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ARAŞTIRMA / RESEARCH

Is neuropathic pain an overlooked symptom in axial spondyloarthritis?

Nöropatik ağrı aksiyal spondiloartritte gözden kaçan bir semptom mu?

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Abstract

Purpose: Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatologic disease. Pain is the most common symptom affecting quality of life in axSpA patients. It has been showed that pain is not always correlated with inflammation in patients. The aim of our study was to investigate the frequency of neuropathic pain in axSpA patients and relationship between neuropathic pain and patient characteristics.

Materials and Methods: Patients diagnosed as axSpA according to the Assessment of SpondyloArthritis International Society classification criteria, who presented in our outpatients clinics from January to March 2019 were included in this study. The neuropathic component of pain was evaluated with Douleur Neuropathique en 4 Questions (DN4) questionnaire.

Results: Eighty seven axSpA patients were included in the study. Thirty of patients had neuropathic pain according to DN4 questionnaire (DN4>4). Neuropathic pain was higher in active disease group depending on both of ASDAS-CRP and BASDAI. DN4 score of patients was found moderately correlated with ASDAS-CRP and BASDAI score. A weak positive correlation was found between patients education level and DN4 score.

Conclusion: We showed that neuropathic pain could be seen in patients with axSpA and it could be correlated with disease activity. The studies have proven that neuropathic pain could lead to impaired quality of life and social & emotional functions. Patients with neuropathic pain could not benefit from antiinflammatory treatments. Therefore evaluating of neuropathic pain is important in axSpA patients. Further studies on management of neuropathic pain in axSpA patients are needed.

Keywords:. Neuropathic pain, spondyloarthritis, disease activity, inflammatory pain

Öz

Amaç: Aksiyal spondiloartitler (axSpA) kronik inflamatuar romatolojik hastalıklardan olup ağrı yaşam kalitelerini etkileyen en sık semptomdur. Literatürde ağrının her zaman inflamasyonla korele olmadığı gösterilmiştir. Bu çalışma ile aksiyal spondiloartrit hastalarında nöropatik ağrının frekansının gösterilmesi ve nöropatik ağrı ile hasta özelliklerinin arasındaki ilişkinin gösterilmesi amaçlanmıştır.

Gereç ve Yöntem: Kliniğimizde Ocak- Mart 2019 ayları arasında takip edilen, Assessment of SpondyloArthritis International Society klasifikasyon kriterlerine göre axSpA kabul edilen hastalar çalışmaya dahil edilmiştir. Nöropatik ağrı Douleur Neuropathique en 4 Questions (DN4) ölçeği ile değerlendirildi.

Bulgular: Seksen yedi axSpa hastası çalışmaya dahil edildi. Hastaların 30'unda DN4 ölçeğine göre (DN4 >4) nöropatik ağrı var kabul edildi. Nöropatik ağrı aktif hasta grubunda (ASDAS- CRP ve BASDAI' ye göre) daha fazla saptandı. DN4 skoru ASDAS- CRP ve BASDAI skoru ile orta düzeyde korele saptandı. Hasta eğitim düzeyi ile DN4 skoru arasında hafif düzeyde korelasyon saptandı.

Sonuç: Çalışmamızda axSpA hastalarında inflamatuvar ağrıya ek olarak nöropatik ağrının görülebileceği ve hastalık aktivitesi ile korele olabileceği gösterildi. Nöropatik ağrı hastaların yaşam kalitesini bozduğu, sosyal ve emosyonel bozukluklara yol açtığı literatürde gösterilmiştir. Hastalar standart anti inflamatuvar tedavi yaklaşımlarından fayda görmeyebilir. AxSpA hastalarında nöropatik ağrının değerlendirilmesi önem kazanmaktadır. AxSpA hastalarında nöropatik ağrının tanı ve tedavi sürecinde ileri çalışmalara gereksinim duyulmaktadır.

Anahtar kelimeler: Nöropatik ağrı, spondiloartritler, hastalık aktivitesi, inflamatuar ağrı

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INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatologic disease that predominantly affects the spine and sacroiliac joints. AxSpA patients could be classified as radiographic (ankylosing spondylitis) and nonradiographic axSpa according to x-ray findings. This distinction has limited effect on management of patients and disease burden. However, the classification is important for studies and epidemiology.

AxSpA can cause pain and progressive spinal stiffness. Pain is the most common symptom affecting quality of life in axSpA patients. Pain can be classified as inflammatory, nociceptive and neuropathic[1]. In the presence of low back pain unresponsive to treatment in axSpA, fibromyalgia comes to mind first in the differential diagnosis. However, in the literature, it has been shown that the frequency of neuropathic pain increases in rheumatic diseases. In a study conducted by Rifbjerg-Madsen et al., it was found that the frequency of neuropathic pain was increased in patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis[2]. In a meta-analysis conducted by Kim et al., the neuropathic pain component was found to be 41.5% in patients with ankylosing spondylitis (AS)[3]. Wu et al. in their study, found that AS patients had brain gray matter abnormalities compared to the control group, and these abnormalities were correlated with neuropathic pain[4]. They emphasized that low back pain in AS is a mixed pain syndrome. The neuropathic pain component may lead to an overestimation of disease activity in SpA patients. In a study by Gok et al., neuropathic pain was detected in one-third of patients with axSpA, and higher disease activity was found in patients with neuropathic pain[5].

Neuropathic pain could be diagnosed by clinical and physical assessment. There were some screening tests for neuropathic pain as Douleur Neuropathique 4 (DN4), painDetect Questionnaire (PD-Q), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire[6]. There was not any gold standart test for diagnosis. This situation made difficult the diagnosis and thus the treatment of neuropathic pain. Assessment of neuropathic pain is important in the management of axSpA patients since approximately 37% of patients with chronic low back pain have neuropathic pain[7] and overlooking neuropathic pain may cause to treatment failure.

In the literature, the frequency of neuropathic pain in SpA patients had been reported at varying rates. This might be related to the patient population studied and neuropathic pain assessment methods. The recognition of pain characteristics is important because it can change the treatment approach to the patient.

The aim of our study was to investigate the frequency of neuropathic pain in axSpA patients and we expected to demonstrate an increased risk of neuropathic pain in axSpA patients. Additionally, it was aimed to investigate the relationship between neuropathic pain and sociodemographic characteristics, clinical features and disease activity.

MATERIALS AND METHODS

Study design and population

This cross-sectional study was conducted in rheumatology outpatient clinic of Çukurova University, Adana, Turkey. Patients diagnosed as axSpA according to the Assessment of SpondyloArthritis International Society classification criteria for axSpA from January to March 2019 were consecutively enrolled. Study protocol was approved by the local ethics committee of Çukurova University (reference number:84/38, date: 04.01.2019) and written informed consent was obtained from all patients. Patients under 18 years of age, with a history of neuropathic pain-related disease (fibromyalgia, diabetes mellitus, thyroid disease, psychiatric disease, vitamin deficiency, neurological disease), who had previously been diagnosed with neuropathic pain and taking medications for neuropathic pain were excluded.

Evaluation of study population

Demographics, clinical data and status of exercise adherence (regular, irregular or no exercise) were recorded by same researchers. Disease activity was assesed with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP) during the outpatient visits.

BASDAI score

The BASDAI score was involved six questions and patients answered the questions according to their complaints in the last week. The ASDAS- CRP score was involved four questions about their pain and one

laboratory finding (CRP value). Physician calculated the score according to patients answers and CRP value. The patients with an ASDAS-CRP score above 3.5 and with a BASDAI score above 5.1 were considered to have active disease[8-11].

Douleur Neuropathique en 4 Questions

The neuropathic component of pain was evaluated with Douleur Neuropathique en 4 Questions (DN4) questionnaire by the same researchers[12] during the outpatient visits. The DN4 questionnaire consists of 10 question; the first seven items are related to pain characteristics and three questions are related to physical examination. The questions were asked by researcher to the patients. Physical examination was made by researcher. For each question, 1 point is given if the answer is 'yes', and 0 if 'no'. The patient is considered to have neuropathic pain if the total score is more than 4. The DN4 questionnaire has been validated in Turkish patients[13].

Statistical analysis

Statistical analyses was performed by using Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, N.Y., USA). The analyses of the demographic data were examined by descriptive statistics. Data was expressed as mean ± SD or percentage unless indicated otherwise. Kolmorogov-Smirnov test was used to asses for normality of distribution. Pearson's or Spearman's correlation analysis was used to detect correlations between variables according to normality. The categorical variables were analysed by using Chi-square test. Neuropathic pain was compared with clinical and demographic data of patients by using t test and Chi-square test. In order to evaluate the statistical power of our results, we used the results of Külcü et al. and the power of our study was calculated as 99.4% in the post-hoc power analysis using the Type 1 margin of error at 0.05 [14]. For all statistics, $p < 0.05$ was considered statistically significant.

Table 1. Demographic and clinical data of the patients

Variable	
Sex (female/male), n (%)	44/43 (51/49)
Age, mean ± SD	49.3 ± 9.06
Disease duration, (month) (min-max)	120 (2- 362)
Treatment	
bDMARD n(%)	51 (58.6)
csDMARD	24 (27.6)
Education level n (%)	
Illiterate	2 (2)
Primary school	32 (37)
Secondary school	13 (15)
High school	23 (26)
University	17 (20)
Comorbidities, n (%)	
Hypertension	7 (8)
Coronary artery disease	3 (3)
Depression	2 (2)
Others	5 (8)
Exercise, n (%)	
Regular	19 (22)
Irregular	35 (40)
No	33 (38)
ASDAS- CRP, mean ± SD	2.78 ± 0.98
BASDAI, mean ± SD	4.34 ± 2.10
Patients with neuropathic pain, n (%)	30 (35)
DN4 value, mean ± SD	3.32 ± 2.78

DMARD: Disease-modifying antirheumatic drugs, ASDAS- CRP: The Ankylosing Spondylitis Disease Activity Score with C- Reactive Protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, DN4:

RESULTS

Out of 101 consecutive patients who were evaluated for enrollment, 14 patients were excluded (8 diabetes mellitus, 2 fibromyalgia, 4 vitamin deficiency). 87 axSpA patients (44 females, 43 males; mean age 49.3 ± 9.06 years) were included in the study. All patients were under treatment with nonsteroidal antiinflammatory drugs (NSAIDs) regular or on-demand

In addition, 51 patients (59%) were treated with biologic disease modifying antirheumatic drugs (bDMARDs), 24 patients (28%) were using conventional disease modifying antirheumatic drugs (csDMARDs). The demographic and clinical data of the patients are given in Table 1. 30 patients had neuropathic pain according to DN4 questionnaire (DN4>4). The mean DN4 value was 3.32 ± 2.78..

Mean BASDAI value of patients was 4.34 ± 2.10 and mean ASDAS-CRP score was 2.78 ± 0.98. According to BASDAI/ASDAS-CRP, 29/17 patients (33%/20%) had active disease. Neuropathic pain was higher in active disease group depending on both of ASDAS-CRP and BASDAI (p=0.019 and p<0.001, respectively)

Mean ASDAS-CRP and BASDAI value were 3.28 ± 0.79/ 5.65 ±1.83 in patients with neuropathic pain and 2.51± 0.96 /3.65 ± 1.90 in patients without neuropathic pain. Both of ASDAS-CRP and BASDAI scores were higher in patients with neuropathic pain (p <0.001/ p<0.001). Similarly, mean VAS-pain score was 6.41 ±2.09 in patients with neuropathic pain and 3.77 ± 2.50 in patients without neuropathic pain. VAS- pain score was also higher in patients with neuropathic pain (p<0.001) (Table 2).

DN4 score of patients was found moderately correlated with ASDAS score p<0.001, ϱ= 0.423) and also with BASDAI score (p<0.001, ϱ= 0.466) (Table 3). A weak positive corelation was found between patients education level and DN4 score (p=0,012, ϱ= 0.270). Neuropathic pain was detected more frequently in females than in males (p=0.002). There was no relationship between neuropathic pain and age, disease duration, exercise.

Table 2. Comparison of demographic and clinical features of patients with and without neuropathic pain

Variable	Patients with neuropathy n:30 (%35)	Patients without neuropathy n:57(%65)	p value
Sex (female/male), n	22/8	22/35	**0.002***
Age mean ± SD	48.7± 9.22	49.61 ± 9.04	0.669*
Disease duration (month) (min-max)	123.8 (4-360)	118.84 (2-362)	0.784*
ASDAS CRP, mean ± SD	3.28 ± 0.79	2.51± 0.96	**<0.001***
BASDAI, mean ± SD	5.65 ±1.83	3.65 ± 1.90	**<0.001***
VAS pain, mean ± SD	6.41 ±2.09	3.77 ± 2.50	**<0.001***
Patients doing regular exercises	6	12	0.845**

ASDAS- CRP: The Ankylosing Spondylitis Disease Activity Score with C- Reactive Protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, VAS: Visual Analogue Scale, Douleur Neuropathique en 4 Questions
*Analysis was made with Chi-square test**Analaysis was made with Student's T-test

Table3. Correlation between disease activity score and patient DN4 score

	Spearman' s Rho*	p value*
ASDAS- CRP	0.423	p<0.001
BASDAI	0.466	p<0.001

ASDAS- CRP: The Ankylosing Spondylitis Disease Activity Score with C- Reactive Protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; *Correlation analysis was made with Spearman correlation analysis

DISCUSSION

In the current study, the neuropathic pain was found in 30% of AxSpa patients. In addition, neuropathic pain was found to be moderately correlated with disease activity indexes (BASDAI, ASDAS- CRP). Neuropathic pain was more common in females. AxSpA is a chronic inflammatory rheumatic disease. Enthesitis, inflammation of the sacroiliac, spinal and peripheral joints could occur as well as new bone formation, syndesmophytes and ankylosis. The disease could lead to pain, structural damage and a decrease in quality of life[15]. The pain in ankylosing

spondylitis is usually thought to be inflammatory and antiinflammatory treatments are administered to the patients. However the cause of pain may not always be disease related. Neuropathic pain could also be present in AS patients. Prevelance of neuropathic pain in general population is unclear. Previous studies have demonstrated that the prevelance of neuropathic pain is approximately 7-8%[16]. There were few studies in the literature about neuropathic pain in AS patients and the results vary (8-31%)[5,17-19]. In our study we found neuropathic pain in 35% of SpA patients. This result was similar with the study of Gok et al. Evaluation of neuropathic pain with different tools may have lead to the different results in the literature.

It is not always easy to distinguish neuropathic pain from inflammatory pain. However it is important for management of patients. It had been reported in the literature that pain is not always correlated with inflammation in AS patients. These patients could have additional paresthetic symptoms which could not be explained with inflammatory diseases[3,20]. Response to antiinflamamtory treatment may not be satisfactory in patients with neuropathic pain. Accordingly, the patients with pain resistant to antirheumatic treatment should be evaluated for neuropathic pain.

Neuropathic pain could be evaluated with patient history and physical examination. There is no gold standard test for evaluating neuropathic pain and screening tests such as Douleur Neuropathique 4 (DN4), painDetect Questionnaire (PD-Q), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire can be used for assesment of patients[6]. All of these three questionnaires had been studied in AS patients to assess neuropathic pain and scores of which were found to correlate with each other[5,6,13]. However in the study of Turkish validation of DN4, DN4 had higher sensitivity than LANSS[13]. PDQ is also used in clinically practice but it does not include sensory examination. In the light of these views, in our study, we evaluated the patients with DN4 questionnaire. In the diagnosis of neuropathic pain, it is recommended to demonstrate the somatosensory system involvement by neurological examination and confirm with additional diagnostic tests[21]. Nevertheless, there is no standard diagnostic procedure for the diagnosis of neuropathic pain. Furthermore small fiber neuropathy can not even be detected by standart procedures except skin biopsy. Several studies have used questionnaires for the evaluation of neuropathic pain in rheumatic diseases.

Neuropathic pain was more frequent in active AS patients depending on both BASDAI and ASDAS-CRP in the current study. In addition, neuropathic pain score was moderately correlated with BASDAI and ASDAS- CRP. This result was consistent with other studies in the literature. Gok et al also showed that neuropathic pain was associated with higher BASDAI and ASDAS score in AS patients. In that study, nonradiographic spondyloarthritis and radiographic axial spondyloarthritis patients had evaluated and both of these two groups had similar symptoms[5]. Neuropathic pain was seen in females more as in our study. Although there are contradictory results, female sex was found to be associated with neuropathic pain in a metaanalysis[3,14]. Fibromyalgia has also female gender dominance and may share common clinical and in pathophysiological features with neuropathic pain[22]. This may be the reason of the higher female ratio in neuropathic pain. Gok et al found that in patients with neuropathic pain, depression and anxiety, physical impairment, patient and physician global assessment, visual analog scale of pain had higher scores. These patients had poorer quality of life. AS-pain score was found to be higher than in patients with neuropathic pain in current study, similar with the literature[5]. In the current study, there was no association between neuropathic pain and age, disease duration, exercise adherence. There are different results regarding the relationship between age and neuropathic pain. While Choi et al found the neuropathic pain component to be associated with age in AS patients, a similar relationship was not found in the study of Gok et al.[18]. Due to the deterioration of pain inhibitor mechanisms with age, the frequency of chronic pain may increase in elderly patients[23]. Similar to the study conducted by Gok et al., in our study, there was no association between neuropathic pain and age. Since different mechanisms are involved in the pathogenesis of neuropathic pain in AS, a significant relationship may not be found.

Recognising neuropathic pain is important in AS patients' follow-up. Treatment alternatives are different, and failure of treatment could affect quality of life of patients. A relationship was found between neuropathic pain and impairment in quality of life. In the studies, quality of life, physical and emotional functions were evalueated with measurements as Ankylosing Spondylitis quality of life questionnaire,

Short Form 36, The Bath Ankylosing Spondylitis Functional Index, Nottinham Health Profile. The scores of quality of life, vitality, sleep, social and emotional role, physical mobility were found to be worse in patients with neuropathic pain[5,19].

Mechanism of neuropathic pain in AS is not clear. Wu et al. designed a study to show the neuropathic pain component in AS and the brain gray matter abnormalities associated with neuropathic pain symptoms. They reported thinning of the cortex, and increased gray matter volume in AS patients compared to the controls. In addition, neuropathic pain score (painDETECT) was correlated with decreased grey matter in primary somatosensory cortex and with increased gray matter in motor cortex, anterior cingulate cortex, prefrontal cortex, tahalamus and striatum. As well as brain gray matter abnormality, inflammatory mediators were found to be associated with local inflammation of spine without mechanical compression. This inflammatory radiculopathy also could cause neurologic symptoms[4]. In the pathogenesis of neuropathic pain, the role of neurotransmitters are also considered. Serum norepinephrine, dopamine, glutamate, seratonin levels were high in patients with neuropathic pain. Norepinephrine and seratonin are related to pain and have a role on regulating algesic and analgesic process. Neurotransmitters have regulatory effect on local neurocytes[17,24].

Neurological complications of AS are reported rarely in the literature. They have a wide spectrum from root sendroms- radiculopathies, to cauda equina syndrome and compression of the spinal cord - myelopathy. Assessment with electromyography in AS was studied in few study. Khedr et al assesed neurologic complications of AS in their study with 24 patients. They evaluated neuropathy according to electromyography (EMG) and they found 8% patients had neuropathic features. They also evaluated the radiculopathy and myleopathy according to somatosensory evoked potentials (SSEP) and motor evoked potentials (MEP) and they found in 50% patients SSEP abnormality and in 53% patients MEP abnormality[25-27]. Further studies are needed to determine whether neuropathic pain is a result of neurological complications.

Our study has some limitations. Electrophysiological evaluation was not performed on the patients. Evaluation of the somatosensory system with invasive or non-invasive diagnostic tests has also been suggested in the literature[21]. The patients were not evaluated for quality of life, physical functions, psychological status which can affect the neuropathic symptoms. The relationship between neuropathic pain and body mass index and smoking status were not assessed in the current study. However, there are limited studies in the literature investigating the association between neuropathic pain and AS. Our study will raise awareness about this issue. Using DN4 questionnaire for assesing neuropathic pain was strength of this study because it contains also clinical evaluation as well as patient report and questionnaire was administered by same clinician.

In conclusion, we showed that, in addition to inflammatory pain, neuropathic pain could also occur in patients with axSpA. Neuropathic pain could be associated with disease activity and can lead to an inaccurate assessment of disease activity. Previous studies have proven that neuropathic pain could lead to impaired quality of life and social/emotional role. Antiinflammatory treatment alternatives could be insufficient in patients with neuropathic pain. Evaluating of pain characteristics is important for management of patients. Further studies on the management of pain in axSpA are needed.

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