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Orjinal Araştırma / Original Article

The Impact of Fibromyalgia in Disease Activity Assessment and Treatment Response in Axial Spondyloarthritis

Aksiyal Spondiloartritte Fibromiyaljinin Hastalık Aktivitesi Değerlendirilmesine ve Tedavi Yanıtına Etkisi

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Abstract

Aim: Spondyloarthritis represents a group of diseases with common clinical features. When axial symptoms are predominant, the disease is called axial SpA (axSpA). Fibromyalgia frequently accompanies rheumatological diseases and affects the evaluation of disease activity measurements and treatment responses. In this study, we aimed to compare axSpA patients with and without accompanying fibromyalgia syndrome (FS).

Material and Method: The patients with axSpA were retrospectively reviewed according to the Assessment of Spondyloarthritis international Society classification criteria. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), erythrocyte sedimentation rate, and C-reactive protein data were used to evaluate disease activity. The Bath Ankylosing Spondylitis Functional Index (BASFI) was used to evaluate the functional status of the patients.

Results: The study included a total of 300 patients, including 162 (54%) males and 138 (46%) females. The median age of the patients (25%-75% IQR) was 35 (30-46) years. In the comparison of the two axSpA groups with and without FS, age, BASFI, ESR and CRP levels, and the rate of receiving biological therapy were similar. In the FS group, female gender was dominant (n=46, 92%; p=0.000) and the rates of peripheral arthritis and BASDAI were significantly higher (p=0.024 and p=0.004, respectively).

Conclusion: AxSpA is frequently accompanied by FS, especially in women. The symptoms of FS cause an increase in disease activity scores. Therefore, it is evaluated as low treatment response. The disease activity of FS and axSpA should be carefully evaluated to lower treatment costs and apply more accurate treatment.

Keywords: Axial spondyloarthritis, fibromyalgia, disease activity, treatment response

Öz

Amaç: Spondiloartritler, ortak klinik özellikleri olan bir grup hastalığı temsil eder. Aksiyal semptomların baskın olduğu aksiyal SpA (axSpA) olarak tanımlanır. Fibromiyalji sıklıkla romatolojik hastalıklara eşlik eder ve hastalık aktivitesi ölçümleri ve tedavi yanıtlarının değerlendirilmesini etkiler. Bu çalışmada, axSpA'da eşlik eden fibromiyalji sendromu olan hastaları, axSpA hastaları ile karşılaştırmayı amaçladık.

Gereç ve Yöntem: Aksiyel spondiloartritli hastalar, Assessment of Spondylo Artritis International Society sınıflandırma kriterlerine göre geriye dönük olarak incelendi. Bath AS Hastalık Aktivite Endeksi (BASDAI), eritrosit sedimantasyon hızı ve c-reaktif protein verileri hastalık aktivitesine erişmek için kullanıldı. Hastaların fonksiyonel durumlarını değerlendirmek için Bath AS Fonksiyonel İndeks (BASFI) kullanıldı.

Bulgular: Çalışmaya 162 (% 54) erkek ve 138 (% 46) kadın olmak üzere toplam 300 hasta dahil edildi. Hastaların ortanca yaşı (25-75 IQR) 35 (30-46) idi. İki grubun karşılaştırılmasında: axSpA ve FM+axSpA; yaş, BASFI, ESR ve CRP seviyeleri ve biyolojik tedavi alan hastaların oranı benzerdi. AxSPA+FM grubunda kadın cinsiyet dominant 46 (% 92) (p=0.000), periferik artrit ve BASDAI anlamlı olarak yüksekti (p=0.024, p=0.004).

Sonuç: AxSpA'ya özellikle kadınlarda sıklıkla FM eşlik eder. FM semptomları hastalık aktivite skorlarında artışa neden olur. Bu nedenle düşük tedavi yanıtı olarak değerlendirilir. FM ve axSpA'nın hastalık aktiviteleri, daha düşük tedavi maliyetleri ve daha doğru tedavi için dikkatlice değerlendirilmelidir.

Anahtar Kelimeler: Aksiyel spondiloartrit, fibromiyalji, hastalık aktivitesi, tedavi yanıtı

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INTRODUCTION

Spondyloarthritis (SpA) refers to a group of inflammatory arthritis diseases with spinal involvement, which generally present with chronic inflammatory back pain. Ankylosing spondylitis is a prototype of SpA. Undifferentiated SpA, psoriatic arthritis, reactive arthritis, and inflammatory bowel disease-related SpA are all considered to be among this group of diseases.[1] SpA can be clinically classified into two subgroups as axial SpA (axSpA) in which the signs and symptoms of sacroiliac joint involvement (sacroiliitis) and spinal involvement (spondylitis) are predominant, and peripheral SpA, in which peripheral joint involvement is prominent.[2] If sacroiliitis is detected on x-ray, the disease is described as radiographic axSpA and if detected on MRI, it is referred to as non-radiographic axSpA. However, it remains unclear whether these concepts represent two distinct entities or a single spectrum of different chronologies and disease severities.[3,4]

Fibromyalgia syndrome (FS) is the most common cause of chronic musculoskeletal pain with an unclear pathophysiology and etiology. Pain, fatigue, psychiatric symptoms, somatic symptoms and cognitive disorders are the clinical features of disease.[5,6] FS frequently accompanies rheumatological diseases, such as rheumatoid arthritis, Sjogren's syndrome, and SpA. This association affects the evaluation of disease activity measurements and treatment responses due to the effect of this syndrome on patient symptoms.[7] Therefore, FS in rheumatologic diseases is an important factor in terms of disease and treatment management.

In this study, we aimed to compare axSpA patients with and without accompanying FS in terms of demographic characteristics, clinical characteristics, disease activity assessment, and treatment response.

MATERIAL AND METHOD

This cross-sectional study included 300 patients diagnosed with axSpA according to the following criteria of the Assessment of the Spondyloarthritis International Society (ASAS): 1) sacroiliitis detected in the radiological evaluation the presence of at least one SpA feature or 2) two SpA features in patients with a positive HLA-B27 gene test. The SpA features are inflammatory low back pain, high C-reactive protein (CRP), good response to non-steroidal anti-inflammatory drugs (NSAIDs), HLA-B27 positivity, enthesitis, arthritis, dactylitis, uveitis, psoriasis, inflammatory bowel disease, and a family history of SpA.[8]

The American College of Rheumatology (ACR) 2010 criteria were used in the diagnosis of FS.[9] Patients with an inflammatory joint disease other than SPA, history of cancer, uncontrolled diabetes, and active inflammatory bowel disease were excluded from the study. Peripheral involvement, HLA-B27 positivity, uveitis, family history, drugs, treatment responses, and demographic data of the patients were analyzed. Disease activity was determined using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[10] erythrocyte sedimentation rate (ESR), and CRP. Functional status was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI).[11] The two groups, namely the patients with axSpA alone and those with axSpA+FS were compared.

Ethics committee approval was obtained from the Clinical Studies Ethics Committee of Adıyaman University with the decision numbered 2018/8-1 and conducted in accordance with the principles of the Declaration of Helsinki. Statistical data were analyzed with SPSS version 20. In statistical analyses, categorical variables were given as numbers (%) and continuous variables as median (25-75 IQR) values. The two groups were compared with the Mann-Whitney U test, and the categorical variables were compared with the chi-square and Fisher's tests. A p value of <0.05 was considered significant.

RESULTS

A total of 300 patients, 162 (54%) male and 138 (46%) female, were included in the study. The median age of the patients (25-75 IQR) was 35 (30-46) years. The median (25-75 IQR) delay in diagnosis (time from the first symptom to diagnosis) was 4.5 (3-6.5) years. The median (25-75 IQR) age at diagnosis was 32 (26-41) years. HLA-B27 was positive in 130 patients (43.3%). Among the parameters used in the evaluation of the disease, the median (25-75 IQR) BASDAI was 4.1 (3.1-5.6) and BASFI was 3.6 (3.1-5.3). The median (25-75 IQR) ESR was 13 (11-17) mm/hr, and the median (25-75 IQR) CRP was 3.0 (2.0-6.0) mg/dl (**Table 1**). A total of 101 (33.6%) patients were under antitumor necrosis factor (anti-TNF) or secukinumab (biological therapy) treatment, and 199 (66.4%) patients were using NSAIDs and/or sulfasalazine.

Table 1. Demographic and clinical characteristics of the patients

	Patients (n=300)
Age	35 (30-46)
Age at diagnosis	32 (26-41)
Delay in diagnosis (years)	4.5 (3-6.5)
Gender	
Male	162 (54%)
Female	138 (46%)
HLA-B27 positivity	130 (43.3%)
BASDAI	4.1 (3.1-5.6)
BASFI	3.6 (3.1-5.3)
ESR (mm/h)	13 (11-17)
CRP (mg/dl)	3 (2-6)

Values are given as median (25-75% IQR) or number (%). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

In the comparison of two axSpA and axSpA+FS groups, current age, age at diagnosis, delay in diagnosis, enthesitis, uveitis, BASFI, ESR and CRP levels, the rate of patients receiving biological therapy, and the rate of radiographic axSpA were

similar (p=0.079, p=0.075, p=0.880, p=0.540, p=0.086, p=0.174, p=0.452, p=0.221, p=0.181, and p=0.494, respectively). The number of male patients was significantly higher in the axSpA group (63.2%) while female gender was dominant in the axSpA+FS group (n=46, 92%) (p=0.000). Peripheral arthritis and BASDAI were significantly higher in the axSpA+FS group (p=0.024 and p=0.004, respectively). HLA-B27 positivity was found to be higher in the axSpA group (46%), but this was not statistically significant (p=0.337) (**Table 2**).

Table 2. Comparison of the clinical characteristics of the groups

	Axial SpA+Fibromyalgia (n=50)	Axial SpA (n=250)	p value
Age	38 (34.5-48)	35.5 (31-45)	0.079
Age at diagnosis	35 (31.5-40.5)	31 (27-40)	0075
Delay in diagnosis (years)	3.5 (3-8)	4 (3-6.5)	0.880
Gender			0.000*
Male	4 (8%)	158 (63.2%)	
Female	46 (92%)	92 (36.8%)	
Peripheral arthritis	6 (12%)	14 (5.6%)	0.024*
Enthesitis	12 (24%)	50 (20%)	0.540
Uveitis	6 (12%)	15 (6%)	0.086
HLA-B27 positivity	15 (30%)	115 (46%)	0.337
BASDAI	6.1 (4.1-7.1)	4.2 (3.3-5.4)	0.004*
BASFI	4.1 (3.3-5.2)	3.6 (3-5.2)	0.174
ESR (mm/h)	12 (8.5-14.5)	13 (11-17)	0.452
CRP (mg/dl)	3 (2-4.6)	3 (2-6)	0.221
Biological therapy	16 (32%)	75 (30.0%)	0.181
Radiographic sacroiliitis	10 (20%)	75 (30.0%)	0.494

Values are given as median (25-75% IQR) or number (%). * $p < 0.05$ was considered statistically significant. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

DISCUSSION

The clinical features of SpA include axial system involvement, peripheral arthritis, enthesitis, uveitis, dactylitis, and HLA-B27 positivity.[12] The ASAS diagnostic criteria defined in 2009 have high diagnostic sensitivity and specificity.[13] However, the ASAS criteria may also cause misdiagnosis or overdiagnosis in cases where there is no objective evidence of inflammation or structural damage, and especially in the presence of other diseases that may cause pain, such as FS.[14] The similar clinical features of FS and axSpA (chronic low back pain, sleep disorder, fatigue, and mood disorders) is an important reason for the difficulty in the diagnosis and differentiation of these two diseases. In addition, this situation leads to an incorrect evaluation of SPA treatment response.[15]

FS frequently accompanies rheumatological diseases. In a previous study, the frequency of FM in axSpA was reported between 4% and 17.2%, and significantly higher in women.[16] The female-male ratio of FS was found to be 3.8/1 in ankylosing spondylitis patients and 5.6/1 in axSpA.[15,16] Consistent with previous studies, in our study, female gender was significantly predominant in patients with axSpA accompanied by FS (92%, p=0.000). The clinical features of enthesitis, uveitis and HLA-B27 positivity were similar in the two groups (p=0.540, 0.086, and 0.337, respectively), but peripheral arthritis was more common in the axSpA+FS group (p=0.024). As a result, there was no significant difference in clinical features between the axSpA+FS group compared to the axSpA group.

In SPA, BASDAI is frequently used in evaluating disease activity and BASFI for measuring functional status. In a previous study, it was found that if AS and FM coexist, higher BASDAI and BASFI values were observed in these patients compared to them alone.[17] In a Spanish study of 462 patients, it was observed that the presence of FM in AS patients significantly affected the BASDAI and BASFI scores and caused deviations in the results.[18] In our study, BASFI values of the groups were similar (p=0.174). Among the disease activity parameters, ESR and CRP values were similar between the groups. However, BASDAI was found to be significantly higher in the axSpA+FM group (p=0.004). Since BASDAI is a subjective, inquiry-based index, it can result in an increase in the score of patients with coexisting FS while the ESR and CRP tests did not support high scores in BASDAI and high disease activity. Based on these results, we consider that more objective methods, such as acute phase response and radiological imaging methods should also be used to evaluate disease activity in patients with axSpA accompanied by FM. This would help prevent unnecessary treatments, high treatment costs, and side effects of drugs. However, in a previous study, when the SpA groups with and without FM were compared, the anti-TNF initiation rates were found to be similar.[19] Similarly, in our study, the use of biological therapy did not differ between the two groups. These results suggest that rheumatologists should consider the negative effects of FS in the management of SpA treatment.

CONCLUSION

According to the results of our study, axSpA is frequently accompanied by FS, especially in women. Symptoms of FS, such as widespread pain and morning stiffness can cause an increase in disease activity scores, which are misinterpreted as low treatment response. These factors should be carefully considered to lower treatment costs and provide more accurate treatment. The first limitation of our study is the low number of patients. Second, we reported short-term patient data. Further studies with a long-term follow-up can provide more valuable information in evaluating treatment response.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Medical Ethics Committee of Adıyaman University (Permission granted: 20.11.2020, Decision no: 2018/8-1).

Informed Consent: Due to the retrospective design of the study, informed consent of the patients was not necessary.

Referee Evaluation Process: Externally peer-reviewed.

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