



Central Pain Sensitization in Patients with Chronic Plaque Psoriasis

Francesco Bellinato · Paolo Gisondi · Angelo Fassio ·
Giampiero Girolomoni

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ABSTRACT

Background: Central sensitization (CS) is a condition characterized by a disproportionate response to pain stimuli, and is associated with chronic pain conditions such as fibromyalgia, but also with inflammatory arthropathies such as rheumatoid arthritis and psoriatic arthritis (PsA). CS has never been investigated in patients with psoriasis. The aim of this study is to investigate CS in patients with chronic plaque psoriasis.

Methods: This research involved a cross-sectional observational study of adult patients with moderate-to-severe psoriasis consecutively attending the outpatient clinic of the University Hospital of Verona. Demography, measures of disease severity or activity [i.e., Psoriasis Area and Severity Index (PASI), Disease Activity in Psoriatic Arthritis (DAPSA)], diagnosis of PsA, hypertension, and diabetes were collected.

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F. Bellinato (✉) · P. Gisondi · A. Fassio
Department of Medicine, Section of Dermatology
and Venereology, University of Verona, Verona,
Italy
e-mail: francesco.bellinato@univr.it

G. Girolomoni
Section of Rheumatology, University of Verona,
Verona, Italy

Central Sensitization Inventory (CSI), Dermatology Life Quality Index (DLQI), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9) were administered.

Results: A total of 194 patients, including 115 (59%) men, with mean age of 54 ± 13 years, mean PASI of 12.7 ± 6.7 , and mean DAPSA of 14.4 ± 3.8 were included. In total, 134 patients (79%) had only psoriasis while 60 (31%) had psoriasis and PsA; 19 (10%) patients had CSI score ≥ 40 , which is the threshold for diagnosing CS. The proportion of CS ≥ 40 was higher in patients with PsA compared with psoriasis (17% versus 7%, $p = 0.031$). The mean CSI score in patients with PsA was higher compared with those with only psoriasis (27.5 ± 13.5 versus 20.7 ± 13.7 , $p = 0.002$). An association between CSI and DLQI [$\beta = 1.25$ (95% CI 0.85–1.66)], PASI [$\beta = 1.22$ (95% CI 0.74–1.65)], GAD-7 [$\beta = 2.07$ (95% CI 1.69–2.45)] and PHQ-9 [$\beta = 2.16$ (95% CI 1.76–2.54)] was found independently from age, gender, diabetes, and PsA.

Conclusions: Central sensitization may be associated with psoriasis, particularly in those with high PASI, concomitant PsA, anxiety, depression, and severe quality of life impairment.

Keywords: Psoriasis; Psoriatic arthritis; Central sensitization; Pain

Key Summary Points

Why carry out this study?

Patients with psoriasis could complain of pruritus, burning, pain, and in the case of psoriatic arthritis fatigue, arthralgia and generalized musculoskeletal pain.

Central sensitization (CS) is a condition characterized by a disproportionate response to pain stimuli, which is associated with inflammatory arthropathies such as rheumatoid arthritis and psoriatic arthritis.

The aim of this study is to investigate CS in patients with chronic plaque psoriasis.

What was learned from the study?

CS may also be associated with skin inflammatory disorders such as psoriasis, although it is more frequent in patients with psoriatic arthritis.

CS could be an explanation of those generalized, indefinite painful symptoms that some patients with psoriasis sometimes complain of, but no objective clinical confirmation was found.

INTRODUCTION

Psoriasis is a chronic inflammatory disease resulting from a dysregulation in innate and adaptive immune responses, which is increasingly being recognized as a systemic inflammatory disorder [1]. Patients with psoriasis may complain of several skin-related symptoms such as pruritus, burning, pain, and in the case of psoriatic arthritis (PsA) fatigue, arthralgia and generalized musculoskeletal pain [2–4]. While the association of PsA with musculoskeletal pain is easily explained, pain associated with psoriatic skin lesions is less obvious. Chronic inflammation may modulate pain perception through somatosensory, immune, neuronal,

autonomic, and vascular responses to tissue damage [5]. Central sensitization (CS) is a condition of the nervous system that is associated with the development and maintenance of chronic pain [6]. When CS occurs, the nervous system is regulated in a persistent state of high reactivity [5]. CS has been associated with chronic pain conditions such as fibromyalgia, but also with inflammatory arthropathies such as rheumatoid arthritis and PsA [7]. CS has never been investigated in patients with psoriasis. Chronic inflammation associated with psoriasis might increase central pain sensitivity because it provides a constant and chronic stimulus to skin nerve fibers, whereby patients may become more sensitive to pain [8]. In addition, anxiety and depression, which are common findings in patients with psoriasis, can also increase their pain threshold [9]. The aim of this study is to investigate CS in patients with chronic plaque psoriasis and to investigate to what extent CS correlates with disease severity, quality of life, and comorbidities.

METHODS

This is a cross-sectional study involving patients with psoriasis consecutively attending the dermatology outpatient clinic of the University Hospital of Verona, Italy. Inclusion criteria were: age ≥ 18 years, a diagnosis of moderate-to-severe psoriasis made on a clinical basis (i.e., PASI ≥ 10 and/or DLQI ≥ 10 and/or involvement of sensitive area involvement such as nails, face, genital areas) [10], and having not received medical treatment (topical or systemic) for psoriasis in the previous 3 months. Exclusion criteria were treatment with benzodiazepines, antidepressants, and/or anticonvulsants, previous established diagnosis of major depressive disorders, generalized anxiety disorder, fibromyalgia, and inability to understand and complete the questionnaires. We excluded these conditions because these may bias CS assessment. Patients were checked for the presence of diabetic peripheral neuropathy and excluded. During the enrollment visit, the following patient data were collected: age, gender, body mass index (BMI), presence of

diabetes and hypertension, and disease severity as assessed by Psoriasis Area and Severity Index (PASI) and PsA. Each patient was evaluated by a rheumatologist as having PsA according to the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria [11]. PsA clinical disease activity was measured according to Disease Activity in Psoriatic Arthritis (DAPSA) [12]. Patients with PsA were not receiving treatment for PsA. Four different validated questionnaires were administered: Central Sensitization Inventory (CSI), Dermatology Life Quality Index (DLQI), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9). CSI is a validated tool for identifying symptoms common to central sensitivity symptoms [13]. CSI is made up of five categories of severity, namely subclinical CS (0–29), mild (30–39), moderate (40–49), severe (50–59), and extreme CS (≥ 60). The CSI has been cross-culturally adapted and tested in Italian [14]. DLQI is a patient-reported outcome tool that measures the impact of skin disease on health-related quality of life [15]. DLQI ranges from 0 to 30 and is made up of five ranges: no effect at all on patient's life (0–1), small effect on patient's life (2–5), moderate effect on patient's life (6–10), very large effect on patient's life (11–20), and extremely large effect on patient's life (21–30). The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression [16, 17]. The PHQ-9 total score ranges from 0 to 27 (scores of 5–9 are classified as mild depression, 10–14 as moderate depression, 15–19 as moderately severe depression, and ≥ 20 as severe depression) [16, 17]. The GAD-7 evaluates the frequency of anxiety symptoms, such as worrying, over the past 2 weeks. The total score can range from 0 to 21 (scores of 0–5 are classified as mild anxiety, 6–10 moderate, 11–15 moderately severe, and 15–21 severe). Scores of ≥ 10 are considered a reasonable cut-point in screening for generalized anxiety disorder according to DSM-V criteria [18].

The primary outcome was to compare the proportion of CS (i.e., CSI score ≥ 40) in patients with only psoriasis versus those with psoriasis and PsA. The secondary outcome was to investigate whether CSI correlates with

exploratory clinical and psychological variables including disease severity, quality of life impairment, and levels of anxiety and depression.

The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards and was approved by the local Ethics Committee (protocol 1483CESC). Written informed consent was obtained from all participants included.

Statistical Analysis

CSI was analyzed as either a continuous or dichotomous variable (with a threshold of 40). The unpaired *t*-test was used to compare normally distributed continuous variables, respectively. Fisher's exact test was used for categorical variables. The associations between CS and clinical variables were initially tested by Spearman's correlation analysis. For the linear regression model, linear relationship, independence, homoscedasticity, and normality were checked and tested. A multivariate linear regression analysis was then run to estimate the association between CSI and DLQI, PASI, GAD-7, and PHQ-9, adjusting for age, sex, diabetes, and PsA. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using STATA (version 13 StataCorp, College Station, TX, USA). The patients in this manuscript have given written informed consent to the publication of their case details.

RESULTS

A total of 194 patients, including 115 (59%) men, with mean age of 54 ± 13 years were included. The clinical characteristics of the study population are summarized in Table 1. In particular, the mean PASI was 12.7 ± 4.6 , and 60 out of 194 (31%) patients had PsA with a mean DAPSA of 14.4 ± 3.8 . The mean CSI, DLQI, PHQ-9, and GAD-7 scores were 22.8 ± 14.0 (normal value (n.v.) ≤ 30), 12.8 ± 4.5 (n.v. ≤ 10), 4.3 ± 3.9 (n.v. ≤ 5), and 4.6 ± 4.0 (n.v. ≤ 4), respectively.

Table 1 Clinical characteristics of the study population

	<i>N</i> = 194
Gender, male, <i>n</i> (%)	115 (59)
Age (years), mean ± SD	54.3 ± 13.3
BMI (kg/m ²), mean ± SD	27.5 ± 5.2
PASI, mean ± SD	12.7 ± 6.7
Psoriatic arthritis, <i>n</i> (%)	60 (31)
Diabetes, <i>n</i> (%)	17 (9)
Arterial hypertension, <i>n</i> (%)	59 (30)
CSI, mean ± SD	22.8 ± 14.0
Central sensitivity (CS ≥ 40)	19 (10)
DLQI, mean ± SD	12.8 ± 4.5
PHQ9, mean ± SD	4.3 ± 3.9
GAD7, mean ± SD	4.6 ± 4.0

BMI body mass index, *PASI* Psoriasis Area and Severity Index, *DAPSA* Disease Activity in Psoriatic Arthritis, *CSI* Central Sensitization Inventory, *DLQI* Dermatology Life Quality Index, *PHQ9* Patient Health Questionnaire-9, *GAD-7* General Anxiety Disorder-7

Overall, 19 (10%) patients had a CSI score ≥ 40, which is considered the threshold for clinically significant CS, and 58 out of 194 patients (30%) had a CSI score ≥ 30, which is the threshold for mild CS [13]. Minimal depressive symptoms were found in 52 (27%) patients, mild in 11 (6%), and moderate-to-severe in 7 (4%). A total of 53 (28%) patients had minimal and 20 (11%) moderate symptoms of anxiety (Supplementary Fig. S1).

Clinical characteristics of patients with psoriasis versus those with psoriasis and PsA are reported in Table 2. The two groups did not differ in age, gender, BMI, prevalence of diabetes, and psoriasis severity. The proportion of CS was higher in patients with PsA compared with psoriasis (17% versus 7%, *p* = 0.031). Consistently, patients with PsA had higher mean scores in CSI compared with psoriasis (27.5 ± 13.5 versus 20.7 ± 13.7, *p* = 0.002), whereas DLQI impairment, PHQ-9, and GAD-7 were similar between the two groups (Fig. 1). A

Table 2 Clinical characteristics of the study population in patients with psoriasis versus those with psoriasis and psoriatic arthritis (PsA)

	Psoriasis (<i>n</i> = 134)	Psoriasis and PsA (<i>n</i> = 60)	<i>p</i>
Gender, male, <i>n</i> (%)	88 (65)	27 (45)	0.007
Age (years), mean ± SD	53.2 ± 13.4	56.7 ± 12.8	0.087
BMI (kg/m ²), mean ± SD	27.9 ± 5.4	26.8 ± 4.5	0.158
PASI, mean ± SD	12.6 ± 5.8	11.8 ± 4.9	0.178
Arterial hypertension, <i>n</i> (%)	42 (31)	17 (28)	0.674
Diabetes, <i>n</i> (%)	12 (9)	5 (8)	0.887
DAPSA, mean ± SD	–	14.4 ± 3.8	–
CSI, mean ± SD	20.7 ± 13.7	27.5 ± 13.5	0.002
Central sensitivity (CS ≥ 40)	10 (7)	9 (17)	0.031
DLQI, mean ± SD	12.5 ± 3.5	13.3 ± 5.8	0.320
PHQ-9, mean ± SD	4.0 ± 3.7	5.0 ± 4.4	0.130
GAD-7, mean ± SD	4.5 ± 3.9	4.9 ± 4.4	0.505

moderate correlation between CSI and DLQI (*ρ* = 0.43), PASI (*ρ* = 0.41), PHQ-9 (*ρ* = 0.59) and GAD-7 (*ρ* = 0.57) was found (*p* < 0.001). Independently from age, gender, diabetes, and PsA, an association between CSI and DLQI [*β* = 1.25 (95% CI 0.85–1.66)], PASI [*β* = 1.22 (95% CI 0.74–1.65)], GAD-7 [*β* = 2.07 (95% CI 1.69–2.45)], and PHQ-9 [*β* = 2.16 (95% CI 1.76–2.54)] was confirmed (Table 3).

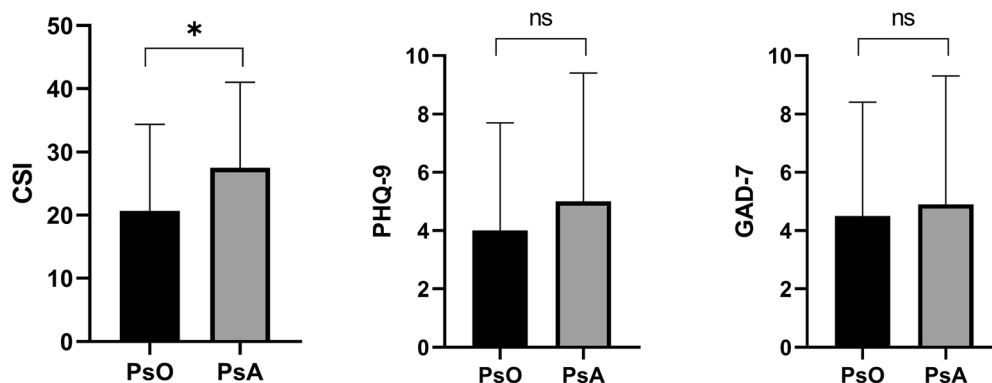


Fig. 1 Mean (± standard deviation), Central Sensitization Inventory (CSI), Patient Health Questionnaire-9 (PHQ-9), and General Anxiety Disorder-7 (GAD-7) scores in patients with psoriasis ($n = 134$) versus psoriatic arthritis ($n = 60$)

Table 3 Multiple linear regression models assessing the associations of CSI with DLQI, PASI, PHQ-9, and GAD-7

Variable	β (95% CI)
<i>DLQI</i>	
Unadjusted model	1.44 (1.03–1.85)
Adjusted model*	1.25 (0.85–1.66)
<i>PASI</i>	
Unadjusted model	1.24 (1.10–1.79)
Adjusted model*	1.22 (0.74–1.65)
<i>PHQ-9</i>	
Unadjusted model	2.31 (1.81–2.82)
Adjusted model*	2.16 (1.76–2.54)
<i>GAD-7</i>	
Unadjusted model	2.11 (1.64–2.57)
Adjusted model*	2.07 (1.69–2.45)

Sample size, $n = 194$. Data are expressed as β 95% CI as assessed by univariate (unadjusted) or multivariable linear regression analysis. *Multivariable regression models adjusted for age, sex, presence of psoriatic arthritis, and diabetes

DISCUSSION

We investigated the prevalence of CS and its association with health-related quality of life and symptoms of anxiety and depression in

patients with psoriasis. The main finding of the study is that CS affects 10% of patients with psoriasis. Higher scores of CSI were associated with psoriasis severity, poor DLQI, concomitant PsA, and symptoms of anxiety and depression.

CS is defined as an increased responsiveness of nociceptors in the central nervous system to either normal or subthreshold afferent input, resulting in hypersensitivity to noxious as well as non-noxious stimuli (such as pressure, cold, and heat) and increased pain response evoked by stimuli outside the area of injury [19]. Pain persists beyond expected tissue healing and pathological recovery time and it can be associated with dysesthesias (e.g., burning, coldness, crawling). Patients with CS often have a history of failed medical treatments to non-steroidal antiinflammatory drugs, and are generally more responsive to antiepileptic and antidepressant medication. CS has been proposed as the root etiology for central sensitivity syndromes (CSSs), which refer to a group of disorders for which no organic cause can be found, including fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome [20, 21]. Moreover, CS has been reported in patients with inflammatory disorders such as rheumatoid arthritis with a prevalence ranging from 20–41% [22]; only one study investigated CS in patients with PsA, reporting a prevalence of 42.9% [23], whereas CS has never been investigated in those with only psoriasis.

In our sample, the proportion of CS was 10%, ranging from 7% in patients with psoriasis

to 17% in those with PsA. When considering mild CS, the proportion reached one-third of the study population. Patients with psoriasis may complain of arthralgia. The preclinical phase of PsA is characterized by heterogeneous symptoms such as fatigue and non-specific joint pain [24]. Zabotti et al. showed, by ultrasonography, that tenosynovitis could be an important contributor to nonspecific musculoskeletal symptoms in patients with psoriasis with arthralgia who are more at risk of developing PsA [25]. Moreover, patients with psoriasis may complain of cutaneous pain, which can be described as aching, burning, stinging, tenderness, cramping, and tingling [2, 3, 26]. According to a survey involving 244 patients with PsO, about one-third reported skin pain, half tingling, and a large majority reported pruritus [27]. In patients with skin pain, a neuropathic component was suggested as assessed by the Douleur Neuropathique 4 (DN4) questionnaire [28]. Patients with skin pain consult dermatologists more often and their quality of life is more impaired. Such patients experience a more severe reduction in quality of life comparable to that seen in other chronic conditions such as diabetes and ischemic heart disease [29].

In skin pain, either a nociceptive component due to inflammation and local tissue damage (i.e., from fissures and involvement of sensitive area), or a neuropathic component due to nerve damage can be found. In plaque psoriasis, different neuropeptides, including substance P, vasoactive intestinal peptide (VIP), and nerve growth factor (NGF), have been identified that may contribute to neurogenic inflammation [30]. Nociceptors, by interacting with dermal dendritic cells, regulate the IL-23/IL-17 pathway and control cutaneous immune responses in mouse models of psoriasis [31]. Substance P binds to neurokinin-1 receptors on mast cells inducing degranulation of proteases and release of proinflammatory products. Higher levels of proteases, such as chymase and tryptase, induce in an autocrine signaling proteinase-activated receptor 2 (PAR2), leading to further activation of mast cells. PAR2 stimulation enhances sensitization of transient receptor potential (TRP) channels in both dermal mast cells and cutaneous SP-containing fibers, which enhances

substance P release [32]. Proinflammatory cytokines (e.g., TNF-alpha, IL-1beta, IL-6, IL17, IL-33) and vasoactive peptides produced by immune cells act directly on nociceptive neurons of the dorsal horn of the spinal cord and contribute to peripheral sensitization and CS [33]. We found a significant correlation between disease severity (i.e., PASI) and CSI, suggesting a higher risk of CS when the inflammation burden increases.

This study has some limitations. We did not stratify patients on the basis of sensitive area involvement, but rather according to the presence or absence of PsA. Only 19 patients had CS, therefore the comparison analysis between PsO and PsA is lacking in strength. We enrolled only patients with moderate-to-severe psoriasis and our results are not easily generalizable to all patients affected by psoriasis. Even if we excluded patients receiving antidepressants or anti-convulsants, and those with major depressive disorders and fibromyalgia, the prevalence of CS could have been possibly overestimated. Patients enrolled in the study were not receiving topical or systemic therapy for psoriasis. Whether and to what extent systemic or topical therapies can modulate CS has yet to be investigated.

CONCLUSIONS

CS may also be associated with skin inflammatory disorders such as psoriasis, although it is more frequent in patients with PsA. CS could be an explanation of those generalized, indefinite painful symptoms that some patients with psoriasis sometimes complain of, but no objective clinical confirmation has been found. The severity of CS is associated with poor quality of life, disease severity, and higher levels of symptoms of anxiety and depression.

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Disclosures. Francesco Bellinato, Paolo Gisondi, Angelo Fassio and Giampiero Girolomoni have nothing to disclose.

Compliance with Ethics Guidelines. The study was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and it was approved by the local Ethics Committee (protocol 1483CESC). Written informed consent was obtained from all participants included.

Data Availability. Data of the study are available on request to the Authors.

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