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## The neuropathic pain features in Psoriatic Arthritis: a cross-sectional evaluation of prevalence and associated factors

**Running head:** Neuropathic pain in PsA

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**Abstract**

**Objective.** To evaluate the prevalence and factors associated with the neuropathic pain features in a cohort of patients with psoriatic arthritis (PsA).

**Methods.** A cross-sectional evaluation was conducted in consecutive patients suffering from PsA with prevalent peripheral joint involvement, referring to three rheumatological centers. For each patient a comprehensive assessment of disease activity, physical function, and disease impact was carried out. The presence of comorbid fibromyalgia syndrome (FMS) was evaluated. Acute phase reactants were also recorded. The neuropathic pain features were investigated through the PainDETECT Questionnaire (PDQ). A logistic regression analysis was therefore conducted using the PDQ as dependent variable.

**Results.** The final evaluation included 118 patients. A comorbid FMS was detectable in 30 of the 118 PsA patients (25.4%). Probable characteristics of neuropathic pain (PDQ  $\geq 19$ ) were found in 30 (25.4%) patients overall, ambiguous (PDQ  $>12$  and  $<19$ ) in 21 (17.8%) patients, and unlikely (PDQ  $\leq 12$ ) in 67 (56.8%) patients.

Using logistic regression analysis, the only independent variable among those investigated able to explain the neuropathic pain features investigated by PDQ was the presence of a comorbid FMS ( $p = 0.0127$ ). Excluding patients with comorbid FMS, an association with disability (measured by Health Assessment Questionnaire – Disability Index) emerges ( $p = 0.0489$ ). In patients with PsA and comorbid FMS, PDQ scores were significantly higher than in patients without comorbid FMS.

**Conclusion.** Neuropathic pain features are common in PsA patients, and the presence of pain sensitization (comorbid FMS) seems to be its main predictor.

**Key words:** Psoriatic Arthritis; Neuropathic Pain Features; Fibromyalgia.

## Introduction

The experience of pain is the characteristic that most unites chronic inflammatory joint diseases, the genesis of which is involved in multiple mechanisms (1). The problem of chronic pain in inflammatory diseases is a very fervent but also controversial area of research: while up to a few years ago it was considered only a symptom, at present there is increasing evidence that chronic pain is a disease in its own right (2, 3).

In the field of inflammatory joint diseases, being able to correctly assess pain is essential since it is a parameter that enters into the computation of the main disease activity indices, for example in the Disease Activity Score 28 joints (DAS28) and in the Clinical Disease Activity Index (CDAI) for rheumatoid arthritis (RA) (4), or in the Ankylosing Spondylitis Disease Activity Score (ASDAS) for ankylosing spondylitis (AS) (5), or in the Disease Activity index for Psoriatic Arthritis (DAPSA) for psoriatic arthritis (PsA) (6). This is not an irrelevant issue since disease activity indices represent a crucial variable both in daily clinical practice and in observational studies and clinical trials.

While the pain of inflammatory joint diseases could be the prototype of nociceptive pain, as it can fully meet the definition of the International Association for the Study of Pain (IASP) ("pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors") (7), patients with chronic inflammatory joint diseases frequently complain of complex pain symptoms, with neuropathic characteristics (e.g. radiating pain, burning or tingling sensations) that can be regarded in the context of "mixed pain" states (8).

The presence of neuropathic pain features has already been studied in the field of RA and more widely in osteoarthritis (OA) (9-13). As regards RA, it has been revealed that neuropathic pain features are present in at least 13% of patients, that these can be identified at an early stage of the disease, and that their presence impairs the achievement of remission at the six-month follow-up period (10). In OA, the prevalence of neuropathic pain is estimated to be around 23% (13), with significant persistence even when invasive treatment strategies such as total knee replacement are used (12).

In axial spondyloarthritis (axSpA), both AS and non-radiographic axSpA, the presence of neuropathic pain features is just over 30% (14), and is associated with a reduced quality of life, poorer patient-reported outcome measures (PROs), and higher functional limitation (15).

The only data related to the neuropathic pain features in PsA comes from the DANBIO register (16). In this Danish database, the presence of neuropathic pain was assessed through the PainDETECT questionnaire (PDQ). The researchers involved in this study investigated pain under multiple conditions of rheumatological interest. In the context of PsA, the presence of neuropathic pain features has been documented in 28% of patients, a higher percentage compared to both RA and axSpA.

The clinical variables associated with the presence of neuropathic pain features in PsA, to date, are not well known and have been poorly studied. On the basis of these assumptions, the objective of this study was to evaluate the prevalence and the clinical variables associated with the presence of neuropathic pain features in patients with PsA.

## Materials and Methods

### Setting and patients

For the objective of this study consecutive PsA patients from the outpatient clinics of three Italian rheumatological centres were included. Patients were enrolled from November 2018 to May 2019, and represented a sample of the “real life” clinical practice. The criteria for inclusion were: adult patients with the presence of a PsA with peripheral joint involvement (but patients with sacroiliitis or axial skeleton involvement were not excluded), diagnosed according to the Classification criteria for Psoriatic ARthritis (CASPAR) (17). The exclusion criteria were the presence of active skin conditions other than psoriasis (PsO), the presence of inflammatory articular comorbidities (such as gout or calcium pyrophosphate crystal arthropathy), and the presence of coexisting neuropathic conditions demonstrated by instrumental examinations, such as entrapment neuropathies (e.g. carpal tunnel syndrome), cervical or lumbar radiculopathies, and polyneuropathies supported by any etiology.

Patients underwent a cross-sectional evaluation in which, in a single day, an objective musculoskeletal examination was performed in each center by an experienced rheumatologist (respectively FS, FA and

MML), associated with the administration of PROs aimed at investigating the impact of PsA, functional status, and neuropathic features of pain. The questionnaires package was administered by a second younger rheumatologist (respectively MDC, PM and DB), blind to the results of the objective examination. For each patient were also recorded demographic data, comorbidities, ongoing treatment, and acute phase reactants. The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the local ethics committee (Comitato Etico Unico Regionale, number 0458 AS), and patients signed informed consent for anonymous data collection.

#### Psoriatic arthritis measurements

The objective examination was focused on determining the tender joint count (TJC, 0-68 joints), the swollen joint count (SJC, 0-66 joints), and enthesitis assessed through the Leeds Enthesitis Index (LEI).

The first two parameters, in addition to patient global assessment of disease activity (PGA, 0-10 numerical rating scale [NRS]), to NRS pain (0-10), and to C-reactive protein (CRP, in mg/dl), were used to calculate the DAPSA (6). DAPSA is a composite disease activity index, PsA specific. Currently the index is well recognised internationally and through appropriate cut-off allows to establish the disease activity status:  $\leq 4$  for remission (REM),  $>4$  and  $\leq 14$  for low disease activity (LDA),  $>14$  and  $\leq 28$  for moderate disease activity (MDA), and  $>28$  for high disease activity (HDA) (18).

The LEI focuses on six enthesial sites (lateral epicondyles, medial femoral condyles, Achilles tendon insertions), it is easy to calculate since the final score is given by the sum of the enthesis involved, is considered an acceptable index as it is well correlated to the other disease activity measures (19).

The Psoriatic Arthritis Impact of Disease 12-item (PsAID-12) has been used as a PRO indicative of the overall burden of a protean disease such as PsA in various health domains (20). Composed of 12 NRS, it is easy to calculate, and the final value ranges from 0 to 10, where higher scores indicate a more important disease burden for the patient. Some years ago our research group identified, through a multifactorial analysis, two main factors within the PsAID-12, which were called respectively PsAID Symptom Score, more exploratory of joint symptoms, and PsAID Skin Score, more focused on the impact of PsO in health-related quality of

life. For the purposes of this study we used these two sub-scales, calculated with the following formulas,

PsAID Symptom Score = (NRS pain x 3 + NRS fatigue x 2 + NRS work and/or leisure activities x 2 + NRS

functional capacity x 2 + NRS sleep disturbance x 2 + NRS coping + NRS anxiety + NRS social participation +

NRS depression)/15, PsAID Skin Score = (NRS skin problems x 2 + NRS discomfort x 2 + NRS embarrassment and/or shame)/5 (21).

Functional ability was measured by the Health Assessment Questionnaire - Disability Index (HAQ-DI). The

HAQ-DI assesses the degree of difficulty in performing common daily activities in 8 areas, with respect to

the last week. For each activity the patient is asked to respond on a 4-point scale (from 0 without difficulty,

to 3 impossible), and for each functional area the highest value is considered. The final score is given by the

average of the 8 values (22).

#### Neuropathic pain features assessment

PDQ was used in this study for the evaluation of neuropathic pain features. Developed by the German

Research Network on Neuropathic Pain over 10 years ago, the questionnaire has been validated in different

clinical contexts such as post-thoracotomy pain, neoplasms, low back pain, OA, fibromyalgia syndrome

(FMS), but also in the field of inflammatory joint diseases. It is a completely self-administered

questionnaire, able to distinguish the nociceptive components from the neuropathic components of pain

(23). This symptom-based tool (no physical examination is required) investigates sensations related to the

presence of neuropathic pain, such as allodynia, hyperalgesia, dysesthesia and sudden pain. The PDQ is

composed of seven 5-point scales (0 = never, 5 = very strongly) that investigate the qualitative

characteristics of painful sensations (such as burning, tingling or prickling, pain to light touch, sudden pain

attacks, cold or heat, numbness, slight pressure triggering pain) in body areas where the pain radiates (the

presence of radiated pain has 2 points), indicated on a manikin. There is also a question that investigates

the temporal trend of pain (score from -1 to 1 to 1 depending on the model selected). The final score can

range from -1 to 38, and for scores  $\leq 12$  there is little chance (<15%) that the pain has a neuropathic

component, while a score  $\geq 19$  indicates that the pain has a strong probability of having a neuropathic

component (>90%), and finally the scores between 13-18 indicate an ambiguous result (24). Rilojerg-

Madsen and coworkers studied the PDQ psychometric properties (Rasch analysis and test-retest analysis) in a wide cohort of patients suffering from inflammatory joint diseases (including PsA) and demonstrated acceptable properties in pain classification (25).

#### Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) or as median and interquartile range.

For the purpose of this study, i.e. to establish the influence of clinical and demographic parameters (independent variables) on the presence of neuropathic pain features (dependent variable), a logistic regression analysis was performed. Independent variables included age, body mass index (BMI), duration of articular disease, number of biologic agents (considering both the current and previous treatments), DAPSA, LEI, HAQ-DI, PsAID-12, PsAID Symptom Score, PsAID Skin Score, NRS pain, erythrocyte sedimentation rate (ESR) and CRP. In view of the important influence on painful symptoms, the presence of a comorbid FMS, diagnosed according to the criteria of the American College of Rheumatology (ACR) 2016 (26), was also considered as an independent variable in the analysis. The dependent variable was represented by the PDQ. p values were considered significant for values  $<0.05$ , and analyses were carried out with MedCalc 18.0.0.

#### Results

A total of 118 patients (42 men and 76 women, 35.6% and 64.4% of the population respectively) with PsA were included, with a mean age of 57.67 (SD 12.54) years, and a mean body mass index (BMI) of 27.51 (SD 4.68)  $\text{kg}/\text{m}^2$ . The mean duration of articular disease was 7.97 (SD 7.01) years, and the mean duration of skin disease of 10.71 (SD 8.50) years. Descriptive statistics with reference to demographic and clinical parameters are given in Table 1.

Sixty (50.84%) patients were treated with at least one traditional disease modifying anti-rheumatic drug (DMARD), of which 27 (22.88%) were taking a combination therapy. Specifically, 44 (37.28%) took methotrexate, 17 (14.40%) leflunomide, 15 (12.71%) sulphasalazine, and 9 (7.62%) cyclosporine.

In addition to traditional DMARDs, 65 (55.08%) patients were treated with a biologic DMARD, respectively

45 with an anti-TNF alfa drug (21 etanercept, 13 adalimumab, 10 golimumab, and 1 certolizumab pegol), 15 (12.71%) with secukinumab, and 5 (4.23%) with ustekinumab. Thirteen (11.01%) patients were taking apremilast.

Considering anti-inflammatory drugs, 14 (11.86%) patients were taking low-dose corticosteroids (<5 mg/day prednisone), while 48 (40.67%) patients were taking a non-steroidal anti-inflammatory drug (etoricoxib more frequently). Interestingly, 28 (23.72%) patients were taking drugs potentially used for neuropathic pain, including gabapentinoids (17 patients, 14.40%), duloxetine (7 patients, 5.93%), and tapentadol (4 patients, 3.39%).

With regard to disease activity, the mean DAPSA was 21.22 (SD 12.26), and respectively 22 patients were in HDA, 68 in MDA, 25 in LDA, and 3 in REM.

Considering the neuropathic pain features, the average PDQ was 13.15 (SD 8.07). As prevalence data, in the 25.4% of patients it was possible to identify likely neuropathic pain features (PDQ  $\geq$ 19), in the 17.8% ambiguous neuropathic pain features (12 <PDQ <19), and in the 56.8% unlikely neuropathic pain features (PDQ  $\leq$ 12).

The logistic regression analysis showed that, among the variables under study, the only statistically significant correlation with the presence of neuropathic pain features was the presence of a comorbid FMS ( $p = 0.0127$ ) (Table 2) which was diagnosed in 30 (25.42%) patients. Most importantly, of these 30 patients with comorbid FMS, 28 (93.3%) were women and only 2 (6.7%) were men. Within the patients with comorbid FMS was also concentrated the use of drugs potentially used for neuropathic pain (25 of the 28 patients mentioned above).

At this point it was decided to compare the categories of PDQ in patients without and with FMS and, in this second set of patients, the scores of PDQ were statistically significant higher (Table 3). A second logistic regression analysis was then performed, excluding patients with comorbid FMS. Analyzing the same variables in the remaining 88 patients, the only variable associated with the presence of neuropathic like pain features (with some statistical significance) was HAQ-DI ( $p = 0.0489$ ) (Table 4). In this group of 88 patients without comorbid FMS it was possible to identify a prevalence of likely neuropathic pain features in 12 subjects (13.63%), and of ambiguous neuropathic pain features in 17 subjects (19.31%).



## Discussion

In this study it has been shown that the presence of neuropathic pain features concerns a substantial proportion of PsA patients, with a PDQ  $\geq 19$  found in more than 25% of patients, and with a score between 13-18 in about 17%. From a clinical point of view, this painful symptomatology with neuropathic features can be classified in the context of a comorbid FMS in most patients, largely attributable to the presence of pain sensitization. The results also show the clear prevalence of this kind of painful symptoms in the female population.

Excluding comorbid FMS, the only variable associated with the presence of neuropathic like pain features is disability, measured by HAQ-DI.

To the best of our knowledge, this is the first study that explored demographic and disease-specific clinical parameters associated to the presence of neuropathic pain features in PsA patients.

In the field of joint diseases, both inflammatory and degenerative, the mechanisms underlying the symptom pain have been the subject of intense research in recent years. In particular, there is a growing awareness that, alongside the nociceptive pathway, mechanisms involving a peripheral and central sensitization are involved (27).

Our results are in agreement with those collected by Riefbjerg-Madsen and colleagues who, from the data coming from the DANBIO register, were the first to document the important prevalence of central pain mechanisms in patients with PsA, detecting a PDQ  $> 18$  in 28% of subjects (16).

It is interesting to note that among the other variable studied, neither the disease activity indices, nor the impact of joint or skin disease, is correlated to the presence of neuropathic pain features. Not including patients with comorbid FMS, only an association with disability emerges. The association between neuropathic pain and disability was already known, both in the field of OA and in the area of neurology (28, 29). In chronic inflammatory joint diseases, considering both PsA and RA, the correlation between HAQ-DI and PDQ has already been documented in the DANBIO register (16). In our study we have made a step forward by evaluating the association in PsA patients without comorbid FMS.

It can be said that PDQ is a useful tool for capturing the mechanisms of pain that go beyond synovial or

enthesial inflammation, so important to evaluate to make a proper diagnosis of pain and to avoid therapies often very expensive and potentially harmful. The debate remains open on whether the PDQ actually identifies the presence of peripheral neuropathic pain, or the central sensitization typical of FMS. On the other hand, the sensory profile of the two conditions is very similar (30), and in addition, there is a considerable area of research that considers FMS a disease of the small fibers, being present pathological alterations of the small fibers in about 49% of patients with FMS (31).

The fact that patients with neuropathic pain features meet the criteria for a comorbid FMS has already been documented for RA (32). However, in patients with RA, there is a lower prevalence of neuropathic pain features than in PsA (10, 16, 32). It can be speculated that this difference can be explained by the extent and severity of the PsO, although there are no studies to date.

Also with regard to knee OA, a community study with a large number of participants revealed that FMS is the main risk factor for the presence of neuropathic-like knee pain (33). For this disease, the prognostic value of the presence of neuropathic pain features has been clearly demonstrated, higher scores of preoperative PDQ result in higher probability of persistence of chronic pain at six months from total knee replacement (12).

A prognostic evaluation was also made in patients with early RA and it was documented that high scores of PDQ at baseline resulted in a very low probability of Boolean remission at six months (10).

Citing the limitations of the study, we believe that the main ones are represented by cross-sectional evaluation that did not allow prognostic evaluations, and the mild impact of PsO in our case study, skin disease may probably have an influence on certain pain descriptors of PDQ.

In conclusion, this study documented the high prevalence of neuropathic pain features in patients with PsA (above 25%), and it was demonstrated that this symptomatology is not attributable to disease activity, impact of disease, or demographic characteristics.

Overall, the majority of patients with likely neuropathic pain features meet the 2016 ACR criteria for FMS.

Making a correct differential diagnosis of the pain symptom may be increasingly useful to avoid overtreatment with immunosuppressive drugs using a drug therapy appropriate to the pathophysiological mechanisms.

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**Authors' contributions**

All authors were involved in data collection. MDC and FS analyzed and interpreted the data. MDC was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

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**Table 1.** Demographic and clinical parameters of the whole cohort.

	Mean	Median	Standard deviation	25 - 75 percentiles
Age	57.67	57.50	12.54	50.00 – 65.00
BMI	27.51	26.82	4.68	23.88 – 30.50
PsA duration (years)	7.97	6.00	7.02	2.00 – 12.00
PsO duration (years)	10.71	8.50	10.33	3.00 – 17.00
DAPSA	21.22	19.00	12.26	14.50 – 25.00
SJC (0-66)	1.66	0.00	3.07	0.00 – 2.00
TJC (0-68)	6.05	3.00	8.26	1.00 – 8.00
LEI	0.75	0.00	1.43	0.00 – 1.00
Fingers with dactylitis (number)	0.13	0.00	0.43	0.00 – 0.00
NRS pain	6.48	7.00	2.36	5.00 – 8.00
PaGA	6.40	7.00	2.38	5.00 – 8.00
PsAID-12	4.59	4.10	2.52	2.45 – 6.70
PsAID Skin Score	3.79	3.60	2.58	1.60 – 5.60
PsAID Symptom Score	4.86	4.86	2.63	2.93 – 7.26
CRP (mg/dl)	1.07	0.40	2.25	0.14 – 0.90
ESR (mm/h)	22.11	15.50	20.07	8.00 – 30.00
PhGA	4.34	4.50	1.86	3.00 – 6.00
PDQ	13.15	11.50	8.07	7.00 – 19.00

Abbreviations: BMI = body mass index; PsA = psoriatic arthritis; PsO = psoriasis; DAPSA = Disease Activity Score for Psoriatic Arthritis; SJC = swollen joint count; TJC = tender joint count; LEI = Leeds Enthesitis Index; NRS = numerical rating scale; PaGA = patient global assessment of disease activity; PsAID = Psoriatic Arthritis Impact of Disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PhGA = physician global assessment of disease activity; PDQ = PainDETECT questionnaire.

**Table 2.** Logistic regression analysis of the variables associated with neuropathic pain features (PDQ score, dependent variable) in the whole cohort (118 patients).

Variables	Coefficient	Standard error	Wald	p
Age	0.041895	0.040689	1.0601	0.3032
BMI	-0.10686	0.11523	0.8599	0.3538
Number of biologic DMARDs	-0.17201	0.39037	0.1942	0.6595
PsA disease duration	-0.054908	0.065372	0.7055	0.4009
DAPSA	0.060594	0.050190	1.4575	0.2273
HAQ-DI	0.67158	0.79358	0.7162	0.3974
LEI	-1.06483	0.57784	3.3958	0.0654
PsAID Skin Score	0.38687	0.26817	2.0812	0.1491
PsAID Symptom Score	0.51869	0.37579	1.9052	0.1675
NRS pain	-0.55530	0.34046	2.6603	0.1029
ESR	-0.016822	0.026333	0.4081	0.5230
CRP	-0.23437	0.45772	0.2622	0.6086
FMS presence	4.69187	1.96678	4.9153	0.0127
Constant	-5.03213	4.54624	1.2252	0.2683

Abbreviations: PDQ = PainDETECT questionnaire; BMI = body mass index; DMARDs = disease modifying anti-rheumatic drugs; PsA = psoriatic arthritis; DAPSA = Disease Activity Score for Psoriatic Arthritis; HAQ-DI = Health Assessment Questionnaire – Disability Index; LEI = Leeds Enthesitis Index; PsAID = Psoriatic Arthritis Impact of Disease; NRS = numerical rating scale; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; FMS = fibromyalgia syndrome.



**Table 3.** PDQ categories in PsA patients versus the presence or not of a comorbid FMS.

Comorbid FMS	PDQ categories			
	Unlikely (PDQ $\leq$ 12)	Ambiguous (PDQ >12 and <19)	Probable (PDQ $\geq$ 19)	
No	59	17	12	88 (74.6%)
Yes	8	4	18	30 (25.4%)
	67 (56.8%)	21 (17.8%)	30 (25.4%)	118
Chi-squared	25.791			
DF	2			
Significance level	p <0.0001			
Contingency coefficient	0.424			

Abbreviations: PDQ = PainDETECT questionnaire; PsA = psoriatic arthritis.

**Table 4.** Logistic regression analysis of the variables associated with neuropathic pain features (PDQ score, dependent variable) excluding the patients with comorbid FMS (88 patients).

Variables	Coefficient	Standard error	Wald	p
BMI	0.043506	0.20368	0.04562	0.8309
Age	0.087252	0.063960	1.8609	0.1725
Number biologic DMARDs	-1.01369	0.73950	1.8790	0.1704
DAPSA	-0.091035	0.10793	0.7114	0.3990
HAQ-DI	3.74632	1.90208	3.8793	0.0489
LEI	-17.55864	6716.61311	0.000006834	0.9979
PsAID Skin Score	0.72672	0.63157	1.3240	0.2499
PsAID Symptom Score	-0.079835	0.60550	0.01738	0.8951
NRS pain	0.65431	0.67047	0.9524	0.3291
ESR	-0.073561	0.049778	2.1838	0.1395
CRP	0.061171	0.65208	0.008800	0.9253
Constant	-15.59235	9.38629	2.7595	0.0967

Abbreviations: PDQ = PainDETECT questionnaire; BMI = body mass index; DMARDs = disease modifying anti-rheumatic drugs; PsA = psoriatic arthritis; DAPSA = Disease Activity Score for Psoriatic Arthritis; HAQ = Health Assessment Questionnaire – Disability Index; LEI = Leeds Enthesitis Index; PsAID = Psoriatic Arthritis Impact of Disease; NRS = numerical rating scale; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.