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ARAŞTIRMA / RESEARCH

Should central sensitization and neuropathic pain be considered in disease activity and treatment decision in axial ankylosing spondilitis?

Santral sensitizasyon bozukluğu aksiyel ankilozan spondilitte hastalık aktivitesini değerlendirmede dikkate alınmalı mıdır?

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Abstract

Purpose: The aim of this study was to evaluate the prevalence of central sensitization syndromes and the relation between severity of central sensitization and disease activity in patients with axial ankylosing spondylitis (AS).

Materials and Methods: Study included 105 patients who were diagnosed with AS. Patients' age, sex, body mass index (BMI), disease duration, accompanying disease (diabetes, hypertension) were recorded. The severity of back pain was assessed by visual analog scale (VAS), disease activity by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS_CRP). Central sensitization inventory (CSI) was used for central sensitization.

Results: Central sensitization was found in 45.7% of all participants and neuropathic pain was found in 34.3% of them. When we divided the group according to the central sensitization score ≥40, we found that those who were diagnosed with central sensitization were at an advanced age and have higher BMI, higher erythrocyte sedimentation rate, longer disease duration, higher disease activity, higher neuropathic pain presence and scores than others.

Conclusion: Central sensitization syndromes and neuropathic pain are frequently associated with AS. Positive correlations of central sensitization and neuropathic pain scores with disease activity scores support that chronic pain components should be taken into consideration in the follow-up of the disease.

Keywords: Ankylosing spondylitis, central sensitization, neuropathic pain, disease activity, chronic pain

Öz

Amaç: Bu çalışmanın amacı, aksiyel ankilozan spondilit'li (AS) hastalarda santral sensitizasyon sendromlarının prevalansını ve santral sensitizasyonun şiddeti ile hastalık aktivitesi arasındaki ilişkinin değerlendirilmesidir.

Gereç ve Yöntem: Çalışmamız, AS tanılı 105 hastayı içermektedir. Hastaların yaşı, cinsiyeti, vücut kitle indeksi (VKİ), hastalık süresi, eşlik eden hastalık (diyabet, hipertansiyon) kaydedildi. Bel ağrısının şiddeti görsel analog skala (VAS) ile, hastalık aktivitesi Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI), Bath Ankilozan Spondilit Fonksiyonel İndeks (BASFI) ve Ankilozan Spondilit Hastalık Aktivite Skoru-C-reaktif protein (ASDAS_CRP) ile değerlendirildi. Santral sensitizasyon için santral sensitizasyon envanteri (CSI) kullanıldı.

Bulgular: Tüm katılımcıların %45.7'sinde santral sensitizasyon, (SS) % 34.3'ünde nöropatik ağrı saptandı. Grubu santral sensitizasyon skoru ≥40'a göre ayırdığımızda, santral sensitizasyon tanısı alanlarda ileri yaş, yüksek VKI, yüksek eritrosit sedimentasyon hızı (ESR), uzun hastalık süresi, yüksek hastalık aktivitesi), yüksek nöropatik ağrı varlığı ve skorları tespit ettik..

Sonuç: Santral sensitizasyon sendromları ve nöropatik ağrı sıklıkla AS ile ilişkilidir. Santral sensitizasyon ve nöropatik ağrı skorlarının hastalık aktivite skorları ile pozitif korelasyonu, hastalık takibinde kronik ağrı bileşenlerinin dikkate alınması gerektiğini desteklemektedir.

Anahtar kelimeler: Ankilozan spondilit, nöropatik ağrı, hastalık aktivitesi, kronik ağrı, santral sensitizasyon

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INTRODUCTION

Ankylosing Spondylitis (AS) is a progressive and inflammatory joint disease that causes chronic back pain[1]. It is also known as radiographic axial spondyloarthritis (SpA), typically at an early age and affects the axial skeleton and may result in spinal ankylosis. The etiology of the disease is not clear except for the genetic predisposition associated with HLA B27 antigen. The clinic of the disease is characterized by chronic inflammatoy pain in the lumbar region or in the sacral area. Apart from the axial skeleton, it may also involve peripheral involvement with enthesitis, arthritis and dactilitis. Entesis is the most pathognomonic finding for all SpA. Magnetic resonance imaging may aid early diagnosis without structural lesions. Treatment includes nonsteroidal anti-inflammatory drugs, conventional and biologic disease modifying anti-rheumatic drugs (DMARDs), tumor necrosing factor-alpha blockers and current IL-17 blocking agents[1,2].

Nowadays, chronic pain is considered as a 'separate disease in itself' besides being the main symptom in rheumatic diseases. Continuation of chronic pain is provided by central sensitization. The central and peripheral nervous system involve different frequencies and mechanisms and pathogenesis of rheumatic diseases. Pain is a versatile phenomenon and involves both synovitis (both cytokine release pathway) and peripheral and central pain-sensitization mechanisms in inflammatory arthritis[3]. Central sensitization (CS) is an abnormal pain management mechanism involving the central nervous system[4]. Central sensitization synaptic plasticity is an increased neuronal response phenomenon in central pain pathways following painfull stimulation. According to the current knowledge, CS is caused by neuroinflammation in the peripheral and central nervous system. The result is the release of cytokines and chemokines in the spinal cord and brain. Central cytokines and chemokines are powerful neuromodulators in the development of hyperalgesia and allodynia. Ongoing release of cytokines and chemokines increases chronic widespread pain in the whole body. In this respect, neuroinflammation causes chronic widespread pain through CS[5].

In some chronic rheumatic diseases such as fibromyalgia, osteoarthritis and rheumatoid arthritis, some patients complain of high pain even during the remission periods. This result suggests that CS may play a role in this clinic situation. Here, we examined the relation of CS and neuropathic pain with disease activity in patients with axial AS.

MATERIALS AND METHODS

Study is designed as prospective and descriptive. One hundred and five (N=105) patients (20 to 76 years old) with axial AS diagnosis according to the 2010 Assesment in Ankylosing Spondylitis International Society (ASAS) Classification Criteria[6], who were admitted to Rheumatology outpatient clinic were included to the study. All participants were follow-up patients, and their examinations were performed by the same experienced physician. The study was approved by the Kahramanmaraş Sütçü İmam University, Faculty of Medicine, regional committee for ethics (protocol no:2018/178) in medical research and complied with Helsinki criteria.

Patients' age, sex, body mass index (BMI), disease duration, accompanying disease (diabetes, hypertension), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded. The severity of back pain was assessed by visual analog scale (VAS), disease activity by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[7], Bath Ankylosing Spondylitis Functional Index (BASFI)[8] and Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS_CRP)[9]. For these three scores, automatic calculation formulas were used on internet. BASDAI> 4; ASDAS_CRP>3.5 were accepted as cut-off value for high disease activity. A visual analog scale (VAS: from 0 = no pain to 10 = the worst pain) is usually used to assess general pain and fatigue.

All AS disease activity scales, sensitization and neuropathic pain scales were applied to all axial AS patients who met the inclusion criteria with the assistance of nurse in outpatient clinic[10].

Measures

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

This scale was used to measure patient-reported disease activity in patients with AS. The instrument was first published in 1994 using visual analog scales.

Bath Ankylosing Sponylitis Functinal Index (BASFI)

This scale was used o define and monitor physical functioning in patients with AS. The index was developed in 1994 using visual analog scales.

Ankylosing Spondylitis Disease Activity Score (ASDAS)

This scale was used to measure disease activity in ankylosing spondylitis (AS) based on a composite score of domains relevant to patients and clinicians, including both self-reported items and objective measures.

Evaluation of Central Sensitization and Neuropathic Pain

For the diagnosis of central sensitization, the presence of neuropathic pain was evaluated and the central sensitization inventory (CSI part A) was used [11,12]. All patients were questioned for CS syndromes (restless leg syndrome, chronic fatigue syndrome, fibromyalgia, temporomandibular joint disease, migraine/headache, irritable bowel syndrome, multiple chemical sensitivities, chronic neck pain, anxiety/panic attack, depression) (CSI part B). Self-Leased assesment of neuropathic symptom and signs (S_LANNS) and Pain-detect questionnaire association were used for the presence of neuropathic pain.

Patients with a history of diabetes, polyneuropathy (alcohol, idiopathic .), psychiatric or cognitive impairment, cerebrovascular disease, pregnancy, malignancy, rheumatic diseases other than AS and spinal surgery were excluded from the study. All groups were divided into two groups with central sensitization presence and then parameters were compared.

Central Sensitization Classification Criteria

The awareness of CS and its primer importance in chronic pain assessment and control is increasing. But there is no gold standard yet in its classification. The classification of central sensitization consists of two main steps: the exclusion of neuropathic pain and the differential diagnosis of CS pain instead of nociceptive.

Then you have to scan 3 main classification criteria. Firstly disproportionate pain, implying that the severity of pain and related reported or perceived disability are disproportionate to the nature and extent of injury or pathology (i.e., tissue damage or structural impairments). The 2 remaining criteria are 1) the presence of diffuse pain distribution, allodynia, and hyperalgesia; and 2) hypersensitivity of senses unrelated to the musculoskeletal system (defined as a score of at least 40 on the central sensitization inventory) [11].

The Central Sensitization Inventory (CSI)

It is a valid and reliable patient-reported instrument designed to identify patients whose presenting symptoms may be related to central sensitization (CS). Part A of the CSI measures a full array of 25 somatic and emotional symptoms associated with CS, and Part B asks if patients have previously been diagnosed with one or more specific central sensitivity syndromes and related disorders. In a study by Neblett et al, they identified a clinically significant level of 40 as providing both good sensitivity and specificity for the presence of central sensitization syndrome[12,13]. Turkish validation of the inventory was done by Düzce et al. from Trakya University Department of Physical Medicine and Rehabilitation[14].

Self-Leeds Assesment Of Neuropathic Symptoms (S-LANNS):

The LANSS pain scale was developed to identify patients with chronic pain whose pain is predominated by neuropathic mechanisms. It has been validated in a number of settings. The usefullness of the LANSS is limited, however, by the need for clinical examination by a physician, and although the examination involves only a pinprick or syringe and cotton, it can be time-consuming and is thus unsuitable for large-scale studies. The S-LANSS is derived from the LANSS, for which the validity and reliability as a diagnostic tool for neuropathic pain are established. The S-LANSS is a self-administered test comprising a total of five items regarding pain symptoms, and subjects are instructed to perform self-examinations to determine the presence of allodynia and altered sensation. The scores of ≤12 indicating low probability of neuropathic pain[15-17].

Pain Detect Questionnaire

In co-operation with the German Research Network on Neuropathic Pain we developed and validated the pain *DETECT* questionnaire (PD-Q). The PD-Q is a reliable screening tool with high sensitivity,

specificity and positive predictive accuracy.

PDQ comprises a main component along with two additional components. In the main component, termed as "gradation of pain," the patient is asked to identify the presence of seven pathological pain sensations: burning, tingling, or prickling sensations, tactile and thermal allodynia, electric shock-like sensations, numbness, and pressure-evoked paIn sensation. The patient grades the presence of each type of pain as follows: 0 = never; 1 = hardly noticed; 2 = slightly; 3 = moderately; 4 = strongly; 5 = very strongly.

This main component of PDQ yields scores from 0 to 35 points. A second component of PDQ, termed as "pain course pattern," is a multiple-choice questionnaire accompanied by four pain charts; the patient is asked to quantify the pattern of experienced pain as follows: persistent pain with slight fluctuations (0 points); persistent pain with pain attacks (−1 point); pain attacks without pain between them (1 point); paIn attacks with pain between them (1 point). The third component of PDQ, termed "radiating pain," asks patients regarding radiation of paIn to other regions of the body (2 points). A total score is calculated by adding the scores from the three components; a high score indicates that the pain is possibly neuropathic in nature. The scores of ≤12 indicating low probability of neuropathic pain18,19.

Statistical analysis

All statistical analyses were performed using SPSS ver. 21.0 program (SPSS Inc., Chicago, IL, USA). All data are presented as mean and standard deviation or median. Data were compared between group 1 (CSI score < 40) and group 2 (CSI score ≥ 40). Continuous variables were analyzed using *t* test while categorical data were analyzed using Chi-squared test or Fisher's exact test where appropriate for two independent samples. Descriptive analyses were based on frequencies and percentages for categorical variables, and mean and standard deviation for continuous variables.

Spearman correlation analysis was used to evaluate the association between BASDAI and BASFI score with CSI score. The differantial diagnosis 'neuropathic pain' is exluded by S-LANSS and Pain-detect (score>12) inventories. A *p* value < 0.05 was considered statistically significant.

RESULTS

Thirty-four (N=34) female and 71 male axial AS patients were included in the study with a mean age of 38 ± 12.1 years. The mean duration of illness was 9.8 ± 12.4 years. The mean BMI was 27 ± 4.8 kg / m^2. The descriptive data for the study are summarized in Table 1. Central sensitization was found in 45.7% of all participants and neuropathic pain was found in 34.3% of them. In central sensitization syndromes, 31.4% has RLS, 43.8% has chronic fatigue syndrome, 29.2% has fibromyalgia, 8.6% has temporomandibular joint problem, 31.4% has migraine/headache, 20% has irritable bowel syndrome, 24.8% has chemical hipersensensitivity, 20% has chronic neck pain (miyofascial syndrome), 25.7% has anxiety / panic attack, 25.7% has depression. The median number of CS syndromes was 3. When we divided the group according to the CS score ≥40, we found that those who were diagnosed with central sensitization were at an advanced age and have higher BMI, higher ESR, longer disease duration, higher disease activity (BASDAI, ASDAS_CRP, BASFI), higher neuropathic pain presence and scores (S_LANNS and Pain detect) than others (Table 2).

In correlation analysis central sensitization score was positively correlated with age (rho = 0.379, p = 0.00), duration of illness (rho = 0.337; p = 0.00), BMI (rho = 0.317; p = 0.001), ESR (rho = 0.353; p = 0.00), ASDAS_CRP (p = 0.00), BASFI (rho = 0.642, p = 0.00), S_LANSS score (rho = 0.474, p = 0.00), pain detect score (rho = 0.604, 0.00), BASDAI_2 (rho = 0,535, p = 0.00), BASDAI_3 (rho = 0,624, p = 0.00), BASDAI_6 (rho = 0,279, p = 0.004). The association of CS presence with disease activity parameters were shown at Figure 1a, b, c, d. In correlation analysis S_LANNS neuropathic pain score was positively correlated with BASFI (rho=0,266; p=0,013), BASDAI_2 (rho=0,49; p=0,00), BASDAI_3 (rho=0,312; p=0.00), BASDAI_6 (rho=0.285; p=0.00), BASDAI_1 (rho=0,45; p=0.00), BASDAI_total (rho=0,478; p=0.00), ASDAS_CRP (rho=0,483; p=0,00) and BMI (rho=0,219; p=0,026). When we divide the group according to gender; in females the presence of central sensitization (p = 0,004), central sensitization score (p = 0,001), migraine / headache (p = 0,027), BASDAI_total (p = 0,026), BASDAI_1 (p = 0,036), BASDAI_3 (p = 0,005) and ESR (p = 0,001) were significantly higher.

Table 1. The descriptive characteristics of the group

Variable	N=105/mean±std/median
Age (year)	38±12.1
Gender (M/F)	71/34
BMI (kg/m²)	27±4.8
Disease duration (year)	Median 6 (min-max/1-32)
ESR (mm/h)	12.5±10.1
CRP (mg/L)	16.4±81.4
BASDAI (0-10)	4.1±2
ASDAS_CRP	2.7±1
BASFI (0-10)	3.6±2.3
BASDAI_1 (0-10)	5.1±2.3
BASDAI_2 (0-10)	5.4±2.3
BASDAI_3 (0-10)	3.3±2.5
BASDAI_6 (0-10)	1.3±2
The number of central sensitization syndrome	Median 3(min-max/0-10)
Central sensitization presence (≥40)	48/45.7%
Central sensitization score (CSI)	35.8±19.1
Neuropathic pain presence (>12)	36/34.3%
S_LANNSS score	9.7±7.4
Pain detect score	12±7.7

BMI: body mass index: ESR: Erythrocytes sedimentation rate. CRP: C-reactive protein; BASDAI: Bath Ankylosing spondylitis disease activity index; BASDAI_1: How would you describe the overall level of fatigue/tiredness you have experienced? BASDAI_2: How would you describe the overal level of AS neck, back or hip pain you have had? BASDAI_3: How would you describe the overal level of pain/swelling in joints other than neck, back, hips you have had? BASDAI_6: How long does your morning stiffness last from the time you wake up? ASDAS_CRP: Ankylosing spondylitis disease activity score-C-reactive protein.

Table 2. Comparison of the groups according to the presence of central sensitization (CS)

	CSI score≥40 (N=50) mean±std	CSI score<40 (N=55) mean±std	*P*
Age* (year)	42.1±12.5	34.5±10.8	0.001
Gender (F/M)	22/28	10/45	0.2
BMI* (kg/m²)	28.6±5.2	25.7±4	0.002
ESR* (mm/h)	15.2±9.9	10.2±9.7	0.015
CRP (mg/dL)	11.1±12.5	7.5±11	0.11
Disease duration*(year)	10.3±7.3	6.8±5.9	0.009
BASDAI_1* (0-10)	6.4±1.9	4.1±2.1	0.00
BASDAI_2*(0-10)	6.5±2.1	4.4±2	0.00
BASDAI_3*(0-10)	4.8±2.3	2.1±2	0.00
BASDAI_6*(0-10)	1.9±2.6	0.8±0.8	0.005
BASDAI_total*(0-10)	5.2±1.7	3.1±1.7	0.00
BASFI*(0-10)	4.8±2.3	2.6±1.8	0.000
ASDAS_CRP*	3.3±1	2.2±0.6	0.000
Restless leg syndrome	14	19	0.7
Chronic fatigue syndrome	25	21	0.096
Fibromyalgia	18	13	0.17
Temporomandibuler joint symptom	4	5	0.87
Migraine/headache	16	17	0.331
Irritable bowel syndrome	12	9	0.104
Chemical hypersensitivity	13	13	0.32
Chronic neck pain	8	14	0.35
Anxiety/panic attack	11	16	0.87
Depression	15	13	0.20
Number of CSS	3.6±2.5	3±3.4	0.39
CSI Score*	52.2±12.6	22±10.8	0.000

Neuropathic pain presence*	29	7	0.007
S_LANSS score*	13.2±7.1	6.9±6.4	0.000
Pain detect score*	16.6±6.8	8.2±6.2	0.000

BMI: body mass index: ESR: Erythrocytes sedimentation rate. CRP: C-reactive protein; BASDAI: Bath Ankylosing spondylitis disease activity index; BASDAI_1: How would you describe the overall level of fatigue/tiredness you have experienced? BASDAI_2: How would you describe the overall level of AS neck, back or hip pain you have had? BASDAI_3: How would you describe the overal level of pain/swelling in joints other than neck, back, hips you have had? BASDAI_6: How long does your morning stiffness last from the time you wake up? ASDAS_CRP: Ankylosing spondylitis disease activity score-C-reactive protein; CSS: central sensitization syndromes; CS: central sensitization; S_LANSS: Self-Leeds Assesment of Neuropathic Symptoms; BASFI: Bath Ankylosing spondylitis functional index. *statistically significance, p<0.05

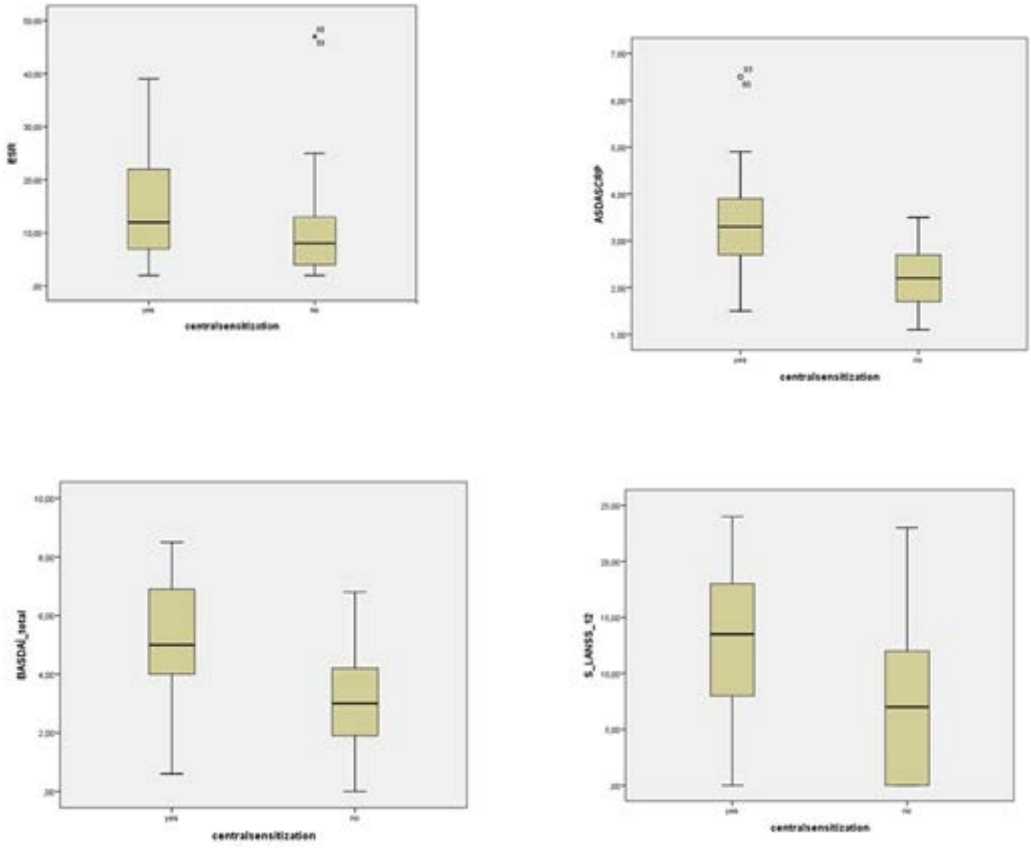

Figure 1a,b,c,d. The association of CS presence with disease activity parameters.

When we excluded the group with neuropathic pain presence, in the remaining group (N = 64), central sensitization presence was 28.1% (N = 18) and mean CS score was 28.1 ± 17. When we divided the group into two groups as CS and non CS group, we found that age (p = 0,044), gender (p = 0,042), BMI (p = 0,044), ESR (p = 0,025), BASDAI_2 (p = 0,002), BASDAI_3 (p = 0.00), chronic fatigue syndrome (p = 0,03), chemical sensitivity (p = 0,001), BASDAI_6 (p = 0,003), pain detect score (p = 0,000), and BASFI (p = 0,007) scores were found higher in CS group.

DISCUSSION

We observed the presence of neuropathic pain in one third and central sensitization in half of the group. These ratios are quite high compared to the general population. These both scores were also positively correlated with disease activity scores. We also observed that the CS-diagnosed group consists of people with an advanced age, high BMI, long disease duration, high ESR, high disease activity scores such as BASDAI, BASFI, ASDAS_CRP and

neuropathic pain scores. In addition, CS score was positively correlated with age, BMI, disease duration, disease activity scores and neuropathic pain scores. Also in females central sensitization presence and score, migraine / headache presence, BASDAI_1 (How would you describe the overall level of fatigue / tiredness you have experienced?), BASDAI_3 (How would you describe the overall level of pain /, hips you have had?), total BASDAI scores was found significantly higher than males.

The association of nociceptive (inflammatory) and neuropathic pain components in chronic painful joint disorders describes joint inflammation, structural changes, pain intensity, inconsistencies between sensory disorders in the peri-articular tissues[20]. Numerous evidence has been obtained that the neuroinflammation from the peripheral and central nervous system serves as a pivot in the continuation of chronic pain. Immune cell infiltration into the peripheral nervous system and activation of glial cells such as microglia and astrocytes in the central nervous system increase the production of secretory proinflammatory cytokines and chemokines. These mediators promote neuroimmune activation and can sensitize primary afferent neurons and contribute to pain hypersensitivity[21]. In the last years, the Janus kinase (JAK), the signal transducer of activation (STAT) pathway has been recognized as a pivotal component in both the inflammatory process and in the central nervous system[3]. Central sensitization is the psychological phenomenon that the central nervous system neurons are hyper-excitable. A painful or non-painful stimulus results in hypersensitivity.

Treatment of chronic pain types such as inflammatory pain and neuropathic pain is difficult and inadequate. Tissue damage, inflammation or injury of the nervous system may result in chronic neuropathic pain characterized by increased sensitivity to painful stimuli (hyperalgesia), the perception of innocuous stimuli as painful (allodynia) and spontaneous pain[22]. Recently, it has become clear that inflammatory and immune mechanisms both in the periphery and in the central nervous system play an important role in neuropathic pain[23]. A small number of clinical trials with the inherent presence of neuropathic pain in AS have found a positive correlation with disease activity [2]. Choi JH et al[24] showed that neuropathic pain component is associated with age, high disease activity, presence of current enthesitis, and depression similar with our study. Gok K et al.[25] observed that neuropathic component may be important in axial SpA patients with negative effect on disease severity, unlike the nonaxial group similar with our study. Wu Q and et al[26] have reported that abnormal brain gray matter and neural correlates of neuropathic pain are concordant with the clinical picture of AS, which includes sensorimotor and mood deficits as well as neuropathic pain symptoms. The study suggests that back pain is a mixed pain condition that includes a neuropathic pain component[27]. In all inflammatory rheumatic diseases, even if not initially, symptoms such as chronic pain and fatigue related with neuropathic pain and central sensitization continue to persist even after the primary disease is in remission. In many clinical studies, many central sensitization syndromes, especially fibromyalgia, are associated with rheumatic diseases. Underlying new pathophysiological pathways will emerge to explain this relationship.

In the study of Bevilaqua-Grossi D et al[21], CS associated with allodynia and hyperalgesia in osteoarthritis (OA) patients was found to correlate with mild-moderate joint damage. Huysmans et al[27] found that symptoms of CS were significantly associated with psychosocial and cognitive behavioral factors in patients with chronic nonspecific low back pain. The role of central sensitization in OA-related chronic pain[28], fibromyalgia[29], unilateral shoulder [30], and nontraumatic neck pain[31] has been demonstrated by numerous literature data. The presence of neuropathic pain accompanying these diseases requires the addition of centrally acting drugs such as anticonvulsants in addition to anti-inflammatory therapy. However, up to date there is no study about the CS in AS. We are the first study to reveal the relation of AS with CS in our country. We may say that we should consider the CS and neuropathic pain in considering the disease activity and medical management in patients with AS. We should consider if ever the primary rheumatic disease active or not? Many disease activity scales consist of CS findings.

Central pain syndromes are syndromes associated with central nervous system changes that increase peripheral input and / or normalize the face of pain when there is no painful stimulus. Central sensitization syndromes (CSS) are used to describe

nonspecific disorders such as fibromyalgia, chronic fatigue, irritable bowel syndrome, chronic pelvic syndromes, migraine and temporomandibular disorders [30-33]. We observed the presence of at least three CSS in each AS patient. AS patients should be questioned regarding the existence of these syndromes. Patients complain of widespread pain accompanied by fatigue, mood disorder, abdominal discomfort and low quality of life. The lack of multiple co-morbid symptoms and underlying etiology makes it difficult to treat these syndromes. The abnormal regulation of the hypothalamopituitaradrenal axis is often accompanied by these disorders. This axis is the primer stress response system and its activation results in reduced cortisol release and breakdown of the immune response. This explains the neuronal link between immunity and inflammation.[22]

In our study, we found central sensitization and neuropathic pain scores correlated with disease activity scores, so we need to take into account these two central pain management processes in the diagnosis and follow-up of AS. The same can be said for most chronic painful rheumatic diseases. Many of the disease activity scores are based on subject's subjective complaints (such as BASDAI). Similar results have been obtained for ASDAS_CRP, which has become more widespread in recent years. In our study ESR was also found significantly high in the CS group. In the other hand ESR and CRP were not correlated with CS and neuropathic pain scores. When we performed statistical analysis excluding the presence of neuropathic pain, we obtained similar results with a decrease in number of patients. CS is correlated with disease activity independently of neuropathic pain.

Advanced age, long-lasting disease, obesity, high disease activity and female gender appear to be increasing CS. There are some limitation in the study. We diagnosed central sensitization according to the CS score and exclusion of neuropathic pain. Allodynia and hyperalgesia were not questioned.

The limitation of our study is that group consisted mostly of overweight patients. Obesity may also have an effect on central sensitization and neuropathic pain scores.

In AS, both neuropathic pain and CS are correlated with disease severity. Chronic pain components require a different approach in the diagnosis, follow-up and treatment of AS. Neuropathic pain and central sensitization should be questioned especially in AS (axial) patients with an advanced age, female gender, high BMI, long term disease duration, high disease activity.

Yazar Katkıları: Çalışma konsepti/Tasarımı: TTK; Veri toplama: HG; Veri analizi ve yorumlama: TTK; Yazı taslağı: TTK; İçeriğin eleştirel incelenmesi: TTK; Son onay ve sorumluluk: TTK, HG, GYÇ; Teknik ve malzeme desteği: HG, GYÇ; Süpervizyon: TTK; Fon sağlama (mevcut ise): yok.
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