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ORIGINAL RESEARCH

Association of nociplastic and neuropathic pain components with the presence of residual symptoms in patients with axial spondyloarthritis receiving biological disease-modifying antirheumatic drugs

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ABSTRACT

Objective To evaluate the association of nociplastic (NoP) and neuropathic pain (NP) components with residual symptoms in patients with radiographic axial spondyloarthritis (r-axSpA) receiving biological disease-modifying antirheumatic drugs (bDMARDs).

Methods 78 patients with r-axSpA from the GErman SPondyloarthritis Inception Cohort receiving a bDMARD for at least 3 months were included in this analysis. The Widespread Pain Index (WPI) and the PainDETECT (PD) questionnaire were used to quantify the NoP and the NP components, respectively. Axial Spondyloarthritis Disease Activity Score (ASDAS) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) were used as measures of residual symptoms. C reactive protein (CRP) was used as a measure of systemic inflammatory activity. Univariable and multivariable regression analyses of disease activity were performed. The regions of the WPI score and items of the PD score were used for cluster analyses.

Results Linear multivariable regression analysis showed that WPI and PD were independently associated with ASDAS (b=0.1, 95% CI 0.04 to 0.17, and b=0.05, 95% CI 0.02 to 0.08, respectively) and BASDAI (b=0.24, 95% CI 0.08 to 0.39, and b=0.17, 95% CI 0.1 to 0.25, respectively) in r-axSpA patients receiving stable treatment with bDMARDs. Furthermore, WPI and PD were found to be significantly associated with the presence of relevant residual symptoms as defined by BASDAI ≥4 (OR 1.93, 95% CI 1.09 to 4.15, and OR 1.32, 95% CI 1.04 to 1.85, respectively). The effects were present also in patients with normal level of CRP. Cluster analysis revealed three distinct pain distribution profiles and four specific sensory symptom constellations allowing differentiation of different pain subtypes.

Conclusion Both NoP and NP components seem to be associated with residual symptoms in patients with r-axSpA receiving treatment with bDMARDs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A substantial proportion of patients with axial spondyloarthritis (axSpA) do not achieve a symptom-free state despite effective anti-inflammatory treatment.

⇒ Nociplastic (NoP) and neuropathic pain (NP) mechanisms might be responsible for the presence of residual pain in patients with chronic inflammatory disorders.

WHAT THIS STUDY ADDS

⇒ The study demonstrated that NoP and NP components are important determinants of residual symptoms (as reflected by high Axial Spondyloarthritis Disease Activity Score or Bath Ankylosing Spondylitis Disease Activity Index) irrespective of inflammatory activity in patients with axSpA receiving stable treatment with biological disease-modifying antirheumatic drugs.

⇒ Several clusters with particular patterns of pain distribution and pain characteristics were identified.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that the evaluation of NoP and NP components is crucial in patients with axSpA receiving effective anti-inflammatory drugs but not achieving remission/symptom-free state and showing no objective signs of inflammatory activity.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic immune-mediated disease which is characterised by inflammation predominantly in the axial skeleton—sacroiliac joints and spine.[1] Depending on the presence or absence of radiographic changes in the sacroiliac joint,

radiographic (r-axSpA) and non-radiographic forms of axSpA are defined.[2–4] The term ankylosing spondylitis (AS) is often used synonymously with r-axSpA.[4]

The leading clinical symptom of axSpA in most of the patients is chronic back pain,[4] making it an important entry point for the diagnostic approach and classification criteria.[2 5] In the management of axSpA, a step-up approach is usually applied with non-steroidal anti-inflammatory drugs (NSAIDs) being the first-line pharmacological treatment and biological (b) or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) reserved for patients not responding sufficiently to NSAIDs; the current clinical practice is to start with bDMARDs. Currently, two groups of bDMARDs are approved for the therapy of axSpA: tumour necrosis factor-α (TNFα) inhibitors and interleukin-17 (IL-17) inhibitors.[6 7] Both have shown significant reduction in inflammation and improvement of symptoms in clinical trials[8] but in most of the patients no remission state,[9] meaning the absence of clinical and lab signs of disease activity—the primary treatment goal in axSpA[10]—could be achieved. The reasons for non-achieving remission might include uncontrolled inflammation but might also be related to non-inflammatory/non-nociceptive pain mechanisms.

Pain in axSpA has long been considered a classic example of nociceptive pain related to inflammation.[11] According to this view, the pain results from activation of nociceptive afferents by an imbalance of and overproduction of proinflammatory cytokines especially in the IL-23/IL-17 axis.[12] However, the sole involvement of this nociceptive cause in the complex sensation of pain is at odds with the persistence of pain in a high proportion of patients despite therapy with bDMARDs and a significant reduction in inflammation.

The International Association for the Study of Pain defines three mechanistic descriptors of pain. In addition to nociceptive pain, neuropathic pain (NP) and nociplastic pain (NoP) are distinguished.[13] As of today, there are only limited data on the role of NP and NoP as determinants of residual symptoms, which might persist despite sufficient anti-inflammatory treatment in axSpA.

This work aimed to investigate the association of these two components with residual symptoms in patients with axSpA receiving stable treatment with bDMARDs.

METHODS

Patients

Data from patients recruited in the GErman SPondyloarthritis Inception Cohort (GESPIC) were used in this analysis. The initial cohort is described in detail elsewhere.[14] Given the fact that most of the patients were recruited in the original cohort before the introduction of bDMARDs in the clinical practice, a total of 130 patients with r-axSpA who were about to start therapy with a bDMARD (TNFα or IL-17 inhibitor) were additionally recruited between 2015 and 2019. These patients were prospectively followed up according to the original protocol, and in these patients, NoP and NP components were evaluated at follow-up visits. Only patients who received the treatment for at least 3 months at the time of the follow-up examination were included in this analysis. Patients with missing data for NoP or NP were excluded from the analysis. Data from the first visit, for which data on NoP and NP were available, were used for the analysis.

Assessment of pain characteristics

With widespread pain being a common symptom in patients with NoP, the German version of the Widespread Pain Index (WPI),[15] formerly known as Regional Pain Scale,[16] was used to quantify the extent of NoP. WPI is determined by the patient indicating for 19 body regions whether he or she had pain in the last 7 days.[15] WPI is derived from the number of painful regions. A WPI value <4 was considered negative, 4–6 possible and >6 likely to have a NoP component.

NP was examined using the PainDETECT (PD) questionnaire. The PD questionnaire was originally developed as a screening tool for NP in patients with low back pain but has since been used for axSpA. The score consists of seven items capturing the following aspects of sensory symptomatology: burning sensation, tingling/

Table 1 Baseline demographic and clinical characteristics of axSpA patients (n=78) included in the analysis

Parameter	
Female sex	25 (32.1%)
Age (years)	36.87±10.42
BMI (kg/m²)	25.55±4.42
HLA-B27 positive	72 (92.3%)
Symptom duration (years)	11.96±10.43
BASDAI	5.48±1.36
ASDAS	3.46±0.79
CRP (mg/l)	13.47±15.37
Elevated CRP (>5 mg/L)	46 (61.3%)
NSAID intake	63 (80.8%)
bDMARD (TNFi/IL-17i)	76 (97.4%)/2 (2.6%)
Arthritis, ever	23 (29.5%)
Enthesitis, ever	36 (46.2%)
Dactylitis, ever	6 (7.7%)
Uveitis, ever	19 (24.4%)
Inflammatory bowel disease, ever	5 (6.4%)
Psoriasis, ever	12 (15.4%)

Continuous variables are expressed as mean±SD and categorial variables as n (%).
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; CRP, C reactive protein; HLA, human leucocyte antigen; IL, interleukin; NSAID, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor; WPI, Widespread Pain Index.

prickling, allodynia, sudden pain attacks, thermal sensitivity, numbness and pressure-induced pain. The intensity can be indicated on a scale of 0–5, where 0 stands for never and 5 for very strong. In addition, pain radiation to other body regions and pain progression over time are included in the score, resulting in an overall score that can range from −1 to 38. Patients with a PD score <13 were evaluated as negative, 13–18 as possible and >18 as likely to have a neuropathic component to their pain.[17]

Residual symptoms

The level of residual symptoms was assessed using both the Axial Spondyloarthritis Disease Activity Score (ASDAS) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). ASDAS scores ≥2.1 and BASDAI scores ≥4 were used as thresholds for the definition of the presence of relevant residual symptoms in the logistic regression analysis.

Statistical analysis

Continuous variables were expressed as mean±SD and categorial variables as n (%). A comparison between the baseline characteristics of the study cohort and patients that were excluded was done using t-test for continuous variables and χ^2 test for categorial variables. Univariable and multivariable linear and logistic regression analyses were performed to assess the association of WPI and PD with residual symptoms reflected by BASDAI and ASDAS. The following parameters were included in the models as potential confounding factors: sex, age, body mass index, human leucocyte antigen-B27 status, symptom duration, ASDAS at baseline, CRP level at baseline and, at the follow-up timepoint, NSAID intake. A sensitivity analysis was performed in patients with normal CRP (≤5 mg/L) at follow-up.

Hierarchical cluster analyses were performed to identify specific symptom patterns. The 19 regions of the WPI score were used in the cluster analysis with Ward's method to differentiate groups of patients with a specific pain pattern. Distances were calculated with the Jaccard method. The seven items of the PD score were used to query the severity of specific symptoms. For each patient, the average of these items was subtracted from the individual scores to eliminate interindividual differences in NP severity. Euclidean distances were calculated and

Table 2 Univariable and multivariable linear and logistic regression analysis of factors associated with residual symptoms as defined by ASDAS

	Linear regression outcome: ASDAS		Logistic regression outcome: ASDAS ≥2.1	
	Univariable B (95% CI)	Multivariable B (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)
WPI	0.15 (0.09 to 0.22)	0.1 (0.04 to 0.17)	1.56 (1.23 to 2.08)	1.95 (1.21 to 3.6)
PD	0.09 (0.06 to 0.12)	0.05 (0.02 to 0.08)	1.25 (1.11 to 1.44)	1.09 (0.9 to 1.36)
Female sex	0.03 (−0.35 to 0.41)	−0.14 (−0.4 to 0.12)	1.09 (0.38 to 3)	1.45 (0.2 to 11.07)
Age (years)	0.02 (0 to 0.04)	0.02 (0 to 0.03)	1.07 (1.02 to 1.13)	1.07 (0.97 to 1.19)
BMI (kg/m²)	0.03 (0 to 0.07)	−0.01 (−0.03 to 0.02)	1.09 (0.98 to 1.21)	1.06 (0.87 to 1.34)
HLA-B27 positivity	0.13 (−0.53 to 0.79)	0.53 (0.12 to 0.94)	2.35 (0.35 to 46.33)	26.12 (1.05 to 2028.77)
Symptom duration (years)	0.02 (0 to 0.04)	0 (−0.02 to 0.01)	1.07 (1.02 to 1.13)	1.02 (0.94 to 1.12)
ASDAS at baseline	−0.01 (−0.25 to 0.22)	−0.01 (−0.21 to 0.19)	0.92 (0.49 to 1.72)	1.07 (0.24 to 5.07)
CRP at baseline (mg/L)	−0.01 (−0.02 to 0.01)	−0.01 (−0.02 to 0)	0.98 (0.94 to 1.02)	0.92 (0.82 to 1)
CRP at follow-up (mg/L)	0.09 (0.06 to 0.13)	0.12 (0.09 to 0.14)	1.18 (1.06 to 1.36)	1.52 (1.19 to 2.17)
Current NSAID intake	0.5 (0.16 to 0.85)	0.1 (−0.14 to 0.34)	3.32 (1.24 to 9.28)	0.53 (0.06 to 3.27)

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C reactive protein; HLA, human leucocyte antigen; NSAID, non-steroidal anti-inflammatory drugs; PD, PainDETECT; WPI, Widespread Pain Index.

Table 3 Univariable and multivariable linear and logistic regression analysis of factors associated with residual symptoms as defined by BASDAI

	Linear regression outcome: BASDAI		Logistic regression outcome: BASDAI ≥4	
	Univariable B (95% CI)	Multivariable B (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)
WPI	0.42 (0.28 to 0.56)	0.24 (0.08 to 0.39)	1.48 (1.16 to 1.98)	1.93 (1.09 to 4.15)
PD	0.22 (0.17 to 0.28)	0.17 (0.1 to 0.25)	1.38 (1.18 to 1.68)	1.32 (1.04 to 1.85)
Female sex	0.3 (–0.51 to 1.12)	–0.26 (–0.92 to 0.4)	1.36 (0.41 to 4.22)	1.49 (0.16 to 12.9)
Age (years)	0.05 (0.02 to 0.09)	0.04 (0.01 to 0.08)	1.09 (1.03 to 1.15)	1.17 (1.02 to 1.43)
BMI (kg/m²)	0.07 (–0.02 to 0.15)	0 (–0.06 to 0.07)	1.17 (1.03 to 1.34)	1.27 (1 to 1.74)
HLA-B27 positivity	0.72 (–0.71 to 2.15)	1.26 (0.24 to 2.29)	1.32 (0.19 to 26.21)	58.48 (0.96 to 33675.14)
Symptom duration (years)	0.05 (0.01 to 0.08)	–0.02 (–0.05 to 0.02)	1.04 (0.99 to 1.1)	0.92 (0.79 to 1.02)
ASDAS at baseline	–0.15 (–0.65 to 0.35)	–0.07 (–0.58 to 0.44)	0.93 (0.45 to 1.88)	1.43 (0.27 to 7.93)
CRP at baseline (mg/L)	–0.02 (–0.04 to 0.01)	–0.01 (–0.03 to 0.02)	0.96 (0.9 to 1.01)	0.87 (0.71 to 1.01)
CRP at follow-up (mg/L)	0.05 (–0.03 to 0.14)	0.08 (0.01 to 0.15)	1.04 (0.92 to 1.16)	1.26 (0.97 to 1.76)
Current NSAID intake	1.23 (0.5 to 1.97)	0.16 (–0.45 to 0.77)	3.5 (1.14 to 11.6)	0.23 (0.02 to 1.96)

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C reactive protein; HLA, human leucocyte antigen; NSAID, non-steroidal anti-inflammatory drugs; PD, PainDETECT; WPI, Widespread Pain Index.

clustered according to Ward's method. To compare the characteristics of the resulting clusters, statistical analyses were conducted using χ^2 test for categorial variables and the analysis of variance for metric variables.

The significance level was set at α=0.05 for all analyses.

All statistical analyses were conducted using statistical software R V.4.3.1.

RESULTS

Of the 130 patients with r-axSpA initially included in the extension of GESPIC, 78 could be included in the analysis. The characteristics of the included patients are presented in table 1. The description of the excluded patients is given in online supplemental table 1. No significant differences between excluded and included patients were recorded, except for bDMARD usage. The follow-up examination with WPI and PD data collection considered for this analysis was performed after an average of 3.52±0.99 years after baseline.

At the time of the follow-up examination, all patients received bDMARD, with 75 (96%) patients receiving TNFα inhibitors and 3 (4%) patients receiving IL-17 inhibitors. A total of 30 (39%) patients received NSAIDs, and only 1 patient received systemic glucocorticoid therapy with a dose <7.5 mg/day. One patient was on therapy with sulfasalazine. No other conventional DMARDs were reported.

At the time of follow-up examination, mean WPI was 2.59±2.29 and mean PD 5.94±5.1. According to the WPI score cut-offs, a possible NoP component (WPI 4–6) was detected in 17 (22%) patients and a likely component (>6) in 4 (5%) patients. At the same time, only 6 (8%) patients had a possible (PD 13–18) and 1 (1%) patient a likely (>18) NP component according to the PD score.

At the follow-up examination, ASDAS was 1.67±0.78, with 24 patients (31%) being in a high disease activity state (ASDAS ≥2.1). Out of these patients, 19 (79.2%) showed either a possible or likely NoP component (WPI≥3) and 5 (20.8%) patients showed a possible or likely NP component.

In patients with low disease activity/inactive disease (ASDAS <2.1), the frequency of possible/likely NoP or NP was substantially lower: out of 54 patients, 15 (27.8%) patients had a possible NoP component, 2 (3.7%) patients

Table 4 Univariable and multivariable linear regression analysis of factors associated with residual symptoms as defined by ASDAS and BASDAI in axSpA patients with normal CRP (≤5 mg/L)

	Outcome: ASDAS		Outcome: BASDAI	
	Univariable B (95% CI)	Multivariable B (95% CI)	Univariable B (95% CI)	Multivariable B (95% CI)
WPI	0.17 (0.12 to 0.22)	0.12 (0.05 to 0.18)	0.44 (0.31 to 0.58)	0.27 (0.11 to 0.42)
PD	0.09 (0.06 to 0.12)	0.05 (0.01 to 0.08)	0.26 (0.2 to 0.33)	0.18 (0.1 to 0.26)
Female sex	0.13 (–0.22 to 0.48)	–0.05 (–0.33 to 0.23)	0.43 (–0.47 to 1.33)	–0.14 (–0.8 to 0.53)
Age (years)	0.02 (0.01 to 0.04)	0.01 (0 to 0.03)	0.06 (0.02 to 0.1)	0.05 (0.01 to 0.08)
BMI (kg/m²)	0.03 (0 to 0.07)	0.01 (–0.01 to 0.04)	0.08 (–0.01 to 0.17)	0.02 (–0.04 to 0.08)
HLA-B27 positivity	0.02 (–0.67 to 0.7)	0.48 (0 to 0.95)	–0.02 (–1.79 to 1.75)	1.37 (0.25 to 2.48)
Symptom duration (years)	0.02 (0.01 to 0.04)	0 (–0.02 to 0.01)	0.06 (0.02 to 0.09)	–0.03 (–0.07 to 0.01)
ASDAS at baseline	–0.09 (–0.31 to 0.14)	0.08 (–0.15 to 0.32)	–0.12 (–0.71 to 0.47)	0.04 (–0.52 to 0.59)
CRP at baseline (mg/l)	–0.01 (–0.02 to 0)	–0.01 (–0.02 to 0)	–0.02 (–0.05 to 0.01)	–0.01 (–0.04 to 0.02)
Current NSAID intake	0.49 (0.17 to 0.81)	0.1 (–0.18 to 0.37)	1.35 (0.53 to 2.17)	0.22 (–0.42 to 0.86)

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C reactive protein; HLA, human leucocyte antigen; NSAID, non-steroidal anti-inflammatory drugs; PD, PainDETECT; WPI, Widespread Pain Index.

had a likely NoP component, while only 2 (3.7%) patients had a possible and none had a likely NP component.

BASDAI was 2.24 (±1.69) at the timepoint of examination, with 16 patients (21%) having high disease activity (BASDAI ≥4).

The results of the linear and logistic regression analyses of the association between ASDAS at the timepoint of the follow-up examination and NoP and NP components are shown in table 2. In a multivariable linear regression model, both WPI and PD were shown to be independently associated with ASDAS. Logistic regression analyses with a cut-off value of 2.1 for ASDAS also showed an independent association with WPI but not for PD.

The results of the regression analysis with BASDAI as a measure of disease activity are shown in table 3. WPI and PD were both independently associated with BASDAI and with the presence of relevant residual symptoms according to BASDAI (BASDAI ≥4). Interestingly, the CRP level at follow-up was associated with BASDAI at the same timepoint in the linear multivariable analysis.

A total of 63 (80.8%) patients had normal CRP at follow-up. In these patients, WPI and PD were both

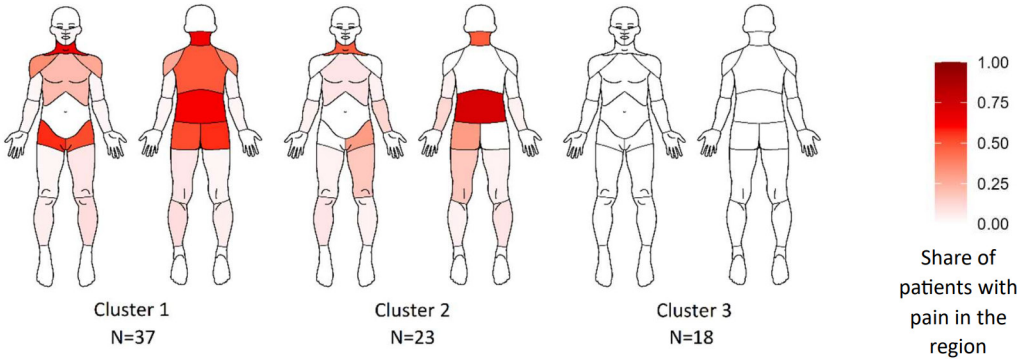

Figure 1 Clusters of pain distribution based on Widespread Pain Index.

Table 5 Characteristics of the pain distribution clusters according to the Widespread Pain Index

Category	Cluster 1 n=37	Cluster 2 n=23	Cluster 3 n=18	P value
WPI	4.1±2.1	2.2±1.4	0±0	<0.001
PD	7.6±5.4	5.9±4.3	2.6±3.8	0.001
Female sex	13 (35.1%)	6 (26.1%)	6 (33.3%)	0.76
Age (years)	41.9±11.8	38.7±9.2	38.8±8.8	0.24
BMI (kg/m²)	26.7±4.8	26.2±4.4	25.2±5.2	0.3
HLA-B27 positivity	34 (91.9%)	22 (95.7%)	16 (88.9%)	0.72
Symptom duration (years)	17.2±11.9	15.2±8.3	12.4±9.4	0.11
ASDAS at follow-up	1.9±0.7	1.9±0.8	1±0.4	<0.001
CRP at baseline (mg/L)	14.2±14.8	10.3±14.5	16.1±17.8	0.85
CRP at follow-up (mg/L)	3.4±4.4	5.1±5.1	2.6±3.4	0.75
Current NSAID intake	19 (51.4%)	8 (34.8%)	3 (16.7%)	0.04

Continuous variables are expressed as mean±SD and categorial variables as n (%). P values were calculated using $\chi 2$ for categorial variables and Analysis of Variance for continous variables.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C reactive protein; HLA, human leucocyte antigen; NSAID, non-steroidal anti-inflammatory drugs; PD, PainDETECT; WPI, Widespread Pain Index.

independently associated with ASDAS and BASDAI in the multivariable linear regression analysis (table 4).

Figure 1 and table 5 show the result of the cluster analysis of the pain regions of the WPI score. Cluster 1 shows a diffuse distribution of pain over the entire torso. It is characterised by high WPI (4.1±2.1) and high PD (7.6±5.4) values. Cluster 2 is characterised by a more localised pain in the lower back and to a lesser extent in the neck. Patients in this cluster have the highest CRP levels (5.1±5.1) compared with the other clusters, although this difference was not statistically significant. Cluster 3 contains all patients who did not indicate any painful regions.

Cluster analysis of the PD items resulted in four specific sensory symptom clusters as seen in figure 2 and table 6. Cluster 4 consists mostly (19 out of 20) of patients who gave a value of zero for all items. Accordingly, patients have low WPI (1±1.2) and PD (0.7±1.9) scores. In cluster 1, flash attacks of pain and pressure sensitivity are particularly prominent. With nine (56%) patients, this cluster had the highest proportion of female patients. In cluster 2, pressure sensitivity is the main symptom with

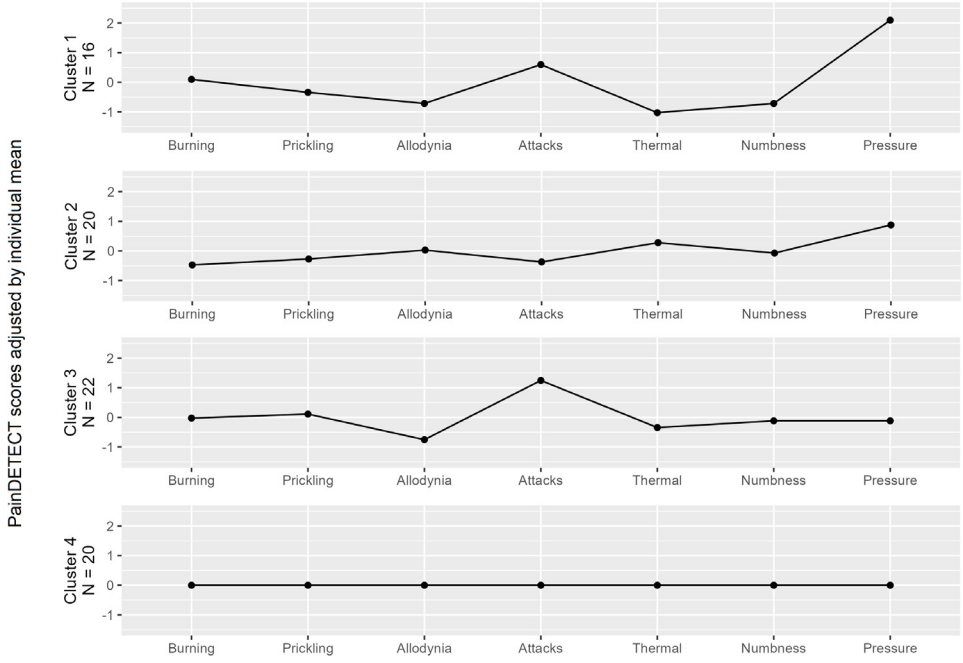

Figure 2 Clusters of sensory symptoms based on PainDETECT.

Table 6 Characteristics of the sensory symptom clusters

Category	Cluster 1 n=16	Cluster 2 n=20	Cluster 3 n=22	Cluster 4 n=20	P value
WPI	2.7±1.9	3.1±2.2	3.5±2.8	1±1.2	0.03
PD	8.6±2.9	6±3.9	8.8±5.6	0.7±1.9	<0.001
Female sex	9 (56.2%)	5 (25%)	9 (40.9%)	2 (10%)	0.02
Age (years)	37.4±8.5	43.5±11.7	43.1±10.2	36.2±9.4	0.58
BMI (kg/m²)	26.9±5.7	26.3±4	27±4.9	24.7±4.5	0.24
HLA-B27 positivity	15 (93.8%)	20 (100%)	19 (86.4%)	18 (90%)	0.4
Symptom duration (years)	14.3±9.2	20.1±12.9	16.5±9.5	10.7±7.6	0.14
ASDAS at follow-up	2.1±0.8	1.8±0.8	1.8±0.7	1.1±0.5	<0.001
CRP at baseline (mg/l)	8.4±6.4	19.9±19.2	11.7±13.4	13.1±17.1	0.87
CRP at follow-up (mg/l)	4.4±5.1	4.6±5.7	3.4±3.8	2.6±2.8	0.14
Current NSAID intake	6 (37.5%)	6 (30%)	14 (63.6%)	4 (20%)	0.03

Continuous variables are expressed as mean±SD and categorial variables as n (%). P values were calculated using $\chi 2$ for categorial variables and Analysis of Variance for continous variables.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C reactive protein; HLA, human leucocyte antigen; NSAID, non-steroidal anti-inflammatory drugs; PD, PainDETECT; WPI, Widespread Pain Index.

a moderately pronounced thermal sensitivity. Patients in this group had the lowest average PD score, excluding cluster 4. For patients in cluster 3, flash attacks of pain were particularly prominent. Patients in this cluster had the highest PD (8.8±5.6) and WPI (3.5±2.8) values, despite having lower CRP values at follow-up (3.4±3.8) than cluster 1 (4.4±5.1) and cluster 2 (4.6±5.7), although this difference did not reach statistical significance.

DISCUSSION

Our study revealed a possible nociplastic component of pain (WPI 4–6) contributing to residual symptoms in 17 (22%) and a likely component in 4 (5.1%) patients with radiographic axSpA receiving stable treatment with bDMARDs. Although we could not find published data on the prevalence of NoP in axSpA, previous studies indicated the presence of signs of central sensitisation (CS) in 45%–60% of axSpA patients as detected by Central Sensitisation Inventory (CSI ≥40).[18–22] Since CS plays a significant role in the pathophysiology of NoP, these numbers might correspond to the frequency of NoP. Nevertheless, NoP is not synonymous with CS, and the exact background is not yet sufficiently understood. Another proxy for the prevalence of NoP can be seen in the prevalence of fibromyalgia syndrome (FMS). The syndrome is considered a classic example of NoP. The prevalence of FMS fulfilling the 2010 criteria of the American College of Rheumatology in patients with axSpA was found to be 21.7% in a meta-analysis.[23] This prevalence of FMS is thus significantly lower than our estimated prevalence of NoP. This is not surprising—NoP can be seen as a spectrum with FMS being an extreme part of this spectrum.

Possible or likely NP component according to the PD score (PD >12) was found only in seven patients (9%). This number was substantially lower than the reported prevalence of NP in patients with r-axSpA ranging from 22% to 56.9%.[24 25] Previous data indicated that patients with NP responded worse to the therapy,[26] but at the same time, an improvement of NP by the therapy could be demonstrated.[27 28]

Our results showed a clear and consistent association between WPI and PD as scores reflecting the NoP and PN components with residual symptoms measured by ASDAS and BASDAI. These effects were independent of systemic inflammatory activity.

The results are in line with previous studies, which showed an association between disease activity and CS,[18–22 29] FMS[30–33] and NP.[24 29 34 35] At the same time, this is to our knowledge the first study that attempted to address all three components of pain showing an independent contribution of all components to the residual symptoms in a homogeneous group of patients with axSpA receiving bDMARDs. These results have clear clinical relevance: in patients with axSpA receiving effective anti-inflammatory therapy for at least 3 months and not being in low-disease activity/remission, it is worthwhile to evaluate the presence of NoP and NP to adjust the treatment accordingly. This would be especially relevant for patients not demonstrating any objective signs of inflammatory activity (normal CRP, no inflammation on MRI).

In the cluster analysis, we identified three clusters according to the distribution of pain. Residual symptoms were found to be present in patients from clusters 1 and 2. Cluster 1 is characterised by a wide distribution of pain with a high probability of NoP predominance. Cluster 2 patients, on the other hand, are characterised by comparatively high levels of inflammation with lower PD/WPI values compared with cluster 1. In these

patients, inflammation might be the leading cause of the symptom. These patients are most likely to benefit from optimisation of anti-inflammatory therapy.

In a cluster analysis of PD, four specific clusters with sufficiently large group sizes were defined. An association between specific symptom constellations and pain mechanisms has been postulated in the past and studied for various diseases involving NP[36–38] or NoP[39]; therefore, we assume that this can be true for axSpA as well. For patients from cluster 1, a combination of pressure-induced pain and sudden pain attacks is prominent. This constellation has been found by Mahn *et al* to be very specific for patients with radiculopathy.[38] The assumption is that these attacks are not spontaneously autonomously arising pain attacks but that they occur as a consequence of irritation in the area of the ganglion due to the interaction of disc herniation and inflammation of the nerve.[38] This finding is interesting in that radiculopathy is generally considered rare in patients with axSpA and is therefore poorly studied. In a study with 24 patients with AS, Khedr *et al* found that 16.7% of patients had clinical signs of radiculopathy,[40] which is close to the cluster 1 frequency of 20.5% that we found. In fact, patients in this group show comparatively high PD values of 8.62±2.87, which could imply an aetiological relationship of NP with radiculopathy. Considering the limited amount of research on the subject, further research is needed.

Cluster 2 is characterised by pressure sensitivity. This is a classic symptom of CS[41] and NoP.[13] In fact, this constellation of symptoms has been found in patients with FMS.[39] The mildly pronounced involvement of thermal sensitivity could also indicate a nociplastic component.

In cluster 3, pain attacks are prominent. Indeed, spontaneous pain attacks are a well-known sign of NP. These result from ectopic formation of action potentials in the affected nerves without the need for an excitatory stimulus.[42] This symptom constellation has also been reported in patients with lower back pain,[37] painful diabetic neuropathy, postherpetic neuralgia[36 38] and chronic radiculopathy.[38]

Based on the data presented above, we believe that with screening tools such as WPI and PD physicians might be able to differentiate between different pain components defining patient symptoms that would trigger further examination (if needed) and appropriate treatment modification.

Our work has some limitations. First, it is the lack of a gold standard for quantifying NoP and NP. The PD score has been widely used to identify NP, but it had been developed before the introduction of the NoP concept. The distinction between NP and NoP continues to be difficult due to similar symptomatology. For this reason, Bailly *et al* suggest that NoP might often be wrongfully categorised as NP in patients with rheumatic disease.[43] Furthermore, we used the WPI (without symptom severity scale) as an indicator of NoP without further confirmation of the presence of the nociplasticity. Quantitative sensory testing may help to better distinguish pain modalities in axSpA. Second, patients completed WPI and PD for the first time being already on bDMARDs at the follow-up examination. We do not have, therefore, information on the baseline situation in these patients and if achieving remission/low disease activity could be predicted already at baseline based on the scores of WPI and PD. To control for inflammation as a possible confounder, CRP was used in the regression analysis; furthermore, a sensitivity analysis was done in patients with normal CRP levels. We had, however, no information concerning residual inflammation in the spine or sacroiliac joints as detected by MRI. As the WPI and PD scores are only available at the follow-up examination, the predictive value of these scores is limited. Specifically, the change in the scores over time after treatment initiation as well as a possible association between treatment success and initial WPI and PD values could not be assessed and necessitates further research. Another limitation is the small number of patients with likely NP or NoP. This limits the significance of the inter-individual differences in PD and WPI scores to the effect of NP or NoP. The size of the total sample also posed a limitation for the cluster analysis, as it limited the number of distinguishable clusters with sufficient group size.

In conclusion, our data suggest a significant contribution of NoP and NP component in residual symptoms in patients with radiographic axSpA being on stable treatment with bDMARDs that was independent of inflammatory activity. Evaluation of non-nociceptive pain components might be, therefore, important in patients not achieving low disease activity/remission based on ASDAS or BASDAI to guide further management strategy. Patients with low disease activity according to ASDAS or BASDAI values but still suffering from symptoms (pain) might also benefit from a thorough evaluation of NoP or NP components.

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Correction notice This article has been corrected since it was first published online. In this paper, the authors used the Widespread Pain Index (WPI) to identify nociplastic pain (NoP) components in patients with radiographic axial spondyloarthritis (r-axSpA). They defined patients with a WPI score between 3 and 6 as having possible NoP, while patients with a WPI score ≥ 7 were considered likely to have NoP. These cut-offs were derived from the 2010 ACR criteria for fibromyalgia syndrome (FMS) (1). According to these cut-offs, a possible NoP component (WPI 3–6) was detected in 32 (41%) patients and a likely component (>6) in 4 (5%) patients. However, the 2010 ACR criteria use the WPI cut-off values in conjunction with the Symptom Severity Score, which was not available in our setting. For WPI alone, the following categorization was proposed and evaluated: 0, 1-3, 4-6, and ≥7, respectively (1). Therefore, we recalculated the frequency of possible NoP, defined as a WPI of 4-6: 17/78 (22%) patients; likely NoP (WPI >6) was observed in 4/78 (5%) patients (unchanged). Thus, the corrected frequency of NoP (taking the possible and likely groups together) was 21/78 (27%).Another possible NoP detection approach involves using the generalised pain criterion from the 2016 ACR criteria for FMS, which identifies pain in at least 4 out of 5 defined body regions, as determined using the WPI (2). According to this approach, the study population includes 16/78 (20.5%) patients with widespread pain that may indicate the presence of a NoP component.Since the authors did not use a dichotomized WPI value for the analysis, the models and the main study results remained unchanged.

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Contributors All authors have made substantial contributions to the conception or design of the work or to the acquisition, analysis or interpretation of data for the work and drafting the work or revising it critically for important intellectual content. Finally, all authors approved the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DP is responsible for the overall content as the guarantor.

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Correction: *Association of nociplastic and neuropathic pain components with the presence of residual symptoms in patients with axial spondyloarthritis receiving biological disease-modifying antirheumatic drugs*

Al Mohamad F, Rios Rodriguez V, Haibel H, *et al*. Association of nociplastic and neuropathic pain components with the presence of residual symptoms in patients with axial spondyloarthritis receiving biological disease-modifying antirheumatic drugs. *RMD Open* 2024;10:e004009. doi: 10.1136/rmdopen-2023-004009

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