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Investigation of Neuropathic Pain and Related Factors in Patients with Ankylosing Spondylitis

Ankilozan Spondilitli Hastalarda Nöropatik Ağrı ve İlişkili Faktörlerin Araştırılması

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ABSTRACT Objective: The aim of this study was to evaluate the neuropathic pain component in patients with Ankylosing Spondylitis (AS) and to examine the relationship of neuropathic pain with disease activity, functional capacity, and quality of life. **Material and Methods:** This intervention-type study included 27 AS patients diagnosed according to the The Assesment of Spondyloarthritis International Society criteria and 27 healthy subjects. Neuropathic pain was assessed with the painDETECT questionnaire, disease activity was assessed with the Bath AS Disease Activity Index (BASDAI), functional status with the Bath AS Functional Index (BASFI), and quality of life with the AS Quality of Life Scale (ASQoL). **Results:** No significant difference was found between patients with AS and healthy individuals in terms of demographic data. The prevalence of neuropathic pain in AS patients was 33.3%. Patients with neuropathic pain (painDETECT>12) had higher BASDAI, BASFI and ASQoL scores compared with patients without neuropathic pain ($p<0.05$). There were significant positive correlations between neuropathic pain score and disease activity (BASDAI: $r=0.850$), functional status (BASFI: $r=0.788$) and quality of life (ASQoL: $r=0.799$) ($p<0.05$). **Conclusion:** Neuropathic pain is a common condition in AS patients and is associated with disease activity, functional capacity and quality of life. Therefore, the neuropathic pain component should be considered in AS patients and treatment options should be organized accordingly.

Keywords: Ankylosing Spondylitis; neuropathic pain; Bath Ankylosing Spondylitis Disease Activity Index; Bath Ankylosing Spondylitis Functional Index; painDETECT

ÖZET Amaç: Bu çalışmanın amacı Ankilozan Spondilitli (AS) hastalarda nöropatik ağrı bileşenini değerlendirmek ve nöropatik ağrının hastalık aktivitesi, fonksiyonel kapasite ve yaşam kalitesi ile ilişkisini incelemektir. **Gereç ve Yöntemler:** Müdahale tipi bu çalışmaya Uluslararası Değerlendirme Derneği kriterlerine göre tanı konmuş 27 AS hastası ve 27 sağlıklı birey dâhil edilmiştir. Nöropatik ağrı painDETECT anketi ile, hastalık aktivitesi Bath AS Hastalık Aktivite İndeksi [Bath AS Disease Activity Index (BASDAI)] ile, fonksiyonel durum Bath AS Fonksiyonel İndeksi [Bath AS Functional Index (BASFI)] ile ve yaşam kalitesi AS Yaşam Kalitesi Ölçeği [AS Quality of Life Scale (ASQoL)] ile değerlendirildi. **Bulgular:** AS'li hastalar ile sağlıklı bireyler arasında demografik veriler açısından anlamlı fark elde edilememiştir. AS hastalarında nöropatik ağrı prevalansı %33,3 idi. Nöropatik ağrısı olan hastaların (painDETECT>12) BASDAI, BASFI ve ASQoL skorları nöropatik ağrısı olmayan hastalara kıyasla daha yüksekti ($p<0,05$). Nöropatik ağrı skoru ile hastalık aktivitesi (BASDAI: $r=0,850$), fonksiyonel durum (BASFI: $r=0,788$) ve yaşam kalitesi (ASQoL: $r=0,799$) arasında anlamlı pozitif korelasyonlar saptandı ($p<0,05$). **Sonuç:** Nöropatik ağrı AS hastalarında sık görülen bir durumdur ve hastalık aktivitesi, fonksiyonel kapasite ve yaşam kalitesi ile ilişkilidir. Bu nedenle, AS hastalarında nöropatik ağrı bileşeni göz önünde bulundurulmalı ve tedavi seçenekleri buna göre düzenlenmelidir.

Anahtar Kelimeler: Ankilozan Spondilit; nöropatik ağrı; Bath Ankilozan Spondilit Hastalık Aktivite İndeksi; Bath Ankilozan Spondilit Fonksiyonel İndeksi; painDETECT

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Ankylosing Spondylitis (AS) is an inflammatory, chronic, rheumatic disease of unknown etiology, affecting the spine and sacroiliac joint, in which extra-articular findings including the lungs, heart, eyes, kidneys, and nervous system may also be observed.[1] AS patients usually present with chronic low back pain.[2] Although pain in these patients is predominantly of nociceptive origin, the presence of symptoms such as burning sensation, hyperalgesia, and allodynia cannot be fully explained by nociceptive mechanisms alone. The control of pain in patients with AS is difficult and the degree of inflammation is not always directly related to pain intensity; moreover, the persistence of pain even when inflammation is suppressed suggests that other mechanisms play a role in pain perception.[3,4]

It has been shown that many diseases leading to nociceptive pain also have a neuropathic component in recent years. Although different rates are given regarding the prevalence of neuropathic pain in the population, chronic pain with neuropathic character has been reported in 6-8% of the general population.[5] Mechanisms effective in the pathogenesis of neuropathic pain are divided into 2 groups as peripheral and central. Peripheral mechanisms are defined as spontaneous ectopic discharge in axons, peripheral nociceptor sensitization, interaction between sympathetic efferents and sensory afferents in the dorsal root ganglion, abnormal interaction between primary afferents, inflammatory and autoimmune lesions in peripheral nerves, and all mechanisms depend on changes in the primary afferents. The central mechanisms can be listed as central sensitization, central synaptic reorganization, and disinhibition.

There are few studies on the presence of a neuropathic component in pain caused by AS.[6,7] However, there are studies indicating the presence of neuropathic pain components in rheumatic diseases such as rheumatoid arthritis, primary Sjögren's syndrome and fibromyalgia.[8-10] There are also limited data on the relationship of neuropathic pain with disease severity, functional capacity and quality of life in patients with AS.[11,12] This study aimed to evaluate the neuropathic pain component in patients with axial spondyloarthritis and to investigate the relationship of neuropathic pain with disease activity, functional capacity and quality of life.

MATERIAL AND METHODS

The sample size and power calculation required for the study were calculated using the G*Power (Heinrich Heine University, Düsseldorf, Germany) Ver.3.1.9.4 programme. In the power analysis based on the results of the comparison of VAS mean scores in the study of Kimyon et al. with the condition of α=0.05 risk, 1-α=0.95 accuracy rate, the sample size to represent the population was calculated as 0.94 actualpower: 0.95, it was concluded that a minimum of 27 people should participate in each group. The study was completed with 54 participants.[13]

The population of this intervention-type study consisted of 27 patients with axial spondyloarthritis and 27 healthy individuals according to The Assesment of Spondyloarthritis International Society (ASAS) criteria who were being followed up in Elazığ Medical Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients between the ages of 18-65 years, whose medical treatment had not changed in the last 3 months, and who were followed up at Elazığ Medical Hospital with a diagnosis of AS were included in the study. Patients who were pregnant, those with a diagnosis of malignancy, those with other concomitant systemic inflammatory rheumatic diseases, those with neuropsychiatric disorders (e.g. radiculopathy, polyneuropathy, neuropathy, depression, fibromyalgia), and those with musculoskeletal disorders (e.g. surgery, fracture) and/or endocrine diseases (e.g. diabetes mellitus) were excluded.

OUTCOME MEASUREMENTS

The subjects were questioned about their name and surname, age, height, weight, comorbidities, medications, disease duration, previous operation, and alcohol and cigarette use, and their information was recorded.

The Bath AS Disease Activity Index (BASDAI) was used to assess disease activity, the Bath AS Functional Index (BASFI) to assess functional status, and the AS Quality of Life Scale (ASQoL) scale to

assess quality of life. The painDETECT questionnaire was used to assess neuropathic pain.

The BASDAI has a score from 0 to 10 to measure the severity of fatigue, spinal and peripheral joint pain, local tenderness, and morning stiffness in patients with axial Spondyloarthritis (SpA). The final BASDAI score has a range of 0-10, with lower numbers representing less severe disease activity. For the assessment of disease activity, a BASDAI cut-off value of 4 points was determined; that is, BASDAI values greater than 4 indicate the presence of active disease.[14]

BASFI is used to assess physical functioning in patients with AS. It includes tasks in which patients assess their own abilities by marking a vertical line on a 100 mm horizontal line. The ten tasks that make up the BASFI are as follows: 1) putting on socks, 2) bending forward to pick up a pencil, 3) reaching up to a high shelf, 4) getting up from a chair without arms, 5) getting up from the floor lying on their back, 6) standing without support, 7) climbing stairs without a handrail, 8) looking over their shoulder, 9) performing physically demanding activities, and 10) performing a full day of activities. The total BASFI score is calculated by adding all ten points and dividing by 10.[15]

The ASQoL consists of 18 disease-specific yes/no questions assessing the quality of life of patients with AS. It assesses disease-related symptoms, functioning, and concerns. "Yes" answers are given 1 point and "no" answers are given 0 points; the total score ranges from 0 to 18. Higher scores indicate a worse quality of life.[16]

The painDETECT scoring system was used to evaluate neuropathic pain.[17] According to this scoring system, 0 to 12 indicates no neuropathic pain, 13 to 18 indicates an uncertain outcome but a neuropathic pain component may be present, and>18 indicates neuropathic pain. According to PainDETECT, neuropathic pain was taken as>12 in our study.

ETHICS COMMITTEE

Written permission was obtained from the Fırat University Non-Interventional Research Ethics Committee (date: August 5, 2024; no: 26170) and the institution where the study was conducted before the data were collected. In addition, all study participants were informed about the nature of the study and that participation was voluntary. Informed consent was obtained from all participants.

STATISTICAL ANALYSIS

In the statistical method, the suitability of the data for normal distribution was analyzed by Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare non-normally distributed data in 2 independent groups. The chi-square test was applied in the evaluation of qualitative data. The correlation between variables was analyzed by Spearman's correlation. Mean±standard deviation, minimum and maximum values for numerical variables and number and % values for categorical variables were given as descriptive statistics. SPSS Windows version 22.0 package programme was used for statistical analyses and $p<0.05$ was considered statistically significant.

RESULTS

No significant sociodemographic difference was observed between the groups ($p>0.05$) (Table 1). The medications used by the patients are given in Table 1.

The diagnostic period of AS patients was found to be 9.55±7.01. A significant difference was observed between the groups in terms of clinical parameters ($p<0.05$) (Table 2).

AS patients were divided into 2 groups as neuropathic pain (PainDetect score>12, n=18) and non-neuropathic pain (PainDetect score≤12, n=9) according to the PainDetect questionnaire (Table 3).

While no significant difference was found between the 2 groups with and without neuropathic pain in terms of age, BMI and disease duration ($p>0.05$), a significant difference was found in other parameters ($p<0.05$) (Table 3). A significant correlation was found between the PainDetect score and the VAS, BASDAI, BASFI and ASQoL scores in the AS group ($p<0.05$) (Table 4).

DISCUSSION

Recent studies have suggested the presence of a neuropathic pain component in addition to nociceptive pain because pain persists despite the suppression of inflammation in some patients, although pain in AS

TABLE 1: Demographic and clinical characteristics of the AS and control groups

Parameters ($\bar{X}$±SD) (Minimum-maximum)		AS Group (n=27)	Control Group (n=27)	p value
Age/year		44.44±11.16 (25.00-69.00)	41.51±11.55 (23.00-65.00)	0.860
Kilogram/kg		73.03±12.61 (50.00-110.00)	76.88±14.39 (52.00-110.00)	0.527
Height/cm		170.22±9.39 (155.00-186.00)	171.62±7.81 (158.00-186.00)	0.668
BMI/kg/cm^2		25.31±4.57 (17.99-38.51)	26.00±3.90 (20.52-38.51)	0.160
Gender	Female	11 (%40.7)	13 (%48.1)	0.584
	Male	16 (%59.3)	14 (%51.9)	
Working status	Working	17 (%63)	19 (%70.4)	0.773
	Not working	10 (%37)	8 (%29.6)	
Smoking	Yes	17 (%63)	10 (%37)	0.102
	No	10 (%37)	17 (%63)	
NSAID	Yes	12 (%44.4)		
Sulfasalazine	Yes	6 (%22.2)		
Anti-TNF	Yes	7 (%25.9)		
Secukinumab	Yes	2 (%7.40)		

SD: Standard deviation; AS: Ankylosing Spondylitis; BMI: Body Mass Index; NSAID: Non-steroidal anti-inflammatory drugs; TNF: Tumor necrosis factor

TABLE 2: Comparison of the clinical parameters of the AS and control groups

Parameters ($\bar{X}$±SD) (Minimum-Maximum)	AS Group (n=27)	Control Group (n=27)	p value
PainDetect	9.96±6.64 (1.00-23.00)	2.70±1.81 (0.00-6.00)	**<0.001**
VAS-nowadays	3.96±2.17 (1.00-10.00)	1.33±0.91 (0.00-3.00)	**<0.001**
VAS-the severe of the last 4 weeks	5.29±2.79 (1.00-10.00)	1.81±1.07 (0.00-3.00)	**<0.001**
VAS-average of the last 4 weeks	4.29±2.26 (1.00-10.00)	1.62±0.92 (0.00-3.00)	**<0.001**
BASDAI	4.22±2.38 (0.00-10.00)	1.12±1.10 (0.00-3.20)	**<0.001**
BASFI	2.95±2.16 (0.00-8.40)	1.04±0.67 (0.00-1.90)	**<0.001**
ASQoL	7.48±5.86 (0.00-17.00)	1.81±2.20 (0.00-6.00)	**<0.001**

SD: Standard deviation; AS: Ankylosing Spondylitis; VAS: Visual Analogue Scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire

patients is considered of inflammatory origin. It has been argued that pain in AS is a neuroimmune process consisting of inflammatory and neuropathic components.[18] In this study, in which the neuropathic pain component was evaluated in patients with AS and the relationship of neuropathic pain with disease activity, functional capacity and quality of life was evaluated, the mean of the painDETECT scale was found to be 9.96±6.64. When we compared patients with the painDETECT scale above and below 13 points, a significant difference was obtained in terms of pain, disease activity, function, and quality of life. In addition, there was a significant relationship between neuropathic pain and pain, disease activity,

TABLE 3: Comparison of clinical parameters between the groups with and without neuropathic pain

Parameters ($\bar{X}$±SD)(Minimum-Maximum)	PainDetect Questionnaire Score ≤12 (n=18)	>12 (n=9)	p value
VAS-nowadays	3.22±1.69 (1.00-6.00)	5.44±2.35 (1.00-10.00)	**0.007**
VAS-the severe of the last 4 weeks	4.16±2.00 (1.00-8.00)	7.55±2.87 (1.00-10.00)	**0.004**
VAS-average of the last 4 weeks	3.38±1.61 (1.00-6.00)	6.11±2.36 (1.00-10.00)	**0.002**
BASDAI	2.96±1.42 (0.00-5.00)	6.74±1.85 (4.30-10.00)	**<0.001**
BASFI	1.84±1.27 (0.00-4.10)	5.17±1.84 (2.30-8.40)	**<0.001**
ASQoL	4.55±4.76 (0.00-14.00)	13.33±2.39 (10.00-17.00)	**<0.001**
Duration of the disease	8.55±5.30 (2.00-24.00)	11.55±9.65 (3.00-30.00)	0.631
BMI	24.50±3.95 (19.78-33.30)	26.93±5.51 (17.99-38.51)	0.160
Age	43.22±9.94 (25.00-65.00)	46.88±13.60 (32.00-69.00)	0.860

SD: Standard deviation; VAS: Visual Analogue Scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire; BMI: Body Mass Index

TABLE 4: Correlation analyses of the PainDETECT scores and related parameters

	AS Group Pain Detect Questionnaire score (n=27)	
	Spearman r	p value
VAS-nowadays	0.699	**<0.001**
VAS-the severe of the last 4 weeks	0.699	**<0.001**
VAS-average of the last 4 weeks	0.733	**<0.001**
BASDAI	0.850	**<0.001**
BASFI	0.788	**<0.001**
ASQoL	0.799	**<0.001**
Duration of the disease	0.092	0.650
BMI	0.308	0.118

AS: Ankylosing Spondylitis; VAS: Visual Analogue Scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASQoL: Ankylosing Spondylitis Quality of Life Questionnaire, BMI: Body Mass Index

function, and quality of life. The results demonstrated that neuropathic pain affects disease-specific findings in patients with AS. Therefore, it is important to evaluate neuropathic pain in patients with AS.

Neuropathic pain is pain that occurs as a direct result of a lesion or disease affecting the somatosensory system.[19] The presence of neuropathic pain-like symptoms such as burning sensation, hyperalgesia, and allodynia in patients with AS cannot be adequately explained by nociceptive pain. Among the studies that included patients with a score of 19 and above according to the PainDetect questionnaire results in the neuropathic pain group, Garip et al. reported neuropathic pain in 28% of AS patients, Mesci et al. in 30% of AS patients, and Geler-Külcü et al. in 14% of AS patients.[12,20,21] It was accepted 13 points and above as neuropathic pain according to the PainDetect questionnaire results and showed that 11 of 17 AS patients (64.7%) had neuropathic pain. In this study, a score above 12 was accepted as neuropathic pain and found that 33.3% of the patients had neuropathic pain. The disease activity scores of the patients who participated in this study were low (BASDAI=4.22±2.38). Therefore, the proportion of patients with neuropathic pain may have been lower compared with other studies. Wu et al. evaluated the neuropathic pain component in AS using the painDETECT Questionnaire and the McGill Pain Questionnaire and showed that patients with AS had an neuropathic pain component.[11] They also re-

ported abnormality in brain gray matter in these patients. Pain in AS patients was described by Bidad et al. as a neuroimmune process.[18] Pain in AS patients was described by Bidad et al. as a neuroimmune process consisting of inflammatory and neuropathic components. Although acute inflammation markers such as IL-6 and CRP decreased with treatment in these patients, the persistence of pain was attributed to the presence of the neuropathic pain component.[3]

It was concluded that neuropathic pain was associated with disease activity, quality of life, and function in patients with AS in this study. In the study by Gök et al, BASDAI, BASFI, and ASQoL scores were found to be statistically significantly higher in the group with neuropathic pain compared to the other group according to the PainDetect questionnaire results.[22] In the study by Choi et al, BASDAI, peripheral arthritis, and enthesitis scores were found to be statistically significantly higher in the neuropathic pain group compared to the group without neuropathic pain according to the PainDetect questionnaire results.[7] In Külcü et al. study, BASDAI, ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score based on C-reactive protein), ASDAS-ESH, and BASFI values were found to be statistically significantly higher in AS patients with neuropathic pain compared to AS patients without neuropathic pain.[21] In a meta-analysis including neuropathic pain studies in AS patients, it was concluded that patients with neuropathic pain had higher pain severity and disease activity scores and lower quality of life compared to patients without the neuropathic pain component.[2] The results of our study are in parallel with the literature. Recently, it has been shown, especially in case studies, that tumor necrosis factor inhibitors may also cause peripheral neuropathy. Several theories have been proposed as the reason for this. When tumor necrosis factor (TNF) levels fall, TNF-alpha in particular reacts synergistically with interferon-gamma, another important inflammatory mediator. This can induce cytotoxic damage within the nerve myelin sheath and increase vascular permeability. Thus, it may expose the nerve to more pro-inflammatory cytokines. It has also been reported that TNF inhibitors may have a direct toxic effect on nerve cells.[23] The association between neuropathic pain and disease activity in our study may be explained by this mechanism.

The current mean pain score was 3.29, the most severe pain score in the last 4 weeks was 5.29, and the mean pain score in the last 4 weeks was 4.29 in this study. The results of Rifbjerg-Madsen et al. investigating pain mechanisms in patients with inflammatory arthritis are also consistent with our study. It was reported that patients with high painDETECT scores also had high VAS scores and patients presenting with neuropathic pain characteristics had a 10-fold higher risk of having high-level pain.[24] Freynhagen et al. also reported that VAS scores were significantly higher with increasing painDETECT scores.[25] Torrance et al. also reported that neuropathic pain was rated more intensely by patients in their study.[26] Similarly, in the meta-analysis by Kim et al., it was reported that VAS scores were higher in the neuropathic pain group in AS patients. These results suggest that chronic pain with neuropathic features is generally more severe than other types of chronic pain.[2]

Our study had some limitations. The low sample size and our inability to apply the evaluation parameters to the control group can be considered as limitations.

CONCLUSION

This study was designed to evaluate the neuropathic pain component in patients with AS and to examine its relationship with disease-specific parameters. It was concluded that the prevalence of neuropathic pain was 33.3%. In addition, it was found that disease activity, function and quality of life were different when patients with and without a score above 13 were compared. In addition, neuropathic pain was associated with disease activity, function, and quality of life in these patients. These results suggested that neuropathic pain is associated with disease-specific parameters. Therefore, the neuropathic pain component should be considered for treating patients with AS. A neuropathic component should be sought in patients with high pain intensity, and if present, treatment options should be considered.

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