Determinants of non-nociceptive pain in Rheumatoid Arthritis

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ABSTRACT

Introduction: Features suggestive of neuropathic pain (NP) have been described in rheumatoid arthritis (RA) in addition to nociceptive pain. We aimed to determine the clinical predictors of NP in RA patients and study its association with radiographic structural damage.

Methods: Cross-sectional study was performed with RA patients followed at our Rheumatology department. Patients with diagnosed neuropathy of other origin, non-RA related risk factors for NP (e.g. diabetes mellitus) or fibromyalgia, according to expert opinion, were excluded. Demographic and clinical data were collected and disease activity/functional measures were evaluated. Two questionnaires were applied to assess NP: the Leeds Assessment of Neuropathic Symptoms (LANSS) and the painDETECT questionnaire (PDQ). Radiographs performed in up to 12 months before/after the evaluation were classified according to the modified van der Heijde Sharp's method. Univariate and multivariate logistic regression were performed to identify the predictors of NP.

Results: 112 patients were included. 86 (77%) were women, with a mean (SD) age of 55.1 (10.8) years and median disease duration of 13 [2-41] years. 45 (40%) patients had NP by the LANSS (≥12) and 28% had a possible/likely NP in the PDQ (≥13). Female sex was predictive of NP by both tests and disease duration was inversely associated with LANSS NP. After adjusting for those two variables, pain Visual Analog Scale (VAS) and TJC were positive predictors of NP by both tests. The same was not true for SJC, ESR or CRP levels. DAS28-CRP was significantly associated with PDQ NP, losing its statistical significance after adjustment for TJC and pain VAS. The HAQ score increased the odds of NP for both tests, independently of DAS 28-CRP. Positivity for ACPA and previous/current hydroxychloroquine treatment had lower odds of NP. 90 patients performed radiographic evaluation. Joint narrowing score was a significant negative predictor of LANSS NP. After adjusting for global radiographic score, current methotrexate treatment had lower odds of LANSS NP and previous/current leflunomide was a positive predictor of NP by both tests.

Conclusion: NP was associated with disease activity/functional scores but not with objective inflammatory measures. Greater structural damage, increased disease duration and anti-cyclic citrullinated peptide antibodies (ACPA) positivity did not seem to increase the odds of NP. Possible association of NP and underlying csDMARD treatment was uncovered.

Keywords: Nociceptive pain; Radiographic damage; Neuropathic pain; Chronic pain; Rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disorder frequently associated with significant pain and disability. During the past 30 years, notable advances were made in RA treatment through the implementation of treat-to-target strategy and the introduction of biological Disease Modifying Antirheumatic Drugs (bDMARDs). These strategies deeply improved the control of disease activity and joint damage[1-4]. Nevertheless, RA pain remains undertreated, with unchanged mean self-assessed pain over the past 20 year-period[5]. In fact, pain was considered to be the highest priority in nearly 70% of RA patients[6] and in a survey conducted in 2010, 75% of European patients reported moderate-to-severe pain in spite of controlled disease activity[7]. In another study, significant pain per-

sisted in more than 11% of patients meeting Disease Activity Score 28 C-Reactive Protein (DAS28-CRP) remission criteria. Moreover, chronic pain was not significantly associated with inflammatory markers nor it was reduced with inflammation control, supporting the idea that causes other than peripheral inflammation may be involved in RA related pain[8].

Although RA pain is frequently described with nociceptive-like symptoms, some patients also reported neuropathic pain (NP) descriptors[9, 10]. In accordance to this, recent studies found that between 33-44% RA patients presented possible/likely NP applying the painDETECT questionnaire (PDQ)[11-14]. Additionally, the application of other NP screening tools, such as the Leeds Assessment Neuropathic Symptoms score (LANSS) and the *Douleur Neuropathique* 4 (DN4) questionnaire, also revealed a NP component in RA[15,16]. Again, no association between NP and objective inflammatory measures or underlying treatment was found, whereas relations were found with subjective measures, such as the tender joint count (TJC) and self-reported physical/mental health[12-14]. Besides RA, NP has also been reported in other rheumatic conditions, such as osteoarthritis (OA)[17] and spondyloarhtritis[14, 18].

NP is classically defined as "pain that is caused by a lesion or disease of the somatosensory system[19], persisting in the absence of a noxious stimulus[20]. In RA, impaired central pain processing, namely by increased central sensitization (CS) and loss of descending analgesia have been described as plausible underlying mechanisms of non-nociceptive RA chronic pain[21-27]. On the other hand, peripheral causes of pain, such as structural joint damage, have been only scarcely explored in RA[28, 29].

Recent evidence thus suggests that neuropathic processes may be involved in the maintenance of pain in RA patients, which has the potential to conduce to new diagnostic and therapeutic strategies. Therefore, the aim of this study was to assess the frequency of increased scores in tools indicating NP (PDQ and LANSS) and to determine whether NP component is associated with: disease duration, disease activity, disability, radiographic joint damage and underlying treatment regimen.

METHODS

STUDY DESIGN AND PARTICIPANTS SELECTION

An observational, cross-sectional study was conducted at the Rheumatology Department of Centro Hospitalar São João. Participants were consecutively recruited by their rheumatologist between October 2015 and October 2016. Inclusion criteria were defined as adult patients (≥18 years) with RA diagnosis, according to 1987 ACR or 2010 ACR/EULAR classification criteria[30, 31], with unchanged DMARD treatment during the previous three months. Patients with non-RA related risk of NP or a diagnosed neuropathy were excluded, namely: diabetes mellitus, current neoplasm, current/previous chemotherapy and/or radiotherapy, Human Immunodeficiency Virus infection, end-stage renal disease, vasculitis, chronic alcoholism, radiculopathy and uncontrolled thyroid disease. Patients with previous diagnosis of fibromyalgia (FM) according to their rheumatologist expert opinion were also excluded. Eligible patients were later evaluated in a medical visit where data were collected by a rheumatologist and recorded in The Rheumatic Diseases Portuguese Register (Reuma.pt). All participants gave written informed consent. Use of the Reuma.pt database was registered with the Portuguese Data Protection Authority and the study protocol was approved by the Ethics Committee of Centro Hospitalar de São João.

VARIABLES AND OUTCOME MEASURES

Demographics and clinical data

Patient data were collected in a medical visit, using a protocol designed for this study, which included: background data (age, gender, height and weight, education level; smoking and alcohol habits); RA disease duration in years; rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) positivity; RA extra-articular manifestations; previous diagnosis of depression; treatment with corticosteroids and conventional synthetic or biologic DMARDs (cs/bDMARD) (current/previous therapies and duration) and analgesic medication.

Disease activity evaluation

RA disease activity was evaluated by application of DAS 28-Erythrocyte Sedimentation Rate (DAS-28--ESR) and DAS28-CRP, which include: 28 swollen joint count (SJC) and TJC performed by a trained rheumatologist, patient Visual Analog Scale (VAS) for general disease activity [0-100mm] and ESR and CRP levels[32,33]. Additionally, 66/68 SJC and TJC were evaluated to assess other potential painful joints not included in DAS 28.

Functional evaluation

Functional disability was assessed using Health Assessment Questionnaire (HAQ) score, which includes questions about the ability of patients to perform activities of daily living and about the use of aids and devices[34].

Pain evaluation

The VAS for pain intensity [0-100] was applied. Regarding NP screening, two scores were used: the LANSS and the PDQ. The LANSS is a screening tool with a reported sensitivity and specificity for NP diagnosis ranging from 82-91% and 80-94%, respectively[35,36]. It was previously applied in RA[15] and it is validated for the Portuguese population[37]. It contains 5 items with dichotomous answer (yes/no) and 2 clinical examination items. The latter evaluate allodynia and abnormal pinprick pain threshold (PPT) which were applied on the most painful reported joint area and contralateral non-painful area. The score ranges from 0-24, with values ≥12 being classified as probable NP. The PDQ score is a self-reported questionnaire which has 85% sensitivity and 80% specificity for NP[38]. It was widely applied in RA[11-14] and has shown good reliability in this disease[39]. Although PDQ was translated to Portuguese language, no validation to Portuguese population was yet performed. PDQ contains 9 items not requiring physical examination: 7 weighted sensory descriptor items classified into 5 categories and 2 items related to spatial and temporal patterns of pain. PDQ score ranges from 1-38, where scores ≤12 indicate unlikely NP, score ≥19 suggest likely NP and values ranging 13-18 indicate possible NP.

Radiographic damage

Radiographic studies of the wrists, hands and feet were performed in up to 12 months before/after the medical visit and were classified according to the modified van der Heijde Sharp's method (mSVdHS) by one trained reader, blinded for patient clinical variables and treatment allocation. The mSVdHS method classifies joint erosion (JE) [0-5] and joint space narrowing (JSN) [0-4], with a maximal global score (GS) of 448[40, 41].

STATISTICAL ANALYSIS

Patients classified with possible/likely NP on PDQ (≥13) and/or NP on LANSS (≥12) were compared to patients without NP regarding several variables. The distributions of continuous variables were compared between groups using either Student's t test (normally-distributed variables) or Mann-Whitney's U test (non-normally distributed variables). The chi-squared test was applied to compare the distributions of categorical variables. Correlation and agreement between the two questionnaires were estimated through Pearson's correlation coefficient and Cohen's kappa, respectively. Predictors of NP (two dichotomous outcomes were defined as LANSS ≥ 12 and PDQ ≥ 13, separately) were then identified through computing crude or adjusted odds ratios (OR) and 95% confidence intervals (CI 95%) estimated using unconditional logistic regression. Final models were adjusted for potential confounders and for variables with statistically significant associations in univariate analysis. Separate analysis was done adjusting for radiographic GS. The significance level was set at 0.05. The statistical analysis was conducted using the SPSS (23.0) and Stata (11.0) software.

RESULTS

PATIENT CHARACTERISTICS

Characteristics of the patients included are shown in Table I. In total, 115 RA patients were initially evaluated, of whom 3 were excluded as they presented exclusion criteria (1 patient had cutaneous vasculitis, 1 current neoplasm and 1 had diabetes). From the 112 included patients, 86 (77%) were females, with a mean (standard deviation, SD) age of 55.1 (10.8) years and median (range) disease duration of 13 (39) years. Ninety two patients were seropositive for RF and/or ACPA. One hundred and two (91%) were treated with csDMARDs and 42% with a bDMARD, of whom 8% in monotherapy.

The mean (SD) DAS28 4V-CRP was 3.2 (0.9), 38% had low disease activity and 21% were in remission, according to DAS28-CRP criteria. Regarding radiographic damage, 90 out of 112 patients had recent hands/feet radiographs. The median (range) JE score was 28 (140), the JSN score was 46 (123) and the GS was 73 (262). Patients with radiographic evaluation had higher frequency of NP, as defined by LANSS or PDQ (56% *versus* 14%, p=0.001) and lower median disease duration (12 *versus* 18 years, p=0.01) in comparison to patients without radiographs, with no other statistically significant differences found.

NEUROPATHIC PAIN FREQUENCY AND ASSOCIATED FEATURES

Forty-five (40%) patients had NP using LANSS (≥12)

TABLE I. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Female sex – n (%)	86 (77%)
Age – mean (SD), years	55 (10.8)
Education, median (min-max), years	6 (0-20)
BMI – n (%) (n=97)	
Normal	48 (43%)
Overweight	39 (35%)
Obese	20 (18%)
Current smoking - n (%)	15 (13%)
Current alcohol use - n (%)	24 (21%)
Disease duration - median (min-max), years	13 (2-41)
RF and/or ACPA positivity – n (%) (n=110)	92 (84%)
Extra-articular manifestations- n (%)	25 (22%)
Previously diagnosed depression – n (%)	22 (20%)
Glucocorticoids – n (%)	73 (65%)
csDMARD – n (%)	102 (91%)
Methotrexate	78 (70%)
Leflunomide	29 (26%)
Sulfassalazine	9 (8%)
Hydroxychloroquine	12 (11%)
bDMARD- n (%)	47 (42%)
TNFα blockers	29 (26%)
Tocilizumab	14 (13%)
Riuximab	4 (3.5%)
NSAIDs – n (%)	79 (71%)
Paracetamol – n (%)	10 (9%)
Opiates – n (%)	7 (6%)
Antidepressant – n (%)	19 (17%)
Pain VAS (0-100mm) – mean (SD)	46 (21.5)
DAS 28 CRP – mean (SD)	3.2 (0.9)
DAS 28 ESR – mean (SD)	3.7 (1.0)
DAS 28 (CRP) – n (%)	
Remission	23 (21%)
LDA	43 (38%)
MDA	43 (38%)
HDA	3 (3%)
DAS 28 (ESR) – n (%)	
Remission	13 (12%)
LDA	29 (26%)
MDA	64 (57%)
HDA	6 (5%)
HAQ – mean (SD)	1.0 (0.6)
JSN score – median (min-max) (n=90)	46 (10-133)
JE score – median (min-max) (n=90)	28 (3-143)
Global score – median (min-max) (n=90)	73 (14-276)

and 28% had NP according to PDQ (17% possible and 11% likely NP). 47% of patients had NP in at least one (LANSS and/or PDQ group) and 21% in both tests (Table II). No statistically significant differences were found between possible and likely PDQ NP patients regarding demographic or clinical variables (supplementary Table I). On LANSS examination, 24 (21%) patients presented allodynia and 71 (64%) altered PPT. A moderate agreement (κ= 0.41, p<0.001) and a moderate linear correlation (r=0.58, p<0.001) were observed between the two questionnaires.

Neuropathic associated features are described in Table III. Lower disease duration was observed in PDQ and/or LANSS NP group (11 *versus* 15 years, p=0.005). A higher proportion of women was observed in PDQ NP (90% *versus* 72%, p=0.045), but no differences were found when considering PDQ and/or LANSS NP group. A slightly lower frequency of ACPA positivity was found in the NP group according to PDQ and/or LANSS (71% *versus* 88%, p=0.03). Concerning RA treatments, significantly higher proportion of leflunomide (LFN) treated patients (currently/previously) was noted in the NP group. Additionally, in the PDQ NP group, a lower proportion of methotrexate (MTX) treated patients was observed (52% *versus* 76%, p=0.02). Moreover, lower mean scores of PDQ and LANSS was found in MTX group (8.4 *versus* 11.7 and 9.1 *versus* 12.0, respectively, p<0.05). LANSS and/or PDQ NP patients had a higher frequency of non-steroidal inflammatory drugs (NSAIDs) and any analgesics use when compare to non-NP patients. No significant differences were found regarding specific analgesic treatments. Higher median pain VAS scores and TJC[68], mean disease activity scores and HAQ were found in LANSS and/or PDQ NP group. Conversely, median SJC[66], ESR and CRP levels were not significantly different between the two groups. Regarding radiographic damage, NP patients presented lower median JSN scores, but no significant differences were found for the other scores. No other statistically significant differences were found

ACPA: anti-cyclic citrullinated peptide antibodies; bDMARD: biological DMARD; BMI: Body mass index; csDMARD: conventional synthetic DMARD; DAS 28 CRP/ESR: Disease Activity Score 28 C-Reactive Protein/Erythrocyte Sedimentation Rate; HAQ: Health assessment questionnaire; JE: joint erosion; JSN: joint space narrowing; LDA: low disease activity; MDA: moderate disease activity; Max: maximum; Min: minimum; RF: Rheumatoid factor; SD: standard deviation.

TABLE II. PREVALENCE OF NEUROPATHIC PAIN AND CORRELATION/AGREEMENT BETWEEN QUESTIONNAIRES

painDETECT NP – n (%)	
no	81 (72%)
possible	19 (17%)
likely	12 (11%)
LANSS NP - n (%)	45 (40%)
Allodynia	24 (21%)
Abnormal PPT	71 (63%)
Reduced PPT	54 (48%)
Higher PPT	17 (15%)
painDETECT and LANSS NP – n (%)	23 (21%)
painDETECT and/or LANSS - n (%)	53 (47%)
painDETECT and LANSS agreement (k)	0.41
painDETECT and LANSS correlation (r)	0.58

LANSS: Leeds Assessment Neuropathic Symptoms; NP: neuropathic pain; PPT: pinprick pain threshold; K: kappa coefficient analysis; r: spearman coefficient

regarding the remaining variables.

CLINICAL DETERMINANTS OF NEUROPATHIC PAIN

In crude regression analysis, female sex was predictive of LANSS and PDQ NP and disease duration was inversely associated with LANSS NP (Table IV). After adjusting for those two variables, pain and patient global activity VAS and 68 TJC were positive predictors of NP by both tests. The same was not true for SJC, ESR or CRP levels. DAS28-CRP was significantly associated with PDQ NP, losing its statistical significance after adjustment for 68 TJC and pain VAS. HAQ score increased the odds of NP for both tests and this association was independent of DAS 28-CRP for PDQ NP. Patients with positivity for ACPA and previous/current Hydroxychloroquine (HCQ) treatment had lower odds of LANSS and PDQ NP, respectively, remaining significant after adjustment for disease activity. Current NSAIDs treatment was associated with PDQ NP, although not independently of DAS 28-CRP. Length of exposure to each csDMARD was not significantly associated to NP outcomes.

RADIOGRAPHIC DAMAGE ASSOCIATION WITH NEUROPATHIC PAIN

JSN radiographic score was a significant weak negative predictor of LANSS NP (Table V). After adjusting for global radiographic score, neither sex nor disease duration were associated with NP. Again, pain VAS, patient global activity and the TJC were positive predictors of NP by both tests and SJC, ESR or CRP levels were not significantly associated with NP. DAS 28-CRP and HAQ score were associated with NP according to each test and positivity for ACPA was a negative predictor of LANSS NP once more. Previous/current HCQ treatment was again a negative predictor of PDQ NP independently of disease activity. Differently from the previous results, in this subgroup of patients, current MTX treatment had lower odds of NP on both tests, but only remained significant after DAS28-CRP adjustment for PDQ NP. Previous/current LFN was differently a significant positive predictor of NP in both tests, persisting for LANSS NP after DAS 28-CRP adjustment.

DISCUSSION

In this study, a sizable proportion of patients (47%) presented features suggestive of NP in at least one of the screening tests, 40% patients according to LANSS and 28% according to PDQ. This was the first study applying more than one screening NP tool in RA. Previous studies reported a slightly higher proportion of possible/likely PDQ NP in RA, ranging from 33-44%[11-14]. The LANSS test was only applied in RA in one study and the frequency of NP was not clearly defined, since no diagnostic cut-off point was used[15]. The different proportions of NP according to LANSS and PDQ may be explained by different diagnostic performance of those tools. We found a moderate agreement and correlation between LANSS and PDQ which supports different measurement properties of those tests. In OA patients, a slightly lower agreement (k=0.35) between PDQ and self-report LANSS version (S-LANSS) was previously reported[42], yet performance of those tests has not been previously studied in RA. Besides, no gold-standard for NP diagnosis was used, thus no firm conclusions can be drawn regarding diagnostic properties of these tools in RA.

In accordance to previous evidence[12, 13], we found that RA patients with NP features had higher intensity of self-reported pain and global disease activity, higher TJC, self-reported disability and disease activity composite scores. Again, no association with objective inflammatory parameters (i.e ESR/CRP levels and SJC) was found by our group. Besides, the association of NP with DAS 28-CRP score did not remain significant

TABLE III. COMPARISON BETWEEN PATIENTS WITH NEUROPATHIC COMPONENT AND WITHOUT NEUROPATHIC PAIN (ACCORDING TO PAINDETECT AND/OR LANSS NP)

	No NP component	NP component (PDQ / LANSS)	P value
Female Sex – n (%)	41 (69%)	45 (85%)	0.073
Age (years) - mean (SD)	56.0 (9.5)	54.0 (12.0)	0.337
BMI – median (min-max)	25.8 (18-40)	25.3 (20-46)	0.878
Education (years) – median (min-max)	6 (3-20)	6 (0-18)	0.951
Current smoking – n (%)	7 (12%)	8 (15%)	0.782
Current alcohol use – n (%)	17 (29%)	7 (14%)	0.064
Disease duration – median (min-max)	15 (3-41)	11 (2-31)	0.005
RF / ACPA - n (%)	51 (87%)	41 (79%)	0.302
ACPA – n (%)	52 (88%)	37 (71%)	0.033
Extra-articular manifestations – n (%)	14 (24%)	11 (21%)	0.821
Secondary Sjögren Syndrome –n (%)	4 (6.8%)	4 (7.5%)	1.000
Depression – n (%)	13 (22%)	9 (17%)	0.635
Glucocorticoids – n (%)	35 (59%)	38 (72%)	0.233
Methotrexate – n (%)	45 (76%)	33 (62%)	0.149
Leflunomide – n (%)	14 (24%)	15 (28%)	0.670
Leflunomide (previous/current) – n (%)	19 (32%)	28 (53%)	0.035
Sulfasalazine – n (%)	6 (10%)	3 (5.6%)	0.495
Hydroxychloroquine – n (%)	7 (12%)	5 (9%)	0.766
bDMARDs – n (%)	28 (47%)	19 (36%)	0.252
TNFα inhibitors – n (%)	18 (31%)	11 (21%)	0.284
NSAIDs – n (%)	35 (59%)	44 (83%)	0.007
All analgesics - n (%)	37 (63%)	45 (85%)	0.010
VAS - pain [0-100mm] – median (min-max)	40 (10-90)	50 (0-100)	0.010
VAS – patient global activity [0-100mm] – median (min-max)	40 (0-80)	50 (0-100]	0.001
TJC (68)– median (min-max)	4 (1-20)	9 (1-24)	0.010
SJC (66) – median (min-max)	2 (0-9)	2 (0-14)	0.440
ESR mm/1st hour – median (min-max)	19 (2-75)	16 (2-58)	0.330
CRP mg/L – median (min-max)	3.6 (0-84)	2.8 (0-169)	0.131
DAS 28 –CRP – mean (SD)	3.0 (0.83)	3.4 (0.83)	0.021
DAS 28 –CRP remission– n (%)	18 (31%)	5 (9%)	0.009
DAS 28 – ESR - mean (SD)	3.4 (0.98)	3.8 (1.01)	0.031
DAS 28 – ESR remission - n (%)	9 (15%)	4 (8%)	0.247
HAQ – mean (SD)	0.87 (0.67)	1.22 (0.57)	0.010
JE score - median (min-max) (n=90)	25.5 (4-143)	29 (3-120)	0.810
JSN score - median (min-max) (n=90)	56 (14-133)	44 (10-115)	0.021
GS - median (min-max) (n=90)	76 (27-276)	63 (14-235)	0.172

ACPA: anti-cyclic citrullinated peptide antibodies; bDMARD: (biological DMARD); BMI: Body mass index; csDMARD: (conventional synthetic DMARD); DAS 28 CRP/ESR: Disease Activity Score 28 C-Reactive Protein/Erythrocyte Sedimentation Rate; GS: global mSVdHS; HAQ: Health assessment questionnaire; JE: joint erosion mSVdHS; JSN: joint space narrowing mSVdHS; LANSS: Leeds Assessment of Neuropathic Symptoms; Max: maximum; Min: minimum; NP: Neuropathic pain; PDQ: painDETECT questionnaire; RF: Rheumatoid factor; SD: standard deviation; SJC 66: swollen joint count; TJC 68: 68 tender joint count.

after adjustment for TJC and pain VAS. As reported by Christensen AW *et al*, no statistically significant association was found between PDQ scores and imaging inflammatory scores (ultrasound Doppler and magnetic resonance imaging (MRI) scores)[13]. This supports that mechanisms independent of inflammatory activi-

TABLE IV. CLINICAL PREDICTORS OF LANSS AND PDQ NEUROPATHIC PAIN

N=112	LANSS NP OR 95% [CI]	p value	PDQ NP OR 95% [CI]	p value
Female sex	3.44 [1.19- 9.88]	0.022	3.70 [1.02- 1.35]	0.046
Age (years)	0.98 [0.95-1.02]	0.264	0.97 [0.9-1.0]	0.099
Disease duration (years)	0.92 [0.87-0.97]	0.004	0.96 [0.91-1.01]	0.173
	0.92 [0.87-0.98]**	0.005		
Depression	0.83 [0.3-2.27]*	0.710	0.78 [0.27-2.30]*	0.656
ACPA positivity	0.23 [0.08-0.69]*	0.009	0.45 [0.16-1.24]*	0.125
	0.26 [0.07-0.63]**	0.006		
Pain VAS	1.02 [1.00-1.04]*	0.035	1.03 [1.01-1.06]*	0.002
Patient global activity VAS	1.02 [1.00-1.04]*	0.017	1.05 [1.02-1.07]*	0.017
TJC (68)	1.11 [1.01-1.20]*	0.019	1.13 [1.03-1.23]*	0.006
SJC (66)	1.07 [0.91-1.2]*	0.399	1.13 [0.97-1.3]*	0.120
ESR/CRP levels	0.97 [0.94-1.0]*	0.180	0.97 [0.94-1.0]*	0.080
	0.95 [0.87-1.02]*	0.063	0.93 [0.84-1.02]*	0.120
DAS 28-ESR	1.24 [0.81-1.89]*	0.331	1.46 [0.91-2.34]*	0.120
DAS 28-CRP	1.47 [0.9-2.4]*	0.129	1.77 [1.03-3.03]*	0.039
			0.69 [0.31-1.54] ***	0.359
HAQ	2.16 [1.08-4.28]*	0.028	3.61 [1.64-7.93]*	0.001
	1.95 [0.92-4.10]**	0.080	3.19 [1.38-7.39]**	0.007
NSAIDs current use	2.51 [0.96-6.56]*	0.061	3.40 [1.06-10.90]*	0.039
			3.15 [0.97-10.26]**	0.056
MTX (current)	0.71 [0.29-1.74]*	0.459	0.41 [0.16-1.0] *	0.052
HCQ (current/previous)	0.49 [0.16-1.49]*	0.209	0.19 [0.42-0.93] *	0.040
			0.20 [0.42-0.97] **	0.046
LFN (current/previous)	2.04 [0.88-4.7]*	0.099	1.75 [0.72-4.16] *	0.217
bDMARDs	0.63 [0.27-1.49]*	0.294	0.85 [0.35-2.10] *	0.730
TNFα inhibitors	0.49 [0.18-1.32]*	0.158	0.80 [0.29-2.18] *	0.655

Logistic regression. *adjusted for disease duration and sex. **adjusted for disease duration, sex and DAS 28 CRP. ***adjusted for TJC and pain VAS. ACPA: anti-cyclic citrullinated peptide antibodies; bDMARD: (biological DMARD); CI: confidence interval; DAS 28 CRP/ESR: Disease Activity Score 28 C-Reactive Protein/Erythrocyte Sedimentation Rate; HAQ: Health assessment questionnaire; HCQ: Hydroxycloroquine; LANSS: Leeds Assessment of Neuropathic Symptoms; LFN: leflunomide; MTX: methotrexate; NP: neuropathic pain; NSAIDs: non-steroidal anti-inflammatory drugs; OR: Odds Ratio; PDQ: painDETECT questionnaire; SJC (66): swollen joint count; TJC (68): 68 tender joint count; VAS: visual analogue scale

ty explain persistence of RA chronic pain, potentially affecting accurate disease activity evaluation and management.

In line with this hypothesis, modified central regulatory pain mechanisms in RA have been described in the literature using neurophysiologic evaluations. Particularly, findings of widespread joint and non-joint lower pain thresholds[23,26,43], increase of pain sensitivity after conditioning stimulus[44] and higher levels of temporal summation were described in these patients in comparison to healthy controls[45]. In addition, a higher proportion of patients fulfilling FM criteria (a prototypical central pain syndrome) was observed in NP RA patients according to PDQ[12]. Also, MRI structural brain changes and electroencephalographic evidence of enhanced cortical responses to noxious stimuli was described in RA[46,47]. Taken together, those results reinforce the hypothesis that centrally mediated pain, namely by enhanced CS and modified conditioned pain modulation, is an underlying mechanism of non-inflammatory pain in RA[21,48]. Although not validated to diagnose it, NP screening tools may assist in the identification of central mediated pain in RA. This is supported by previous evidence of higher PDQ scores in

TABLE V. RADIOGRAPHIC DAMAGE AND CLINICAL PREDICTORS OF NEUROPATHIC PAIN

N=112	LANSS NP OR 95% [CI]	p value	PDQ NP OR 95% [CI]	p value
JE score	0.99 [0.98-1.01]	0.378	0.99 [0.98-1.00]	0.304
JSN score	0.98 [0.96-0.99]	0.018	0.98 [0.97-1.00]	0.247
	0.98 [0.96-1.00]****	0.092		
Global radiographic score	0.99 [0.98-1.00]	0.078	0.99 [0.98-1.00]	0.231
Female sex	2.5 [0.86-7.39]*	0.091	3.43 [0.91-12.86]*	0.068
Age (years)	0.98 [0.94-1.02]*	0.312	0.97 [0.93-1.01]*	0.128
Disease duration (years)	0.96 [0.90-1.03]*	0.238	1.01 [0.95-1.08]*	0.726
Depression (yes)	1.03 [0.37-2.88]*	0.960	0.96 [0.32-2.87]*	0.940
ACPA positivity	0.31 [0.10-0.99]*	0.048	0.46 [0.16 -1.41]*	0.176
	0.21 [0.06-0.74]**	0.015		
Pain VAS	1.02 [1.00-1.04]*	0.048	1.04 [1.01-1.06]*	0.006
Patient global activity VAS	1.02 [1.00-1.04]*	0.028	1.04 [1.02-1.07]*	0.001
TJC (68)	1.16 [1.05-1.28]*	0.003	1.16 [1.05-1.27]*	0.002
SJC (66)	1.18 [0.97-1.44]*	0.09	1.21 [0.99-1.47]*	0.060
ESR/CRP levels	0.99 [0.96-1.02]*	0.369	0.99 [0.95-1.02]*	0.386
	0.97 [0.89- 1.05]*	0.393	0.95 [0.86-1.05]*	0.347
DAS 28 ESR	1.54 [0.952.49]*	0.790	1.66 [0.99-2.81]*	0.057
DAS 28 CRP	1.89 [1.04-0.42]*	0.035	2.06 [1.09-3.85]*	0.024
	0.73 [0.36-2.00]***	0.725	0.68 [0.27-1.75]***	0.430
HAQ	2.68 [1.28-5.61]*	0.009	4.84 [2.01-11.67]*	0.000
	2.23 [1.04-5.01]**	0.039	4.32 [1.72-10.83]**	0.002
NSAIDs consumption (current)	3.09 [1.11-8.64]*	0.031	3.32 [1.01-10.94]*	0.049
	2.95 [1.03-8.50]**	0.044	3.20 [0.94-10.9]**	0.061
Analgesic treatment (current)	3.60 [1.22-10.61]*	0.020	4.47 [1.19-16.84]*	0.027
	3.52 [1.16-10-68]**	0.026	4.52 [1.16-17.67]**	0.030
MTX (current)	0.35 [0.13-0.95]*	0.039	0.17 [0.061-0.47]*	0.001
	0.46 [0.16-1.30]**	0.142	0.21 [0.07-0.61]**	0.004
HCQ (current/previous)	0.34 [0.10-1.16]*	0.084	0.11 [0.01 -0.92]*	0.041
			0.11 [0.01-0.97]**	0.040
LFN (current/previous)	3.41 [1.36- 8.50]*	0.009	2.95 [1.17-7.44]*	0.022
	2.91 [1.14-7.44]**	0.026	2.45 [0.94-6.40]**	0.069
bDMARDs	0.69 [0.28-1.67]*	0.408	1.0 [0.39-2.57]*	0.996
TNFα inhibitors	0.49 [0.18-1.39]*	0.179	0.82 [0.28-2.40]*	0.718

Logistic regression. *adjusted for global radiographic score. **adjusted for global radiographic score and DAS 28 CRP ***adjusted for TJC and pain VAS. ****adjusted for disease duration. ACPA: anti-cyclic citrullinated peptide antibodies; bDMARD: (biological DMARD); CI: confidence interval; DAS 28 CRP/ESR: Disease Activity Score 28 C-Reactive Protein/Erythrocyte Sedimentation Rate; HAQ: Health assessment questionnaire; HCQ: Hydroxycloroquine; JE: joint erosion mSVdHS; JSN: joint space narrowing mSVdHS; LANSS: Leeds Assessment of Neuropathic Symptoms; LFN: leflunomide; MTX: methotrexate; NP: neuropathic pain; NSAIDs: non-steroidal anti-inflammatory drugs, OR: Odds Ratio; PDQ: painDETECT questionnaire; SJC (66): swollen joint count; TJC (68): 68 tender joint count

OA patients with CS diagnosed by quantitative sensory testing and functional MRI[49, 50]. However, further studies in RA are needed to validate NP screening tools application to diagnose CS.

This was the first study addressing the association of radiographic damage and RA NP. We found an inverse association of LANSS NP with JSN score, which did not remain statistically significant after adjustment for disease duration. On the other hand, the global and JE scores had no association with the NP outcomes.

Accordingly, Sokka T *et al* found no significant correlation between pain VAS and radiographic evaluation (Larsen score)[28]. In an early RA cohort, Larsen score only explained 2% of pain variation[29]. Curiously, in OA, discordance of radiographic and pain severity was previously described, with higher CS observed in patients which reported higher pain but presented lower structural damage[51]. Our results thus suggest that structural damage does not seem to increase the odds of NP pain in RA.

Similarly, disease duration had an inverse association with LANSS NP which was independent of sex and disease activity, but not of global radiographic score. When applying PDQ, no association with disease duration was actually observed in our cohort, which is in accordance to previous studies[12,13]. Contrary to our findings, lower pressure pain thresholds were previously described in patients with longer disease duration, suggesting that central mediated mechanisms develop over time[23,27]. Although with a different outcome, no correlation was found between fatigue and disease duration in a systematic review[52]. While those contradictory results could be due to different methods of NP evaluation and different patient case mix, association of non-nociceptive pain with disease duration needs to be further clarified.

Conversely, in this study, self-reported disability (HAQ) was a positive predictor of NP and was independent of radiographic evaluation. Despite its known association with radiographic damage in RA[53,54] these findings are probably explained instead by the subjective nature of HAQ score. Indeed, a stronger correlation of HAQ with pain levels was reported in comparison to structural damage[28,29] and absence of association between HAQ and radiographic score was already described in more recent studies[55]. Besides, this is in line with results described by Christensen AW *et al* where an association of PDQ NP with higher HAQ scores was observed in RA but lost significance after adjustment for other self-reported measures, such as SF-36[13].

Curiously, contrary to our hypothesis, we found an inverse association between ACPA positivity and NP status only according to LANSS, which was independent of other variables, including therapeutics (data not shown). In the previous studies which investigate NP risk in RA using PDQ, no association with ACPA was described, although LANSS tool was not used[12-14]. Moreover, in healthy animal models, injection of either human or murinised ACPA actually resulted in a long lasting pro-nociceptive effect which was independent of joint inflammation[56]. As ACPA positivity is associated with worse prognosis and greater structural damage in RA[57,58], we expected to have higher risk of NP in these patients. However, as shown by our results, NP risk was actually not associated with inflammatory disease activity nor increased structural damage, thus reinforcing that factors other than disease severity or activity mediate chronic pain in RA. Besides, different properties of NP screening tools may explain different results from the literature. Even so, careful interpretation of these results should be carried out and more studies are needed to address the possible ACPA protective role in NP.

Finally, we found several associations regarding RA treatment status. Firstly, higher NP odds was found in NSAIDs/analgesics treated patients. This association lost the significance after adjustment for disease activity, except for the subgroup of patients which performed radiographic evaluation (Table V). Current NSAIDs use may therefore be a marker of underlying non-nociceptive pain unrelated to disease activity.

Additionally, life exposure to HCQ had lower odds of PDQ NP, which was independent of sex, disease duration, disease activity and radiographic GS. Neither association of this treatment with pain VAS nor LANSS NP was found. Besides, no such association was previously studied in RA. In OA, contradictory analgesic effects of HCQ have been described, awaiting further data from randomized controlled trials[59-61]. In Sjögren syndrome, reduction of pain levels was demonstrated in HCQ treated patients[62]. On the other hand, peripheral neurotoxicity is a potential secondary effect of this medication[63]. Although our results suggest a possible protective role of HCQ in terms of risk of NP in RA patients, caution should be taken when analysing this data, as dose and time of exposure were not taken into account.

Current MTX treatment was also negatively associated with both NP outcomes in the subgroup with radiographic evaluation. Previous evidence suggests a potential effect of MTX in NP. In fact, intrathecal administration of MTX in animal models with peripheral neuropathy resulted in reduced microglial spinal activation and NP behaviour[64] and mechanical allodynia[65]. Again, previous studies in RA did not address this issue[12-14].

Life exposure to LFN was positively associated with NP outcomes. In our cohort, 53% of patients ever treated with LFN presented NP in at least one of the tests, yet no statistically significant differences were found

regarding current treatment. Indeed, several case reports of peripheral polyneuropathy secondary to LFN have been described in the literature[66-68]. Those results reinforce the potential neurotoxicity of LFN even in patients which previously stopped this treatment. Even though not confirmed by neurophysiologic tests, NP screening tools may assist in the diagnosis of neuropathy in those patients. Finally, although TNFα inhibitors induced neuropathy is a described complication in a low proportion of patients[69], we did not find differences regarding this treatment in this cohort.

Our study has several strengths. This was the first study which applied two different NP outcomes, particularly a screening tool which included an objective evaluation. The association of radiographic damage and NP in RA was also firstly investigated. Moreover, contrary to previous studies, a more detailed collection of treatment data was performed and has shown to be associated with the NP outcomes.

Some limitations should also be pointed out. Firstly, though validated NP screening tools were applied, no gold-standard for NP diagnosis was actually used. Secondly, although one sole investigator performed radiographic evaluation, no intra-class concordance was calculated. Additionally, as previously mentioned, a high proportion of FM was described in RA patients with NP[12, 13]. FM and NP may share common mechanisms, such as CS. Although patients with associated FM were not recruited for this study, only expert opinion was taken into account and no tender point count or FM diagnostic criteria application was performed. Finally, mental health and sleep disturbances evaluation was not performed, which also have known associations with non-nociceptive pain[13, 70].

CONCLUSIONS

In this study, a sizable proportion of patients presented features suggestive of NP according to PDQ and LANSS tools. Our results suggest that RA NP is a multifactorial process. Non-inflammatory, subjective measures of disease activity and disability were associated with increased odds of chronic non-nociceptive pain in RA. Greater structural damage, increased disease duration and poor RA prognostic factors, such as ACPA positivity, did not seem to increase the odds of NP. Furthermore, a potential association with underlying treatment was uncovered. Particularly, a possible protective role of exposure to HCQ and MTX treatment and increased odds of NP in patients ever treated with LFN was described. Further studies with greater sample and NP gold-standard use are needed to confirm those results.

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SUPPLEMENTARY TABLE I. COMPARISON BETWEEN POSSIBLE AND LIKELY NP GROUPS ACCORDING TO PAINDETECT

	PainDETECT ≥13 (n=19)	PainDETECT ≥19 (n=12)	p value
Female Sex – n (%)	16 (84%)	12 (100%)	0.265
Age (years) – mean (SD)	54.9 (13.4)	48.2 (8.2)	0.127
BMI – median (min-max)	25.3 (22-40)	29.1 (21-30)	0.551
Current smoking – n (%)	3 (16%)	0 (0%)	0.347
Current alcohol use – n (%)	3 (16%)	1 (8%)	1.000
Disease duration – median (min-max)	13 (2-29)	10 (2-31)	0.597
RF - n (%)	12 (66%)	9 (75%)	0.704
ACPA – n (%)	12 (66%)	9 (75%)	0.704
Extra-articular manifestations – n (%)	3 (16%)	3 (25%)	0.653
Depression – n (%)	2 (11%)	4 (33%)	0.174
Glucocorticoids – n (%)	11 (58%)	10 (83%)	0.240
Methotrexate – n (%)	10 (52%)	6 (50%)	1.000
Leflunomide – n (%)	4 (21%)	6 (50%)	0.127
Sulfassalazine – n (%)	0	0	–
Hydroxychloroquine – n (%)	0	0	–
bDMARDs – n (%)	6 (32%)	6 (50%)	0.452
NSAIDs – n (%)	16 (84%)	11 (92%)	1.000
All analgesics - n (%)	17 (89%)	11 (92%)	1.000
DAS 28 –CRP – mean (SD)	3.42 (1.02)	3.63 (0.67)	0.528
DAS 28 –CRP remission– n (%)	3 (16%)	0 (0%)	0.265
DAS 28 – ESR - mean (SD)	3.94 (1.25)	4.00 (0.75)	0.893
DAS 28 – ESR remission - n (%)	3 (16%)	0 (0%)	0.265
HAQ – mean (SD)	1.44 (0.54)	1.28 (0.52)	0.422
JE score - median (min-max)	28 (3-120)	24 (4-114)	0.642
JSN score - median (min-max)	45 (11-115)	37 (10-63)	0.111
GS – median (min-max)	83 (17-235)	59 (14-164)	0.308

ACPA: anti-cyclic citrullinated peptide antibodies; bDMARD: (biological DMARD); BMI: Body mass index; DAS 28 CRP/ESR: Disease Activity Score 28 C-Reactive Protein/Erythrocyte Sedimentation Rate; GS: global mSVdHS score; HAQ: Health assessment questionnaire; JE: joint erosion mSVdHS; JSN: joint space narrowing mSVdHS; Max: maximum; Min: minimum; NSAIDs: non-steroidal anti-inflammatory drugs; SD: standard deviation