 1.62-3.42; $p < 0.001$). No statistically significant associations were observed for age, sex, or disease duration.

In patients with RA, higher HAQ-DI scores were associated with greater odds of DN4 positivity (OR 5.13, 95% CI 2.27-11.62; $p < 0.001$), as was current pain VAS (OR 3.23, 95% CI 1.87-5.57; $p < 0.001$). No statistically significant associations were observed for age, sex, disease duration, or DAS28-CRP (Table 3).

Predictor	SpA OR (95% CI)	p-value	RA OR (95% CI)	p-value
Age (years)	1.00 (0.96-1.05)	0.909	1.02 (0.98-1.06)	0.415
Sex (F vs M)	1.85 (0.63-5.37)	0.261	0.43 (0.11-1.70)	0.227
Disease duration (years)	0.97 (0.93-1.02)	0.230	0.98 (0.93-1.04)	0.557
BASFI	2.12 (1.43-3.17)	<0.001	-	-
HAQ	-	-	5.13 (2.27-11.62)	<0.001
ASDAS-CRP	3.81 (1.80-8.08)	<0.001	-	-
DAS28-CRP	-	-	1.37 (0.93-2.01)	0.107
Pain VAS (0-10)	2.36 (1.62-3.42)	<0.001	3.23 (1.87-5.57)	<0.001

TABLE 3: Univariable logistic regression analyses of factors associated with neuropathic pain-like features (DN4 ≥ 4) in patients with RA and SpA

RA: rheumatoid arthritis; SpA: spondyloarthritis; DN4: Douleur Neuropathique 4; OR: odds ratio; CI: confidence interval; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein; CRP: C-reactive protein; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score in 28 joints using C-reactive protein

In multivariable logistic regression analyses adjusted for disease activity, functional impairment, and current pain intensity, pain VAS was significantly associated with DN4 positivity in both disease groups. Among patients with SpA, higher pain VAS scores were associated with greater odds of DN4 positivity (adjusted OR 1.90, 95% CI 1.26-2.88; p = 0.002). The associations with BASFI (adjusted OR 1.62, 95% CI 0.99-2.65; p = 0.053) and ASDAS-CRP (adjusted OR 1.19, 95% CI 0.46-3.10; p = 0.721) did not reach statistical significance.

Among patients with RA, higher pain VAS scores were also significantly associated with DN4 positivity (adjusted OR 2.77, 95% CI 1.54-4.98; p < 0.001). The associations with HAQ-DI (adjusted OR 2.19, 95% CI 0.79-6.10; p = 0.134) and DAS28-CRP (adjusted OR 0.90, 95% CI 0.53-1.55; p = 0.711) were not statistically significant (Table 4).

Predictor	SpA aOR (95% CI)	p-value	RA aOR (95% CI)	p-value
ASDAS-CRP	1.19 (0.46-3.10)	0.721	-	-
BASFI	1.62 (0.99-2.65)	0.053	-	-
DAS28-CRP	-	-	0.90 (0.53-1.55)	0.711
HAQ	-	-	2.19 (0.79-6.10)	0.134
VAS (0-10)	1.90 (1.26-2.88)	0.002	2.77 (1.54-4.98)	<0.001

TABLE 4: Multivariable logistic regression analysis of factors associated with DN4 positivity

RA: rheumatoid arthritis; SpA: spondyloarthritis; DN4: Douleur Neuropathique 4; aOR: adjusted odds ratio; CI: confidence interval; HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score in 28 joints using C-reactive protein; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein; VAS: visual analogue scale

Discussion

In our cohort of 155 patients with CIRDs receiving targeted therapies, neuropathic pain-like features, defined by a DN4 score ≥4, were identified in 19 (24.4%) patients with RA and 21 (27.3%) patients with SpA, with no statistically significant difference between the two groups. In univariable analyses, functional impairment and pain intensity were significantly associated with DN4 positivity in both disease groups, while disease activity was additionally associated in SpA. In multivariable analyses adjusted for functional impairment, disease activity, and current pain intensity, pain VAS remained significantly associated with DN4 positivity in both RA and SpA, whereas the associations with functional impairment and conventional disease activity indices did not reach statistical significance. Overall, these findings suggest that neuropathic pain-like features are frequently reported among patients receiving targeted therapies and are closely associated with pain intensity, although the underlying pain mechanisms cannot be determined from screening questionnaires alone.

Our findings are consistent with previous studies reporting neuropathic pain-like features in patients with inflammatory rheumatic diseases receiving disease-modifying therapies. Al Mohamad et al. reported neuropathic and nociplastic pain components among patients with axial SpA receiving biologic therapy, highlighting the potential contribution of non-inflammatory pain mechanisms to residual symptoms [20]. Similarly, Ögüt et al. reported neuropathic pain features in patients with axial SpA treated with biologic agents [21]. In RA, Ahmed et al. described neuropathic and sensitization components in pain reporting among patients receiving DMARDs [22]. Although no statistically significant difference in DN4 positivity was observed between RA and SpA in our cohort, this finding should not be interpreted as evidence of equivalent prevalence, particularly given the demographic and clinical differences between the two groups.

An important finding of our study was the relationship between neuropathic pain-like features and functional impairment. In univariable analyses, higher BASFI scores in SpA (OR 2.12, 95% CI 1.43-3.17; p < 0.001) and higher HAQ-DI scores in RA (OR 5.13, 95% CI 2.27-11.62; p < 0.001) were significantly associated with DN4 positivity. However, after adjustment for disease activity and current pain intensity, these associations were attenuated and did not reach statistical significance. In SpA, BASFI showed an adjusted OR of 1.62 (95% CI 0.99-2.65; p = 0.053), while in RA, HAQ-DI showed an adjusted OR of 2.19 (95% CI 0.79-6.10; p = 0.134). These findings do not exclude a potential relationship between functional impairment and neuropathic pain-like features, particularly given the positive association estimate for BASFI and the limited precision of the adjusted estimates. Previous studies have similarly reported poorer functional status among patients with neuropathic pain characteristics. Ahmed et al. found higher HAQ scores in patients with RA presenting neuropathic pain features [22], while Al Mohamad et al. reported greater functional impairment among patients with axial SpA exhibiting neuropathic or nociplastic pain components [20]. Because of the cross-sectional nature of our study, however, the temporal direction of these relationships cannot be

determined. Neuropathic pain-like features, pain intensity, and functional limitation may therefore be interrelated without establishing a causal relationship.

Regarding inflammatory disease activity, ASDAS-CRP was significantly associated with DN4 positivity in SpA in univariable analysis (OR 3.81, 95% CI 1.80-8.08; $p < 0.001$). However, this association was attenuated after adjustment for BASFI and current pain VAS (adjusted OR 1.19, 95% CI 0.46-3.10; $p = 0.721$). In RA, no statistically significant association was observed between DAS28-CRP and DN4 positivity, either in univariable analysis (OR 1.37, 95% CI 0.93-2.01; $p = 0.107$) or in the multivariable model (adjusted OR 0.90, 95% CI 0.53-1.55; $p = 0.711$). These findings should not be interpreted as demonstrating an absence of association between inflammatory disease activity and neuropathic pain-like features. Moreover, conventional disease activity indices incorporate patient-reported components that may overlap with pain intensity. Previous studies have suggested that persistent pain despite inflammatory control may involve mechanisms beyond ongoing peripheral inflammation [2,5]. Central sensitization and nociplastic mechanisms have been proposed as possible explanations for persistent pain in inflammatory rheumatic diseases [23,24]. However, these mechanisms were not directly assessed in our study, and DN4 and painDETECT cannot reliably distinguish neuropathic, nociplastic, and other pain mechanisms. They should therefore be considered possible explanatory mechanisms rather than conclusions derived from our findings.

Pain intensity also showed a strong relationship with neuropathic pain-like features. In univariable analyses, current pain VAS was associated with DN4 positivity in both RA (OR 3.23, 95% CI 1.87-5.57; $p < 0.001$) and SpA (OR 2.36, 95% CI 1.62-3.42; $p < 0.001$). These associations remained statistically significant after adjustment for functional impairment and disease activity. In RA, current pain VAS was associated with greater odds of DN4 positivity (adjusted OR 2.77, 95% CI 1.54-4.98; $p < 0.001$), as was pain VAS in SpA (adjusted OR 1.90, 95% CI 1.26-2.88; $p = 0.002$). These findings are consistent with previous studies reporting greater pain intensity among patients with neuropathic pain-like characteristics [8,22]. However, pain VAS and DN4 both capture dimensions of the patient's pain experience, and the observed association may partly reflect overlapping symptom constructs. Consequently, these results should not be regarded as evidence that pain intensity independently causes or predicts neuropathic pain-like features.

From a clinical perspective, our findings highlight the importance of considering neuropathic pain-like features in patients with persistent pain despite targeted therapy. Persistent pain may not necessarily reflect insufficient inflammatory control, and its assessment should consider the multifactorial nature of pain in inflammatory rheumatic diseases. Screening tools such as DN4 and painDETECT may complement conventional disease activity assessment by identifying neuropathic pain-like symptoms that warrant further clinical evaluation. However, positive screening results do not establish a definitive diagnosis of neuropathic pain, and the clinical utility of routine screening in guiding treatment decisions remains uncertain. Whether this approach could help avoid unnecessary escalation or switching of targeted therapy or improve patient outcomes requires further investigation.

Limitations

Several limitations should be considered when interpreting our findings. First, the cross-sectional nature of the study does not allow causal relationships or the temporal direction of associations to be established. Second, recruitment from a single center during routine intravenous infusions or outpatient visits for prescription renewal may have introduced selection bias, and the relatively modest sample size may reduce the generalizability of the results. The limited number of DN4-positive patients in each disease group (19 in RA and 21 in SpA) also restricted the number of variables included in the multivariable models and may have affected the stability and precision of the estimates.

Although current pain intensity was included in the multivariable models, residual confounding remains possible because other potentially relevant variables, including age, sex, disease duration, diabetes mellitus, corticosteroid use, and treatment class, were not simultaneously adjusted for. Psychological factors such as anxiety, depression, pain catastrophizing, and sleep disturbances were not specifically assessed and may also represent potential confounders.

Third, DN4 and painDETECT are screening tools and do not establish a definitive diagnosis of neuropathic pain or distinguish between different pain mechanisms. Although patients with previously diagnosed peripheral neuropathy or clinical findings suggestive of an active peripheral neurological disorder were excluded, systematic electrophysiological investigations were not performed. Therefore, the presence of unrecognized peripheral neuropathy cannot be entirely excluded. Finally, the demographic and clinical differences between RA and SpA, particularly regarding age, sex, and comorbidities, should be considered when interpreting between-group comparisons. The absence of a statistically significant difference in DN4 positivity does not establish equivalence between the two diseases.

Nevertheless, the study also has important strengths. To our knowledge, no previous Moroccan study has directly compared neuropathic pain-like features between patients with RA and SpA receiving targeted therapies. The use of two validated screening tools, together with disease-specific analyses, provides complementary insight into their frequency and clinical correlates.

Conclusions

Neuropathic pain-like features are frequent in patients with RA and SpA receiving targeted therapies. After adjustment for functional impairment and conventional disease activity measures, pain intensity remained significantly associated with DN4 positivity in both disease groups, whereas the associations with functional impairment and disease activity did not reach statistical significance. These findings highlight the multifactorial nature of pain in inflammatory rheumatic diseases and suggest that screening for neuropathic pain-like features may complement the clinical assessment of persistent pain, without establishing a definitive neuropathic pain diagnosis. Further prospective studies are needed to clarify the underlying pain mechanisms and determine whether incorporating neuropathic pain screening into clinical practice can improve therapeutic decision-making and patient outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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