Retrospective Review

Presence of Fibromyalgia Syndrome and Its Relationship with Clinical Parameters in Patients with Axial Spondyloarthritis

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Background: Fibromyalgia syndrome (FMS) is a disorder with a population prevalence of 1% to 5%. There are insufficient data in the literature on the incidence of FMS in patients with axial spondyloarthritis (SpA), with only a limited number of studies conducted.

Objectives: The aim of this study was to determine the presence of FMS in patients diagnosed with axial SpA and to investigate the effect of this coexistence on clinical and laboratory assessments in patients with ankylosing spondylitis.

Study Design: This research involved a retrospective analysis of prospectively collected data.

Setting: The research took place in an outpatient rheumatology clinic.

Methods: This study included 125 patients diagnosed with axial SpA according to the Assessment of Spondyloarthritis International Society criteria. The presence of FMS was investigated according to the 2010 American College of Rheumatology criteria. Pain during activity, resting, and at night was examined using the Visual Analog Scale. Ankylosing Spondylitis Disease Activity Scores were used for assessment of disease activity, Ankylosing Spondylitis Quality of Life Scale was used for quality of life, Bath Ankylosing Spondylitis Functional Index was used for functionality, and Pittsburgh Sleep Quality Index was used for sleep quality.

Results: Incidence of FMS was 29.6% in the study population, which consisted of patients who were all diagnosed with axial SpA. Comparison of patient groups with and without FMS revealed no statistically significant differences in age, weight, body mass index, marital status, family history, and smoking history ($P > .05$), with a higher rate of female patients in the group with FMS at 55% ($P < .05$). Ankylosing Spondylitis Disease Activity Score-C-Reaktif Protein, Ankylosing Spondylitis Disease Activity Score-Erythyrocyte Sedimentation Rate, Ankylosing Spondylitis Quality of Life Scale, Bath Ankylosing Spondylitis Functional Index, Pittsburgh Sleep Quality Index, and Visual Analog Scale pain scores were significantly higher in the group with FMS ($P < .05$).

Limitation: The study involved a limited number of patients.

Conclusions: FMS is observed in one-third of patients with axial SpA. The presence of FMS negatively affects quality of life, functional status, sleep quality, disease activity, and pain level of patients with ankylosing spondylitis. The possibility for coexistence of FMS should be kept in mind when determining the treatment protocols for patients with axial spondyloarthritis, and adjunctive treatment should be given if necessary.

Key words: Disease activity, fibromyalgia, quality of life, spondyloarthritis, sleep quality

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Spondyloarthritis (SpA) includes a group of rheumatic diseases characterized by inflammatory low back pain, peripheral oligoarthritis, enthesitis, and/or extraarticular involvement (1). Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are the SpA subgroups that are most commonly observed in rheumatology units (2,3). Opinions and observations suggested axial SpA term for early SpAs at preradiographic state to prevent delay in diagnosis. Establishment of a diagnostic algorithm accompanied by clinical findings, laboratory results, and radiological imaging to enhance diagnostic possibility will allow earlier diagnosis and thus, early initiation of treatment in these patients. The ASAS criteria for axial SpA were developed with the goal of improving the ability to define such cases for clinical and research purposes (Table 1) (4).

Fibromyalgia syndrome (FMS) is a disorder with a population prevalence of 1% to 5% (5,6). The most common and characteristic symptoms of FMS include generalized pain involving several anatomical sites, stiffness, fatigue, body aches, and sleep disturbance (7,8). The prevalence of FMS is very high in rheumatology clinics; 12% to 20% of patients are diagnosed with FMS during their first examination (9-11). Since the accompanying symptoms show significant differences between patients and can be very severe, such that they dominate the clinical picture, FMS can mimic a wide variety of diseases such as peripheral arthritis, AS, neurological disorders, polymyalgia rheumatica, disc herniation, and hypothyroidism; FMS may often coexist with other rheumatic diseases (12,13). The 2010 American College of Rheumatology (ACR) criteria for FMS are shown in Table 2 (14).

The distinction between FMS and AS starts with etiology; AS is an autoimmune disease but FMS has often been considered to be psychogenic or psychosomatic with an absence of inflammatory or structural musculoskeletal abnormalities. Family history, chronic pain, fatigue, spine stiffness, and sleep disturbance are common features of both diseases. Headache, primary dysmenorrhea, irritable bowel syndrome, restless leg syndrome, and female urethral syndrome are more common in FMS than in the normal population while uveitis and characteristic pulmonary, cardiac, renal, and gastrointestinal manifestations can be observed in AS. In contrast with AS, there are no obvious abnormalities upon physical examination other than widespread soft tissue tenderness in patients with FMS, and laboratory and radiologic studies of musculoskeletal structures are normal (1-12) (Table 3).

There are insufficient data in the literature on the incidence of FMS in patients with axial SpA, with only a limited number of studies conducted. In this study, we aimed to determine the frequency of FMS in patients with axial SpA and examine the effects of the presence of FMS on disease activity, quality of life, and sleep quality.

Table 1. *ASAS Classification Criteria for Axial SpA in patients with backpain ≥ 3 months and at agoe of onset < 45 years.*

Sacroiliitis* on imaging plus ≥1 other SpA	**OR**	**HLA-B27 plus ≥2 other SpA features****
***Sacroiliitis on imaging:** • Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA or • Definite radiographic sacroiliitis according to modified New York criteria		****SpA features:** • Inflammatory back pain • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn's disease/ulcerative colitis • Good response to NSAIDs • Family history for SpA • HLA-B27 • Elevated CRP

Methods

This study included a total of 125 patients (40 women and 85 men) diagnosed with axial SpA according to ASAS criteria by the specialist physician at the rheumatology outpatient clinic between March 2015 and December 2015. Informed consent was obtained from all individual participants included in this study.

The presence of FMS was investigated according to the 2010 ACR criteria. Results for laboratory parameters of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), mean platelet volume (MPV) on hemogram, and tissue compatibility antigen (HLA-B27) were recorded. Physical examination included measurements for lumbar lateral flexion, cervical rotation, chest expansion, and the modified Schober test.

All patients underwent assessments for pain level using the Visual Analog Scale (VAS) during sleep, rest, and activity; quality of life using the Ankylosing Spondylitis Quality of Life Index (ASQoL), disease activity using the Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP and ASDAS-ESR), functional status using

Table 2. *2010 ACR Fibromyalgia Diagnostic Criteria*

Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale ≥ 5		
or WPI 3 to 6 and SS scale score ≥ 9		
Symptoms have been present at a similar level for at least 3 months		
The patient does not have a disorder that would otherwise explain the pain		
1. WPI: The number of areas in which the patient has had pain over the last week. Score will be between 0 and 19.		
Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right
Upper arm, left	Upper leg, left	Chest
Upper arm, right	Upper leg, right	Abdomen
Lower arm, left	Lower leg, left	Upper back
Lower arm, right	Lower leg, right	Lower back, Neck
2. SS SCALE:		
Fatigue		
Waking unrefreshed		
Cognitive symptoms		
For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale: 0 = no problem; 1 = slight or mild problems, generally mild or intermittent; 2 = moderate, considerable problems, often present and/or at a moderate level; 3 = severe: pervasive, continuous, life-disturbing problems		
Considering somatic symptoms* in general, indicate whether the patient has: 0 = no symptoms, 1 = few symptoms, 2 = a moderate number of symptoms, 3 = a great deal of symptoms		
The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12. * Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.		

Table 3. *Comparison of Axial SpA and FMS features*

	Axial SpA	**FMS**
Etiology	Autoimmune	Uncertain, a form of central sensitization
Incidence	0.05%-1.4%	1%-5%
Age of Onset	< 30 yrs	20-55 yrs
Sex Ratio (Male:Female)	3:1	1:8
Clinical Features	Pain, spinal stiffness, characteristic postural abnormalities involvement of large peripheral joints	Widespread pain, psychiatric and multiple somatic symptoms
Radiological Features	intervertebral joint fusions especially sacroiliac joints	Nonspecific
Laboratory Investigations	Elevated acute phase reactants presence of HLA-B27 in most cases	Nonspecific

the Bath Ankylosing Spondylitis Functional Index (BASFI), and sleep quality using the Pittsburgh Sleep Quality Index (PSQI).

Results

The age of our study population, which consisted of 125 patients diagnosed with axial SpA according to ASAS criteria, ranged between 19 and 72 years, with a mean age of 41.44 ± 11.65 years. There were 85 (68%) male and 40 (32%) female patients. Body mass index ranged between 17.11 and 39.73 kg/m2 with a mean of 26.76 ± 4.36 kg/m2 (Table 4). When occupational dis-

tribution was examined, 4 patients (3.2%) were illiterate, 2 (1.6%) were literate only, 54 (43.2%) were primary school graduates, 24 (19.2%) were secondary school graduates, 28 (22.4%) were high school graduates, and 13 (10.4%) were college graduates. Eight patients (6.4%) were unemployed, 4 (3.2%) were students, 26 (20.8%) were housewives, 16 (12.8%) were retired, 24 (19.2%) were office workers, and 47 (37.6%) were manual workers. Sixty-seven patients (53.6%) were smokers. Forty-eight patients (38.4%) had a positive family history of SpA, 28 (22.4%) had extraarticular involvement, 25 (20%) had previous uveitis, and 43 (34.4%) had comorbidity. Distribution of comorbidities was recorded as diabetes in 5 patients (4%), hypertension in 17 patients (13.6%), cardiovascular diseases in 3 patients (2.4%), hypothyroidism in 5 patients (4%), hyperthyroidism in 1 patient (0.8%), and other diseases in 12 patients (9.6%).

Among 125 patients with axial SpA, 37 had FMS. The incidence of FMS in our study population, which consisted of patients with axial SpA, was 29.6%.

Between-gender comparisons of time data about disease (age of symptom onset, age at diagnosis of AS, disease duration of AS, and delay time in diagnosis) in our patients with axial SpA, all of whom were diagnosed with AS, revealed a statistically significant difference only in mean age at diagnosis (P = .01). Age at diagnosis was significantly higher in female patients (33.42 ± 10.82) compared to male patients (30.16 ± 10.89) (P = .01). Other time data about disease in female patients (delay time in diagnosis, age of symptom onset, and disease duration) showed no significant differences compared to men and were similar in both genders (P > .05) (Table 5).

After dividing the study population of patients with AS into 2 groups of "with" and "without concomitant FMS diagnosis," review of the distribution of above-mentioned time data for AS (age of symptom onset, age at diagnosis of AS, disease duration of AS, and delay time in diagnosis) demonstrated that the distribution of all parameters was similar in both groups (P > .05) (Table 6). Between-group comparisons of mean lumbar lateral flexion, cervical rotation, and chest expansion values showed no significant differences. When laboratory tests for MPV values on hemogram, ESR 1st hour reading, and CRP values were examined, it was observed that the distribution of test values was similar between groups with the exception of CRP values (P > .05). CRP values were significantly higher in the group without FMS compared to the group with FMS (P = .03). The HLA-B27 test was ordered for 98 patients in our study population and of these, 68 patients (69.4%) had a positive result. Between-group analysis of the distribution of HLA-B27 positivity showed no statistically significant difference between groups (P > .05). Between-group comparison of VAS scores (resting, activity, and night) revealed a statistically significant difference (P < .05). Mean values for all

Table 4. *Demographic data.*

	Mean ± SD / %	Minimum	Maximum
Age (yrs)	41.44 ± 11.65	9	72
Height (cm)	1.68 ± 0.09	1.45	1.95
Weight (kg)	76.25 ± 13.05	44	110
BMI (kg/m2)	26.76 ± 4.36	17.11	39.73
Age of Symptom Onset	31.23 ± 10.93	14	70
Age at Diagnosis	35.94 ± 11.46	14	71
Delay Time in Diagnosis of AS	5.12 ± 6.68	0	28
Disease Duration of AS	5.39 ± 6.89	0	37
Smoking (pack/yr)	7.86 ± 11.10	0	50

Table 5. *Between-gender comparison of age at onset of AS symptoms, age at diagnosis, delay time in diagnosis, and disease duration*

	Men	Women	*P* Value
Age of Symptom Onset	30.16 ± 10.89	33.42 ± 10.82	.12
Age at Diagnosis of AS	34.21 ± 11.45	39.63 ± 10.72	.01
Delay Time in Diagnosis of AS (yrs)	4.85 ± 6.71	5.70 ± 6.65	50
Disease Duration of AS (yrs)	6.09 ± 7.65	3.92 ± 4.64	0

Table 6. *FMS-based intergroup analysis of AS symptom onset age, age at diagnosis, age at diagnosis, and duration of disease.*

	Without FMS	With FMS	*P* Value
Age of Symptom Onset (yrs)	31.41 ± 11.57	30.73 ± 9.54	.75
Age at Diagnosis of AS (yrs)	35.43 ± 12.16	37.16 ± 9.63	.44
Delay Time in Diagnosis of AS (yrs)	4.57 ± 6.18	6.43 ± 7.65	.15
Disease Duration of AS (yrs)	5.88 ± 7.66	4.25 ± 4.42	.23

3 VAS scores were determined to be higher in patients with FMS (Table 7). Statistically significant differences were detected in between-group comparisons of mean ASQoL, ASDAS-CRP, ASDAS-ESR, BASFI scores, and PSQI values ($P < .05$). These values were higher in patients with FMS (Table 8).

Table 7. *Between-group comparison of VAS scores.*

	Without FMS	With FMS	*P* Value
VAS Resting	3.60 ± 2.89	5.58 ± 2.63	.001
VAS Activity	3.23 ± 2.83	4.65 ± 2.81	.01
VAS Night	3.48 ± 3.55	5.98 ± 3.09	.001

Table 8. *Between-group comparison of ASQoL, ASDAS-CRP, ASDAS-ESR and BASFI scores*

	Without FMS	With FMS	P Value
ASQoL	7.04 ± 5.05	13.32 ± 3.80	.001
ASDAS-CRP	2.76 ± 1.21	3.45 ± 0.83	.002
ASDAS-ESR	2.38 ± 0.81	4.13 ± 5.74	.006
BASFI	2.63 ± 2.57	4.81 ± 2.41	.001

Abbreviations: ACR, American college of rheumatology; AS, ankylosing spondylitis; ASAS, assessment of spondyloarthritis international society; ASDAS, ankylosing spondylitis disease activity score; ASQoL, ankylosing spondylitis quality of life questionnaire; BASFI, Bath ankylosing spondylitis functional index; BMI, body mass index; CRP, c-reaktif protein; ESR, erytrocyte sedimentation Rate; F, female; FMS, fibromyalgia syndrome; MRI, magnetic resonance imaging; M, male; NSAIDS, nonsteroidal anti-inflammatory drugs; SD, standart deviation; SpA, spondyloartritis.

Discussion

This study was conducted to determine the presence of FMS in patients diagnosed with axial SpA according to ASAS criteria and to evaluate the effect of this coexistence on clinical status, pain, quality of life, disease activity, functionality, and sleep quality.

FMS is a syndrome that is frequently encountered in rheumatology clinics and may sometimes represent a confounding factor in primary rheumatologic diagnosis because of its painful clinical manifestation. Prevalence of FMS is much higher in rheumatology clinics when compared to the general population; 12% to 20% of patients are diagnosed with FMS during their first assessment (9-11). In recent years, there has been growing awareness of the potential for coexistence of these 2 diseases with a predominant clinical manifestation of pain, and limited studies have emphasized that the FMS component should be kept in mind as a factor that can complicate clinical improvement during treatment of axial SpA.

Our study population included 125 patients diagnosed with axial SpA. Our assessment, conducted using the 2010 ACR diagnostic criteria for FMS, showed that the rate of concomitant FMS in axial SpA was 29.6% (n = 37). While this rate was consistent with the mean rate of 30.4% as determined in "a group consisting of female AS patients only" in the review by Yunus (15), it was higher than the prevalence values reported in other studies in the literature.

Salaffi et al (16) investigated the presence of FMS in 402 patients diagnosed with AS according to Modified New York criteria (MNY) criteria or axial SpA according to ASAS criteria. In their study using 2010 ACR diagnostic criteria for FMS, they found an FMS rate of 14.9% in their patient population. In addition, they reported that the rate was significantly higher in female patients (31.3%; $P < .001$), while disease duration was similar in both genders.

Another study that evaluated FMS as a comorbidity in a patient group with SpA was the study of Wach et al. This study was conducted using 1990 ACR criteria and showed concomitant FMS in 13 of 103 patients with SpA (17).

Amiri et al (18) determined an FMS rate of 19.4% based on 1990 ACR criteria for FMS in 36 patients diagnosed with AS according to MNY criteria. In that study, 83.3% of study population were men and 16.7% were women, and the rate of female patients detected to have FMS was 71.5%. A study of 835 patients by Haliloğlu et al (19) included 119 patients with AS as well as patients with different rheumatic diseases. Investigators examined the presence of FMS in these rheumatic disease subgroups using 1990 ACR diagnostic criteria for FMS and evaluated the relationship of concomitant FMS with clinical parameters. They reported an FMS prevalence of 12.6% in 119 patients with AS.

We believe that the higher rate of concomitant FMS in patients with axial SpA in our study as compared to the literature most likely results from the fact that almost all previous studies used 1990 ACR criteria for FMS, which is considered to have a lower sensitivity and a higher specificity than the 2010 criteria. Due to the higher sensitivity of the 2010 criteria, our study probably included more patients in the FMS diagnosis category, resulting in the high rate found in our study. In this context, we believe that our study can be used as guidance for future studies that use the 2010 ACR diagnostic criteria for FMS.

Between-gender comparisons for age at onset of

AS symptoms, age at diagnosis, delay time in diagnosis, and disease duration revealed a statistically significant difference only in mean age at diagnosis ($P = .01$). Age at diagnosis was generally higher in women (39.63 ± 10.72) compared to men (34.21 ± 11.45). No statistically significant differences were observed in other parameters for disease timing (age of symptom onset, delay time in diagnosis, disease duration). Consistent with the literature, these findings further show that the age at diagnosis of SpA is generally higher in female patients compared to male patients, while other time data for disease are not gender-dependent.

We also evaluated our patient population for pain, quality of life, sleep quality, functionality, and disease activity and tried to understand how the presence of FMS might alter these parameters. Resting, activity, and night pain scores assessed by VAS were significantly higher in the group with FMS ($P = .01$; $P = .01$; $P = .001$). Given that pain is the most prominent symptom of FMS, it was a predictable result that FMS makes clinical pain more pronounced in patients with SpA. Review of scores for quality of life (ASQoL), disease activity (ASDAS-CRP, ASDAS-ESR), and functionality (BASFI) revealed statistically significant differences between groups ($P = .001$, $P = .002$, $P = .06$, $P = .001$). All scores tended to be higher in the FMS group, indicating worsening. Similar to our study, Haliloglu et al (19) determined that Bath Ankylosing Spondylitis Disese Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were affected by the presence of FMS in patients with AS and scores were higher in AS patients with concomitant FMS. Azevedo et al (21) found an FMS prevalence of 15% in 71 patients with AS along with significantly higher BASFI and ASQoL scores in patients with FMS compared to patients without FMS.

A cause of deterioration in quality of life in AS is declining sleep quality, which depends on multifactorial causes. Factors negatively affecting sleep quality include night pain that is characteristic of an inflammatory pattern, spinal deformities that can disturb sleep comfort, severe pain, depression, fatigue, and restrictive respiratory abnormalities (22-24). Presence of concomitant FMS in axial SpA causes a further decline in sleep quality. Our study showed statistically significantly higher PSQI scores in the group with FMS compared to the group without FMS ($P < .05$). Similarly, a study conducted by Aydın et al (25) indicated significantly worse sleep quality in patients with AS compared to a healthy control group.

Before initiation of the study, we performed a power analysis to determine the minimum number of patients to be included in our study within a 95% confidence interval. We believe that the fact that we achieved the required number of patients throughout the study ensured the power of our study to obtain significant results in correlation analyses. In addition, all patient exams and assessments were performed by a single clinician under equivalent circumstances; this was another strength of our study that improved the reliability of our data. Observational studies with large sample size should be conducted to gain more data about this topic.

Conclusion

The presence of FMS in patients with AS negatively affected quality of life, functional status, sleep quality, disease activity, and pain level in our study, as in the literature, but our study revealed a higher rate of FMS (29.6%) compared to previous studies of patients with axial SpA. In conclusion, the possibility of the coexistence of FMS should be kept in mind when evaluating patients with SpA. Similarly, patients diagnosed with FMS should be evaluated for SpA and necessary treatments should be added in the presence of comorbidity.

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