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Original Article

Neuropathic Pain and its Relationship With Fibromyalgia, Vitamin D Status and Medication Use in Patients With Ankylosing Spondylitis

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Objective. To determine the frequency of neuropathic pain (NeP) and potentially related new factors including fibromyalgia, vitamin D and medication use in ankylosing spondylitis (AS) patients. **Methods.** In total, 102 patients with AS were prospectively enrolled in this study and evaluated for pain severity (visual analog scale, VAS), disease activity (the Bath Ankylosing Spondylitis Disease Activity Index, BASDAI), fibromyalgia and current medication use. The presence of NeP was also assessed using the painDETECT questionnaire. Blood samples were taken from all patients to analyze serum 25-hydroxyvitamin D and inflammatory marker levels. **Results.** NeP component 32 (21 [20.6%]; clearly NeP and 11 [10.8%]; mixed NeP) was present in patients with AS. Compared to those without NeP, they had significantly higher VAS and BASDAI scores ($p=0.022$ and 0.003, respectively). In addition, there was a highly significant difference of frequency of fibromyalgia between patients with and without NeP (50.0% vs. 5.7%, $p<0.001$). Vitamin D status and medication use were comparable for patients with and without NeP. Logistic regression analysis revealed that only fibromyalgia was a significant predictor of NeP. **Conclusion.** This study confirmed that about one-third of AS patients have the NeP component. In addition, NeP was found to be associated with the frequency of fibromyalgia. However, no relation was found between NeP and vitamin D status and medication use in AS. **(J Rheum Dis 2021;28:126-132)**

Key Words. Ankylosing spondylitis, Neuropathic pain, Vitamin D, Fibromyalgia

INTRODUCTION

Ankylosing spondylitis (AS) is a prevalent form of axial spondyloarthritis (axSpA), with a remarkable link with HLA-B27 [1]. Axial inflammation and new bone formation are two major issues in the pathogenesis of AS. These two ongoing processes are often responsible for chronic back pain and loss of mobility and function in patients with AS. Other common findings related to pain are asymmetric oligoarthritis and enthesitis [2].

Although the pain in AS has an inflammatory nature, recent studies have suggested that neuropathic pain (NeP) component exists in 25%~35.4% of patients [3-5]. A structural magnetic resonance study also revealed the occurrence of additional structural brain abnormalities, which are compatible with neural correlations of NeP, in patients with AS, thereby supporting the existence of a central pain process [6]. NeP is thought to be caused by the immune response due to chronic stimulation of the joints and entheses, leading to neural plasticity in the peripheral and central nervous systems [7]. Current treatments of AS, including the use of biological agents, primarily focus on suppressing inflammation; however, they do not always provide satisfactory pain relief in all patients. One of the reasons for this is that comorbidities associated with accompanying pain in these patients fur-

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ther complicate neuro-immune interactions and affect the character of the current pain [8,9].

Previous studies have reported that NeP in AS is associated with demographic, disease-related (i.e., disease activity or enthesitis) and emotional factors [3-5]. However, other factors affecting pain in AS patients, which are common and potentially associated with NeP, have not been adequately investigated. First, vitamin D deficiency is frequent among patients with AS and potentially related to pain, whereas the impact of vitamin D status on AS-related NeP is unknown [10]. The correlation of the presence and severity of neuropathy with a poor vitamin D status in painful neuropathic diseases has been demonstrated in recent studies [11,12]. Second, in a recent systemic review of axSpA, concomitant fibromyalgia has reported in 13.8% of patients with AS [13]. Studies indicate that patients with axSpA with concomitant fibromyalgia have higher disease burden with higher pain severity and lower quality of life than those without [14,15]. Although pain in fibromyalgia is not included in the NeP classification, recent studies containing primary data on pathophysiology have highlighted the neuropathic component of pain in fibromyalgia, and even the new category as "centralized pain" is proposed [16-18]. Moreover, the effect of concomitant fibromyalgia on NeP in patients with axSpA or other inflammatory arthritis is not clear. Therefore, the purpose of this study is to investigate the frequency of NeP in AS and its relationship with some new potential primary data added.

MATERIALS AND METHODS

This cross-sectional study was conducted between November 2018 and October 2019 at our department's outpatient clinic. The study protocol received ethics approval from the local ethics committee (reference number: 2018/542). All the patients received detailed information about the study protocol and provided signed consent. According to the modified New York criteria, patients 18 years and older diagnosed with AS were consecutively enrolled during their medical appointments. The exclusion criteria were as follows: (i) the presence of accompanying systemic or neurological disorders that can cause NeP, e.g., diabetes mellitus, chronic renal impairment, or polyneuropathy; (ii) the presence of metabolic bone diseases; (iii) the presence of psychiatric disorders; (iv) the use of medications affecting NeP or vitamin D levels, e.g., antidepressants, antiepileptics, or calcium and vitamin D or B12 supplements; (v) chronic alcohol or drug misuse; (vi) a previous diagnosis of vitamin B12 deficiency; and (vii) refusal to participate in the study.

A standardized form was used to gather demographic and disease related data, including age, gender, body length and body weight, educational status, presence of systemic diseases, disease duration, and current medication and duration of use. The patients were questioned for the presence of concomitant fibromyalgia, and noted. The American College of Rheumatology (ACR) 2010 classification criteria were used to diagnose fibromyalgia.

The overall pain intensity of the patients within the last week was evaluated using a horizontal visual analog scale (VAS) scoring system. The disease activity was tested using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which is a simple and valid instrument that includes five main disease parameters, namely fatigue/tiredness, back/hip pain, peripheral joint pain/swelling, localized tenderness, and morning stiffness [19]. The total scores range from 0 to 10, with higher scores showing increased disease activity.

The neuropathic component of the pain was assessed with the painDETECT questionnaire (PD-Q). In adults, the PD-Q questionnaire used to detect NeP components in chronic painful conditions, developed by Freynhagen et al. [20]. The survey contains seven items relevant to the nature and intensity of specific NeP symptoms. The total score ranges from −1 to 38, with <13, $13\sim18$, and ≥19 points representing "unlikely," "mixed" and "very likely" NeP component, respectively. The PD-Q can be easily administered and validated in Turkish [21].

A total of 5 mL of fasting peripheral blood was collected early in the morning. Serum 25-hydroxyvitamin D (25(OH)D) levels were quantitatively determined using liquid chromatography/tandem mass spectrometry method. The vitamin D status was considered sufficient, insufficient, and deficient for patients with serum 25(OH)D levels ≥30 ng/mL, between 21 and 29 ng/mL, and ≤20 ng/mL, respectively [22]. Additional laboratory tests were carried out, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Statistical analysis

Data analyses were performed using SPSS 26.0 statistical software (IBM Co., Armonk, NY, USA). The basic characteristics of the patients were evaluated using descriptive statistics. The Kolmogorov–Smirnov test and graphical methods were used to check the normal dis-

tribution of quantitative data. Based on the total PD-Q score, the patients divided into NeP-negative (NePN, <13 points) and NeP-positive groups (NePP, ≥ 13 points). For comparison of continuous variables between NePP and NePN groups, Student's t-test or Mann–Whitney U-test (if t-test assumptions were not met) was used. Univariate and multivariate analyses were performed to define NEP-related independent predictors for AS. The significance level was accepted at $p<0.05$.

RESULTS

During the study period, 125 patients diagnosed with AS were enrolled; and eventually, 102 patients met eligibility criteria. Of 102 patients, 54 (52.4%) were males and 48 (46.6%) were females. The mean age of patients was 40.5±10.9 years. The demographic and clinical data of the AS patients are shown in Table 1.

Based on their PD-Q score, 31.4% of patients had the NeP component (21 [20.6%]; clearly NeP and 11 [10.8%]; mixed NeP); 68.6% had no NeP component. The clinical data for patients with and without NeP are presented in Table 1. In comparing the NePP and NEPN groups, there were no significant differences in age, gender and disease duration. However, VAS and BASDAI scores were significantly higher in the NePP group than in the NePN group ($p=0.022$ and 0.003, respectively). The serum 25(OH)D levels were low in both the groups, and the between-group difference did not reach statistical significance ($p=0.329$). The two groups were also comparable in terms of vitamin D status ($p=0.973$). The frequency of fibromyalgia was 50.0% and 5.7%, respectively, in NePP and NePN groups, and this difference was highly significant ($p<0.001$).

Correlation analysis showed that PD-Q scores was positively correlated with VAS and BASDAI ($p<0.001$, $r=0.658$ and $p<0.001$, $r=0.633$, respectively), and negatively correlated with duration of tumor necrosis factor

Table 1. Demographic and clinical variables in patients with AS (n=102) based on PD-Q score

Variable	NePN group (n=70)	NePP group (n=32)	Total (n=102)	p-value
Age (yr)	40.33±11.20	40.81±10.34	40.5±10.9	0.836
Sex				
Male	35 (50.0)	19 (59.4)	54 (52.9)	0.379
Female	35 (50.0)	13 (40.6)	48 (47.1)	
BMI (kg/m^2)				
<25	29 (41.4)	12 (37.5)	41 (40.2)	0.707
≥25	41 (58.6)	20 (62.5)	61 (59.8)	
Disease duration (yr)	9.55±8.87	7.94±6.39	9.04±8.18	0.358
AS medication				
NSAID	17 (24.3)	7 (21.9)	24 (23.5)	0.326
DMARD (alone or combination)	4 (5.7)	5 (15.6)	9 (8.8)	
TNF inhibitor	43 (61.4)	19 (59.4)	62 (60.8)	
None	6 (8.6)	1 (3.1)	7 (6.9)	
Duration of TNF inhibitors, months	45.1±27.1	32.1±28.2	41.1±27.9	0.089
VAS pain	3.84±2.42	5.03±2.32	4.22±2.44	0.022
BASDAI	3.19±2.28	4.66±2.29	3.64±2.37	0.003
ESR (mm/h)	11.56±9.68	12.09±10.43	11.7±9.9	0.800
CRP (mg/dL)	9.30±13.06	7.06±7.71	8.6±11.7	0.371
25(OH)D (ng/mL)	19.36±7.06	17.78±8.37	18.9±7.5	0.329
Vitamin D status				
≤20 ng/mL	40 (57.1)	19 (59.4)	59 (57.8)	0.973
21~29 ng/mL	25 (35.7)	11 (34.4)	36 (35.3)	
≥30 ng/mL	5 (7.1)	2 (6.3)	7 (6.9)	
Fibromyalgia	4 (5.7)	16 (50.0)	20 (19.6)	<0.001

Data were expressed as mean±standard deviation or frequency (%). AS: ankylosing spondylitis, PD-Q: painDETECT questionnaire, NePN: neuropathic pain-negative, NePP: neuropathic pain-positive, BMI: body mass index, NSAID: nonsteroidal antiinflammatory drug, DMARD: disease-modifying antirheumatic drug, VAS: visual analog scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, 25(OH)D: 25-hydroxyvitamin D.

Table 2. Factors associated with NeP by univariate and multivariate logistic regression analysis

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.004	0.966～1.044	0.834			
Sex	1.462	0.627～3.409	0.380			
BMI	1.179	0.499～2.784	0.707			
CRP	0.981	0.940～1.024	0.375			
Disease duration	0.974	0.922～1.030	0.356			
AS medication	1.114	0.736～1.686	0.609			
Fibromyalgia	16.500	4.851～56.126	＜0.001	16.500	4.851～56.126	＜0.001
25(OH)D	0.971	0.917～1.029	0.326			
BASDAI	1.315	1.087～1.591	0.005			
VAS	1.233	1.027～1.481	0.025			

NeP: neuropathic pain, OR: odds ratio, CI: confidence interval, BMI: body mass index, CRP: C-reactive protein, 25(OH)D: 25-hydroxyvitamin D, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, VAS: visual analog scale.

(TNF) inhibitors (p=0.039, r=−0.262). However, PD-Q scores were not significantly correlated with age (p=0.767), disease duration (p=0.085) and 25(OH)D levels (p=0.489). In logistic regression, only fibromyalgia was found to be statistically significant as a predictor of NeP (odds ratio [OR], 16.500; 95% confidence interval, 4.851～56.126) (Table 2).

DISCUSSION

Our study provides new insights into the growing literature suggesting that the NeP component is present in patients with axSpA. Of the 102 patients with AS included in the study, 21 (20.6%) clearly (very likely) had the NeP component (PD-Q score ≥19 points). Furthermore, the possible NeP component (PD-Q scores between 13 and 18 points), i.e., mixed pain, was present in 10.8% of the patients. Similar results were obtained in previous studies investigating the prevalence of NeP in patients with AS using the PD-Q [3-5]. These studies revealed the presence of the NeP component in 25%, 32.8%, and 35.2% of patients with AS, respectively. In addition, using the PD-Q, Wu et al. [6], detected the NeP component in 11 out of 17 AS patients with active disease and back pain. A recently published meta-analysis showed that AS patients with NeP had higher pain intensity, higher disease activity, and poorer quality of life than those without NeP. In addition, NeP was higher in females than in males. Moreover, HLA-B27 was present in significantly more patients with NeP, compared to those without NeP. In contrast, age, body mass index, symptom duration, and levels of systemic markers of inflammation (i.e., ESR and CRP level) did not differ between patients with and without NeP [23]. The findings in our study were consistent, except for the gender ratio.

Fibromyalgia was considerably more frequent in patients with NeP, and it was revealed to be an independent predictor of NeP by logistic regression analysis. Considering the current research on NeP in AS patients, it seems confusing whether the presence of fibromyalgia in these patients can be excluded. Choi et al. [5] reported that concomitant fibromyalgia in AS patients with NeP was substantially higher, but it was not an independent predictor of NeP. Gok et al. [4] found similar frequency of fibromyalgia in patients with the NeP component compared to patients without it. On the other hand, in the study conducted by Geler-Külcü et al. [3], patients with AS with concomitant fibromyalgia, despite having similar methodology, were excluded. In our study, 19.6% of patients had fibromyalgia according to the ACR 2010 fibromyalgia criteria, and more than half of them had a NeP component. The total number of female patients included in the study was relatively high, but 12 of the 20 patients with concomitant fibromyalgia were females. Depending on the criteria used, the frequency of concomitant fibromyalgia was found to be between 4% and 25% in patients with AS [24]. However, in another study, interestingly, the frequency of fibromyalgia was found to be 19%–29% by applying the ACR 1990 and 2010 FM criteria to the same AS cohort [25]. Using the PD-Q, a recent study revealed that 52.5% of the patients with fibromyalgia had a NeP component [18]. On the other hand, the PD-Q has been found to have low sensitivity and specificity in distinguishing NeP in patients with fibromyalgia [26].

Understanding the complex relationship between fibromyalgia and NeP is challenging because of their clinical and neurobiological similarities [27]. A study using patient reported questionnaires in patients with diabetic polyneuropathy and fibromyalgia showed that both groups of patients experienced very similar sensory symptoms and that sensory profiles were overlapping in 20%～35% of patients [28]. The presence of NeP in inflammatory arthritis is quite new to diabetic polyneuropathy, and self-assessment questionnaires have generally been used in current research; however, our knowledge of their uses and validity is very limited. Therefore, in cross-sectional studies, it may be not possible to determine whether the NeP component in patients with AS is related to the disease itself or to fibromyalgia and whether fibromyalgia or AS contributes to the patients' current NeP using self-administered questionnaires, such as the PD-Q.

We found no substantial difference in the vitamin D levels or status (sufficiency, insufficiency, and deficiency) between AS patients with and without NeP. Most research has primarily addressed the relationships between diabetic peripheral neuropathy and vitamin D. The results of a recent meta-analysis showed that there is a close relationship between vitamin D and diabetic peripheral neuropathy, and vitamin D deficiency is one of the risk factors for neuropathy [29]. Moreover, some previous studies have reported that vitamin D replacement treatment has beneficial effects on neuropathic signs/symptoms in patients with diabetic NeP and vitamin D deficiency [30,31]. However, in a recently published study, possible NeP was detected in 26.8% of 236 diabetic patients using the PD-Q; no significant relationship was observed when comparing the vitamin D status of patients with and without NeP. The authors interpreted incompatibility with previous studies as a result of the limited sample size and the use of a different neuropathy assessment tool (i.e., the PD-Q) [32]. Yesil et al. [33] detected NeP in 33.3% of 93 patients with rheumatoid arthritis (RA) using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale. In their study, the mean serum 25(OH)D level was lower than 20 ng/mL in patients with NeP and higher than 20 ng/mL in patients without NeP, and there was a significant difference between the two groups. Furthermore, the prevalence of NeP was about six times greater in patients with vitamin D deficiency than in those with sufficient levels of vitamin D. In contrast to RA, the lack of a reasonable association between NeP and vitamin D deficiency in patients with AS could be attributed to the relatively small number of patients with NeP as well as the methodological differences in our study.

In our study, we found no significant difference in medication use between AS patients with and without NeP. The frequency of those using NSAIDs or TNF inhibitors was similar in both groups. There was only a weak negative correlation with the PD-Q scores and the duration of TNF inhibitors. Approximately two-thirds of all patients in our study had been using TNF inhibitors for a long period (at least 6 months). Wu et al. [34] demonstrated that TNF inhibitors could reduce NeP severity in a small proportion of AS patients with NeP. Similarly, in our study, the severity of pain and PD-Q scores of the patients using TNF inhibitors were lower in the NeP group compared to those who did not (data not shown). In a recently published study, almost all 58 AS patients were taking NSAIDs, while 22 patients were taking TNF inhibitors. In this study, NeP was detected in 50% of the patients [35]. Thus, although anti-inflammatory agents appear to alleviate NeP severity in patients with AS, this findings confirm that they are not sufficient for NeP treatment.

Several limitations of the present study need to be noted. We used a self-assessment screening (and not diagnostic) questionnaire to evaluate the NeP component of patients. Therefore, it cannot replace the clinical history and examination, which also assess the functions of the somatosensory system. In addition, the fact that only 32 patients had NeP component may have weakened the strength of logistic regression to evaluate variables. As far as we know, our study is the first to explore the relationship between NeP and vitamin D status in patients with AS. However, our results should be viewed with caution because of the cross-sectional study design. Longitudinal studies are required in patients with AS to validate potential causal relationships between NeP and vitamin D status or medication use.

CONCLUSION

This study confirmed that This study confirmed that about one-third of AS patients have the NeP component. In addition, NeP was found to be associated with the frequency of fibromyalgia. However, no relation was found between NeP and vitamin D status and medication use in AS. Furthermore, the pain severity and disease activity were higher in patients with NeP than in those without

NeP. Further research is necessary to confirm our findings and related mechanisms.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: S.M. and M.K. Data acquisition: S.M., M.K., and İ.C. Formal analysis: S.M and İ.C. Funding: Erciyes University. Supervision: M.K. Writing—original draft: S.M. and İ.C. Writing—review & editing: İ.C. and M.K.

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