Brief Communication

Assessment of widespread and extra-articular pain in psoriatic arthritis: a case-control study.

By

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Abstract

Objective: A remarkable lack of detailed knowledge on pain areas in Psoriatic Arthritis (PsA) is present, and their clinical relevance is quite unknown. The main aim of the study was to explore pain areas in PsA, comparing them with those involved in Fibromyalgia (FM) patients. In addition, to investigate any possible association between pain areas and outcome measures in PsA.

Methods: Case-control study on PsA patients satisfying CASPAR criteria and FM. In all PsA and FM patients a body chart filled in by the patient in 80 body locations was performed. The Widespread Pain Index (WPI) was performed in all PsA and FM patients. In all PsA patients, an assessment of disease activity, treatment target, function, and impact of disease were carried out.

Results: 50 PsA patients and 50 FM controls with FM were evaluated. A significantly higher number of pain areas at body chart and WPI score were found in FM patients when compared to PsA patients. In PsA, the number of areas reported at body chart significantly correlated with DAPSA, HAQ-DI and PsAID. Patients who were not in remission/MDA or have a greater impact of disease or reduced function showed a significant high number of extra-articular pain areas involved.

Conclusion: The main results showed that widespread and extra-articular pain was present in PsA patients, showing that this non-articular pain had an impact on important disease domains. The present study could contribute to an important aspect of this challenging and multifaceted disease, such as the assessment of widespread pain.

Introduction

Psoriatic Arthritis (PsA) is a chronic inflammatory disease characterized by the association of arthritis and psoriasis and by a variable clinical course (1).

Despite the new treatment strategies allow to achieve remission or low disease activity in almost all domains (2-4), the assessment and management of chronic pain in PsA patients still represent an unmet need, and residual pain could be observed (5,6).

Pain in PsA is traditionally considered to be of peripheral nociceptive origin, however, pain hypersensitivity may persist after the control of inflammation and thus become a manifestation of maladaptive pathological changes in the central nervous system (7,8).

Data from DANBIO register showed that more than 20% of patients with inflammatory arthritis had neuropathic pain features. Furthermore, PsA patients seem to have more neuropathic pain rather than other Spondyloarthritis (SpA) patients (9).

However, there is a remarkable lack of detailed knowledge on pain areas in PsA, and their clinical relevance is quite unknown.

Identification of possible underlying pain mechanisms and a more detailed evaluation of pain areas in PsA may, therefore, be of great importance in the clinical decision-making process, helping in differential diagnosis with Fibromyalgia (FM) and in the assessment of disease activity and quality of life. Moreover, the presence of concomitant FM in PsA may increase the burden of the disease.

The aim of this study was to explore, in a more in detail, the areas of pain in PsA patients, comparing them with those involved in FM patients. In addition, we aimed to investigate the possible association between the number and presence of specific pain areas and disease activity, treatment target, joint function and impact of the disease.

Materials and Methods

All adult patients with PsA satisfying the ClASsification criteria for Psoriatic ARthritis (CASPAR) (10) criteria attending our unit from the 1st September 2019 to 31st January 2020 who were on at least 6-month follow-up were considered potentially eligible for the study.

Consecutive adult patients with FM satisfying the ACR 2010 criteria (11) attending our unit in the same period were enrolled as control group.

Exclusion criteria included the presence of diabetic neuropathy, episode of Herpes Zoster in the last 24 months, diagnosis of axonal or demyelinating neuropathy, any musculoskeletal trauma in the previous 24 months.

Moreover, PsA patients who met the ACR 2010 criteria for FM were also excluded to limit the jeopardization of the results.

Demographics and disease characteristics including gender, age, disease duration, level of education, pattern of articular manifestations, the number of tender and swollen joints, enthesitis and dactylitis were collected. Enthesitis was assessed by using the Leeds Enthesitis Index (LEI)(12), and dactylitis as present/absent. Skin evaluation was performed using the body surface area (BSA). The Patient Global Assessment (PtGA) assessment on Visual Analogic Scale (VAS 0-10 cm) was performed by all patients. Physician's global evaluation of disease activity on a VAS scale was also recorded (13). Finally, C-Reactive Protein (CRP) levels was collected within one month from clinical evaluation.

The Disease Activity Index for PsA (DAPSA) was calculated (14). Minimal Disease Activity (MDA) was defined according to Coates et al.(15).

The Patient Acceptable Symptom State (PASS) was also assessed (16).

The Health Assessment Questionnaire Disability index (HAQ-DI)(17) and the Psoriatic Arthritis Impact of Disease (PsAID) were evaluated as measures of function and impact of disease (18). HAQ-DI≤0.5 defined a good functional status and PsAID≤4 a low impact of disease.

The intensity of pain was assessed on a Numerical Rating Scale (NRS, 0-10 cm). In all PsA and FM patients an anterior and posterior body chart filled in by the patient during the intake interview determined the presence of pain (yes=1/no=0) during the past week, in 80 body locations. The chart was reproduced according to Swinnen et. al.(19).

Patients were asked to fill the chart before the clinical examination and no provocative test for pain were used. Furthermore, areas with the clear presence of tender and/swollen joints or enthesitis were subsequently excluded from the analysis to ensure the presence of pain not due to synovitis/enthesitis process.

Finally, the Widespread Pain Index (WPI) was performed in all PsA and FM patients (11). The WPI quantifies the extent of bodily pain on a 0-19 scale, by asking patients if they had pain or tenderness in 19 different body regions.

Statistical analysis

The results were expressed as median/interquartile range (IQR) for non-parametric variables and as a mean/standard deviation (SD) for parametric ones. The prevalence of each body region and location was calculated for all patients. Pain areas between two diseases were univariate compared with chi-square test for frequencies. Furthermore, Mann-Whitney U-test was used to compare the number of pain areas and the WPI between the two groups. Correlation between the number of pain areas and clinical indices were assessed with Spearman rho. The 1-way ANOVA was applied and a multiple comparison between the four DAPSA groups was performed using the Bonferroni correction.

P values <0.05 were considered significant.

Results

During the study period, 50 PsA patients and 50 controls with FM who met the inclusion and exclusion criteria were evaluated. The main demographic and clinical characteristics of patients were summarized in Table 1.

No more than 5 minutes were spent to fill the body chart, showing how quick and feasible was this instrument.

As expected, a significantly higher number of pain areas at body chart and a higher WPI were found in patients with FM when compared to PsA patients (table 1). Interestingly, only 5 PsA patients (10%) did not report any pain areas as well as no pain on NRS. Figure 1 shows the graphical illustration of pain locations displayed as prevalence in patients with PsA and FM. In particular, in patients with PsA, pain was mainly localized at the level of the hands, knees and feet. However, pain was also present in other extra-articular areas. When evaluated the pain areas in FM control group, the locations were, to a certain extent, similar to those in PsA cases but more frequent.

A full comparison of all pain regions for PsA and FM based on WPI are reported in the supplementary file.

In PsA patients, both the number of painful areas assessed with body chart significantly correlated with DAPSA, HAQ-DI and PsAID (rho: 0.69, 0.38 and 0.48 respectively; $p<0.01$). We observed similar results for WPI (rho 0.59, 0.40 and 0.49 respectively; $p<0.01$).

Furthermore, we found statistically significant differences in the median number of pain areas between patients in DAPSA remission, DAPSA low disease activity, DAPSA moderate disease activity and DAPSA high disease activity.

Finally, patients who were not in remission/MDA or have a greater impact of disease or reduced function showed a significant high number of extra-articular pain areas involved (table 2).

Discussion

To our knowledge, this was the first study to detail the topography of pain in PsA and to relate these findings to key clinical outcomes.

The main results showed that widespread and extra-articular pain were present in our patients and seem to have an impact on important disease domains.

Amplification of nervous system signaling may lead to a complex perception of the painful stimulus, potentially inducing the clinician and the patient to an overestimation/underestimation of disease activity. Clinically, these pain mechanisms may translate to widespread pain, a feature seen in about 2–34% of patients with SpA, that resemble those seen in patients with FM (19). Our results are in line with studies that found dissonance between the outcomes reported by doctors and patients (20).

In our study, although the number of areas involved were significantly lower in respect to FM, we found around 20-35% of PsA patients experiencing pain in some specific body areas. This latter result is difficult to be explained based only on body chart and we think that further studies are needed. In fact, potentially, the presence of subclinical synovitis or enthesitis, influencing the pain perception, could not be excluded. The present study also showed that widespread pain was more frequent in PsA patient with high disease activity, in those not achieving MDA, in patients with higher HAQ-DI, higher PsAID and not in a PASS state. All these results could be in keeping with an association between the presence of widespread pain and poor outcome.

Our study had strengths and limitations. The use of body chart has allowed a more detailed assessment of pain in PsA, showing also that is a quick and feasible instrument to adopt in clinical practice.

As a potential limitation, a possible bias is linked to gender differences. This could affect the results because of the different pain expression between the two sexes (21). Furthermore, we did not assess systematically the presence of comorbidities such as depression which may influence the pain perception.

In conclusion, the present study could contribute to an important aspect of this multifaceted disease, such as the assessment of widespread pain in a more detailed fashion. This aspect should be considered by treating physicians, and a more detailed pain evaluation may be useful for the management of PsA, even through personalized treatment strategies and beyond synthetic and biologic DMARDs.

Compliance with ethic standard: The study protocol was in compliance with the declaration of Helsinki and written consent was obtained from each participant. The study was approved by the Institutional Review Board of the University of Molise (protocol n. 0001-09-2017).

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Table 1. Demographic and clinic characteristic of PsA and FM patients

	PsA (n=50)	FM (n=50)	P value
Male sex n. (%)	33 (66)	3 (6)	<0.001
Age, mean (SD)	56.7 (10.5)	58.4 (11.4)	n.s.
Disease Duration (years), median (IQR)	8 (5-10)	8 (4-10)	n.s.
BMI, median (IQR)	27.7 (23.4-30-7)	27.1 (23.1-30.2)	n.s.
Pain on NRS, median (IQR)	5 (0-10)	8 (3-10)	<0.001
WPI, median (IQR)	3 (1-5.75)	7 (1-20)	<0.001
VAS Physician, median (IQR)	3.5 (1-5)		
Tender joints, median (IQR)	3 (0-5)		
Swollen Joints, median (IQR)	1 (0-2)		
PtGA, median (IQR)	5 (2-6.75)		
Number of pain areas, median (IQR)	3 (1-7)	8.5 (6-14)	<0.001
DAPSA, median (IQR)	14.15(5-18.8)		
MDA 5/7, n. (%)	22 (44)		
HAQ-DI, median (IQR)	0.37 (0.125-0.725)		
BSA %, median (IQR)	1 (0-3)		
PsAID, median (IQR)	3 (1-4.8)		
CRP mg/dl, median (IQR)	0.25 (0.02-1.93)		
PASS+, n (%)	30 (60)		
Treatment, n (%), in the past 6 months			
- NSAIDs	10 (20)	8 (16)	n.s.
- Analgesics (acetaminophene, codeine, tramadole)	2 (4)	15 (30)	< 0.001
- Muscle relaxants, antidepressants, anticonvulsant	0 (0)	27 (54)	<0.001
- csDMARDs	8 (16)	0 (0)	<0.01
- bDMARDs	30 (60)	0 (0)	<0.001
- tsDMARDs	4 (8)	0 (0)	n.s.

SD: standard deviation; IQR: interquartile range; NRS: numerical rating scale; WPI: Widespread Pain Index; VAS: visual analogue scale; PtGA: patient's global assessment; DAPSA: Disease Activity score for Psoriatic Arthritis; MDA: Minimal Disease Activity; HAQ-DI: Health Assessment Questionnaire Disability Index; BSA: body surface area; PsAID: Psoriatic Arthritis Impact of Disease; CRP: C reactive protein; PASS: Patient Acceptable Symptoms State; NSAIDs: non-steroidal anti-inflammatory drugs; cs: conventional synthetic; b: biologics; ts: targeted synthetic; DMARDs: disease modifying anti-rheumatic drugs

Table 2. Difference of pain area number based in PsA patients with different pattern of the disease and in patients achieving or not key clinical outcomes

Number of pain area, median (IQR)		p value
HAQ-DI ≤ 0.5 (n=31)	**HAQ-DI > 0.5 (N=19)**	
2 (1-4)	6 (2.5-7.5)	0.032
PsAID≤ 4 (n=33)	**PsAID > 4 (n=17)**	
2 (1-4)	7 (2-10)	0.028
VAS pain ≤ 20 (n=15)	**VAS pain > 20 (n=35)**	
1 (0-1.5)	4 (2.5-7.5)	<0.001
PASS yes (n=30)	**PASS no (n=20)**	
2 (1-3.75)	5.5 (3.75-8.5)	0.032
BSA ≤ 3 (n=44)	**BSA > 3 (n=6)**	
3 (1.75-7)	2.5 (1-4)	0.508
MDA yes (n=22)	**MDA no (n=28)**	
1.5 (1-2.75)	4.5 (2.75-7.25)	<0.001
DAPSA ≤ 14 (n=24)	**DAPSA>14 (n=26)**	
1 (1-2.25)	5.5 (3.25-7.75)	<0.001

HAQ-DI: Health Assessment Questionnaire Disability Index; PsAID: Psoriatic Arthritis Impact of Disease; VAS: visual analogue scale; PASS: Patient Acceptable Symptoms State; BSA: body surface area; MDA: Minimal Disease Activity; DAPSA: Disease Activity score for Psoriatic Arthritis.

Figure 1. Graphical illustration of pain locations displayed as prevalence in patients with PsA and FM