Asociación Colombiana de Reumatología

Revista Colombiana de REUMATOLOGÍA

www.elsevier.es/rcreuma

Original Investigation

Fibromyalgia and associated factors in patients with axial spondyloarthritis: The effect of fibromyalgia on disease activity

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ARTICLE INFO

Article history:
Received 17 August 2022
Accepted 20 October 2022

Keywords:
Axial spondyloarthritis
Disease activity
Fibromyalgia
Fibromyalgia impact questionnaire
Quality of life

ABSTRACT

Introduction/Objective: The aim of this study was to investigate the frequency of fibromyalgia (FM) in axial spondyloarthritis (ax-SpA) patients using the current FM diagnostic criteria (2016 Revised Fibromyalgia Diagnostic Criteria). Additionally, we aimed to investigate the relationship between FM severity and disease activity, functional status, and quality of life (QoL).

Materials and methods: Disease activity, functional disability and QoL were evaluated. FM severity was measured with the fibromyalgia impact questionnaire (FIQ).

Results: One hundred and three patients with ax-SpA (55.3% female; mean age 44 ± 10.85 years) were included. FM was detected in 49.5% of the patients. While FM was detected in 71% of patients with a history of peripheral arthritis, FM was present in 59.2% of patients without ($p = 0.009$). FM-ax-SpA patients showed higher disease activity except for C-reactive protein; functional status and QoL were statistically worse in patients with FM-SpA. Significant positive correlations were found between FIQ and disease activity, functional disability and QoL ($p < .001$).

Conclusions: The most effective features associated with the presence of FM were detected as gender and a history of peripheral arthritis. Presence of FM may cause an overestimation of disease activity, FM severity correlates with disease activity.

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Fibromialgia y factores asociados en pacientes con espondiloartritis axial: El efecto de la fibromialgia en la actividad de la enfermedad

Palabras clave:
Espondiloartritis axial
Actividad de la enfermedad
Fibromialgia
Cuestionario de impacto de la fibromialgia
Calidad de vida

RESUMEN

Introducción/Objetivo: El objetivo de este estudio fue investigar la frecuencia de fibromialgia (FM) en pacientes con espondiloartritis axial (ax-SpA), para lo cual se utilizaron los criterios de diagnóstico de FM actuales (*2016 Revised Fibromyalgia Diagnostic Criteria*). Además, nuestro objetivo también fue investigar la relación entre la gravedad de la FM y la actividad de la enfermedad, el estado funcional y la calidad de vida (CV).

Materiales y métodos: Se evaluó la actividad de la enfermedad, la discapacidad funcional y la calidad de vida. La gravedad de la FM se midió con el cuestionario de impacto de la fibromialgia (FIQ).

Resultados: Se incluyeron 103 pacientes con ax-SpA (55,3% mujeres; edad media 44 ± 10,85 años). Mientras que la FM se detectó en 71% de los pacientes con antecedentes de artritis periférica, estuvo presente en 59,2% de los pacientes sin esta última condición (0,009). Los pacientes con FM-ax-SpA mostraron una mayor actividad de la enfermedad, con excepción de la proteína C reactiva; el estado funcional y la calidad de vida fueron estadísticamente peores en pacientes con FM-SpA, y se encontraron correlaciones positivas significativas entre el FIQ y la actividad de la enfermedad, la discapacidad funcional y la CV ($p < 0,001$).

Conclusión: Las características más efectivas asociadas con la presencia de FM fueron el género y los antecedentes de artritis periférica. La presencia de FM puede causar una sobreestimación de la actividad de la enfermedad, en tanto que la gravedad de la FM se correlaciona con la actividad de la enfermedad.

Introduction

Axial spondyloarthritis (ax-SpA) is a rheumatologic disease involving the axial skeleton, leading inflammatory spinal pain and progressive spinal limitation. Fibromyalgia (FM) is a pain syndrome which is associated with pain, fatigue, sleeping disorders, cognitive impairments and anxiety. In patients with SpA, pain is not always related to inflammation. Pain may be associated with structural damage, vertebral fracture, FM or neuropathic pain.[1] FM is considered as a comorbid disease in rheumatic diseases. The frequency of FM has increased in ax-SpA as in other rheumatic diseases.[2]

One of the most important mimics of non-radiographic ax-SpA (nr-AxSpA) is FM. FM can cause overdiagnosis in patients with spinal pain. Additionally, the presence of FM may cause the clinician to overestimate the disease activity and as a result, may cause overtreatment in SpA patients. FM coexistence in SpA patients may also alter drug response. Molto et al. demonstrated that the presence of FM affects the anti-TNF response.[3] Although the rate of initiation of TNF inhibitors (TNFi) treatment was found to be similar in patients with and without FM, TNFi switch was found to be more common in patients with FM.[4] Contradictorily, misdiagnosis of nr-AxSpA as FM can also cause treatment delays and permanent damage. For these reasons, patients should be examined in detail at each examination in this respect. The diagnosis of FM is made by clinical evaluation; there is no laboratory test, radiographic examination, or biomarker spesific for diagnosis. FM criteria have changed over the years. In the literature, most of the studies on the frequency of FM in SpA patients were carried out using the diagnostic tools developed before the ACR 2016 criteria.[1] In our study, we planned to explore the frequency of FM in ax-SpA patients using the 2016 ACR criteria and to analyze the relations between FM and demographic and clinical characteristics, especially disease activity in ax-SpA patients. Additionally, it was planned to explore the relationship between FM severity and disease activity, the quality of life (QoL).

Material and methods

Patients diagnosed as ax-SpA according to the Assessment of SpondyloArthritis International Society classification criteria for axSpA, who followed in our outpatients clinics from October 2021 to April 2022 were involved in this cross-sectional study.[5] Patients < 18 years, peripheral SpA, psoriatic arthritis (PsA), inflammatory bowel disease (IBD) associated SpA patients, patients with severe cognitive impairment, severe neurological diseases or psychiatric disorders and pregnant patients were extracted from the study.

Age, sex, marital status, duration of disease, smoking, body mass index (BMI), comorbidities, medications were noted. The patients were questioned in terms of a history of peripheral arthritis, dactylitis and enthesopathy. Disease activity was assessed with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP) and erythrocyte sedimentation rate (ASDAS-ESR).[6–8] BASDAI ≥ 4, ASDAS-CRP and ASDAS-ESR ≥ 2.1 were accepted as active disease. The

functional disability of the patients was assessed with the Bath Ankylosing Spondylitis Functional Index (BASFI) and QoL with the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire.[9–11]

The 2016 ACR criteria were used for the detection of FM.[12] According to the 2016 revised ACR criteria, the following criteria must be met in order to diagnose FM. Generalized pain (presence of pain at least four out of five sites), symptoms for at least three months, widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) ≥ 5 or WPI 4–6 and SSS ≥ 9. In patients with fibromyalgia, FM severity was evaluated with the fibromyalgia impact questionnaire (FIQ).[13] The score of FIQ can also be used in treatment follow-up after the initial score has been calculated.

Ethical considerations

Ethical approval was obtained for the study (Date:1.10.2021, reference number:115/9). Patients were informed and written consent was acquired. The study was carried out in compliance with the principles of the Declaration of Helsinki.

Statistical analysis

While categorical variables were given as numbers and percentages, continuous variables were given as mean and standard deviation or median, interquartile range (IQR). The normality of the distribution for continuous variables was checked. Chi-square test, the Student's *t*-test or Mann–Whitney *U* test was used to compare variables. To assess the correlations between scores, Pearson Correlation Coefficient was used. Logistic regression analysis was done to define significant indicators of FM. In univariate analysis, variables with $p < 0.25$ level were used in stepwise logistic regression analysis. IBM SPSS Statistics Version 20.0 statistical software package was used for the analyses. $p < 0.05$ was evaluated as significant in the analyses.

SPSS reference: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Results

One hundred twenty six patients were evaluated for eligibility for the study. Six patients who rejected to take part in the study, two pregnant patients, four patients with cognitive impairment, three PsA patients, three IBD-associated SpA patients and five peripheral SpA were extracted from the study. One hundred and three patients with ax-SpA (55.3% female; mean age 44 ± 10.85 years) were included in the study. Eleven patients (10.67%) had already the diagnosis of FM. The demographic and clinical features of the patients with ax-SpA are demonstrated in Table 1. HLA-B27 result could not be reached in 10% of patients. HLA-B27 positivity was found in 53.7% of AS patients and 30.8% of non-radiographic ax-SpA patients. Using 2016 FM diagnostic criteria, FM was detected in 49.5% of the patients.

The percentage of women in the group with FM was greater than the group without FM (74.5% and 36.5%, respectively, $p < 0.001$) (Table 2). Age, disease duration, marital status, smoking, BMI, history of enthesitis and dactylitis were similar in the group with and without FM (Table 2). The percentage of FM was higher in nr-ax-SpA patients compared to the radiographic (rad-ax-SpA) patients (67.9%, 42.7%, $p < 0.001$, respectively). While FM was detected in 71% of patients with a history of peripheral arthritis, FM was present in 59.2% of patients without (0.009). The proportions of patients using biologic therapy were similar in the FM and non-FM groups (Table 2).

While the level of CRP was similar in the group with and without FM, BASDAI, ASDAS-CRP, ASDAS-ESR, BASFI, and ASQoL were significantly greater in patients with FM (Table 3).

Age, gender, disease duration, presence of rad-ax-SpA or nr-ax-SpA, history of enthesitis, and history of peripheral arthritis were included in the logistic regression analysis. By stepwise method (forward selection), gender and history of peripheral arthritis were found to be significant. The most effective features associated with the presence of FM were detected as gender and history of peripheral arthritis. Being

Table 1 – Demographic and clinical characteristics of the patients.

Female sex, n (%)	57 (55.3)
Age, mean ± SD	44 ± 10.85
Disease duration, (months)	
IQR (25–75)	7 (3–12)
Place of residence	
Province, *n* (%)	88 (85.4)
Marital status	
Married, *n* (%)	75 (72.8)
History of smoking, n (%)	56 (54.4)
BMI, mean ± SD	27.69 ± 4.74
Radiographic ax-SpA, n (%)	75 (72.8)
Non-radiographic ax-SpA, n (%)	28 (27.2)
Treatment	
NSAII, *n* (%)	19 (18.4)
DMARD, *n* (%)	27 (26.2)
Biologics, *n* (%)	57 (55.3)
History of peripheral arthritis, n (%)	31 (30.1)
History of enthesitis, n (%)	32 (31.1)
History of dactylitis, n (%)	3 (2.9)
History of uveitis n (%)	9 (8.7)
HLA B27(+), n (%)	44 (42.7)
Patients with fibromyalgia, n (%)	51 (49.5)
BASDAI, mean ± SD	4.62 ± 2.38
Active disease according to BASDAI, n (%)	59 (57.3)
ASDAS-CRP, mean ± SD	2.86 ± 1.05
Active disease according to ASDAS-CRP, n (%)	78 (75.7)
ASDAS-ESR, mean ± SD	2.89 ± 1.03
Active disease according to ASDAS-ESR, n (%)	77 (74.8)
BASFI, mean ± SD	3.37 ± 2.65
ASQoL, mean ± SD	9.38 ± 5.92

IQR, interquartile range; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drugs; DMARD, disease-modifying antirheumatic drugs; HLA-B27, human leukocyte antigen B27; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP, The Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein; ASDAS-ESR, The Ankylosing Spondylitis Disease Activity Score with ESR; BASFI, The Bath Ankylosing Spondylitis Functional Index; ASQoL; Ankylosing Spondylitis Quality of Life Questionnaire.

Table 2 – Comparison of demographic and clinical characteristics of patients with and without fibromyalgia.

	Patients with fibromyalgia ($n = 51$)	Patients without fibromyalgia ($n = 52$)	p value
Sex, n (%)			
Female ($n = 57$)	38 (74.5)	19 (36.5)	<0.001
Male ($n = 46$)	13 (25.5)	33 (63.5)	
Age, mean ± SD	44.55 ± 10.78	43.56 ± 10.99	0.645
Disease duration, (months)			
IQR (25–75)	7 (3–11)	6.5 (4–12)	0.698
Marital status, n (%)			
Married ($n = 75$)	35 (68.6)	40 (76.9)	0.382
History of smoking ($n = 56$), n (%)	26 (51)	30 (57.7)	0.555
BMI, mean ± SD	28.02 ± 4.26	27.37 ± 5.193	0.489
rad-ax-SpA ($n = 75$), n (%)	32 (62.7)	43 (82.7)	<0.001
nr-AxSpA ($n = 28$), n (%)	19 (37.3)	9 (17.3)	
History of peripheral arthritis, n (%)			
+ ($n = 31$)	22 (43.1)	9 (17.6)	0.009
− ($n = 71$)	29 (56.9)	42 (82.4)	
History of enthesitis, n (%)			
+ ($n = 32$)	20 (39.2)	12 (23.1)	0.091
− ($n = 71$)	31 (60.8)	40 (76.9)	
History of dactylitis, n (%)			
+ ($n = 3$)	2 (3.9)	1 (1.9)	0.618
− ($n = 100$)	49 (96.1)	51 (98.1)	
Treatment			
NSAID ($n = 19$), n (%)	7 (13.7)	12 (23.1)	
DMARD ($n = 37$), n (%)	15 (29.4)	12 (23.1)	0.437
Biologics ($n = 57$), n (%)	29 (56.9)	28 (53.8)	

IQR, interquartile range; BMI, body mass index; rad-ax-SpA, radiographic ax-SpA; nr-AxSpA, non-radiographic axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drugs; DMARD, disease-modifying antirheumatic drugs.

Table 3 – Comparison of disease activity, functional status and quality of life of patients with and without fibromyalgia.

	Patients with fibromyalgia	Patients without fibromyalgia	p value
CRP, mg/l[a]	4 (2.27–10.7)	5.68 (2.96–8.5)	0.486
BASDAI, mean ± SD	6.02 ± 1.82	3.24 ± 2.05	<0.001
BASDAI, n (%)			
≥4	42 (82.4)	17 (32.7)	<0.001
<4	9 (17.6)	35 (67.3)	
ASDAS CRP, mean ± SD	3.36 ± 0.79	2.36 ± 1.05	<0.001
ASDAS-CRP, n (%)			
≥2.1	49 (96.1)	29 (55.8)	<0.001
<2.1	2 (3.9)	23 (44.2)	
ASDAS-ESR, mean ± SD	3.45 ± 0.79	2.34 ± 0.93	<0.001
ASDAS-ESR, n (%)			
≥2.1	50 (98)	27 (51.9)	<0.001
<2.1	1 (2)	25 (48.1)	
BASFI, mean ± SD	4.36 ± 2.16	2.40 ± 2.4	<0.001
ASQoL, mean ± SD	12.37 ± 4.25	6.42 ± 5.88	<0.001

[a] Values are shown as median (25–75th percentile).
CRP, C reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP, The Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein; ASDAS-ESR, The Ankylosing Spondylitis Disease Activity Score with ESR; BASFI, The Bath Ankylosing Spondylitis Functional Index; ASQoL; Ankylosing Spondylitis Quality of Life Questionnaire.

Table 4 – The results of logistic regression analysis to determine predictors of FM.

Variable	P	Odds ratio (OR)	95% CI for OR
Being female	0.001	4.21	1.76–10.05
History of peripheral arthritis	0.041	2.73	1.04–7.13

female increases the risk of having FM 4.21 times compared to being male (Table 4).

Fibromyalgia severity was evaluated with FIQ in ax-SpA patients with FM. The relationship between FM severity and disease activity, functional status and QoL was investigated. Significant positive correlations were found between the FIQ and BASDAI, ASDAS-CRP, ASDAS-ESR, BASFI and ASQoL in patients with FM ($p < 0.001$, $r = 0.529$; $p = 0.014$, $r = 0.342$; $p = 0.004$, $r = 0.396$; $p < 0.001$, $r = 0.563$; $p < 0.001$, $r = 0.559$ respectively).

Discussion

In our study, we investigated FM frequency in ax-SpA patients using the 2016 ACR FM criteria. Additionally, we examined the associations between FM and the demographic, clinical features of the disease activity indices, functional status and QoL in ax-SpA patients. In our study, FM was detected in 49.5% of the patients In the literature, the frequency of FM in ax-SpA patients has been reported as 4.11–44.4%.[14,15] The varying results may be due to different socio-demographic and clinical features in the patient population and the criteria used for FM evaluation. In a study conducted in rheumatoid arthritis (RA) patients, FM was diagnosed at a higher rate using the 2016 ACR criteria compared to the 1990 criteria.[16] To our knowledge, there is no study comparing the 2016 ACR criteria with other criteria in ax-SpA patients. The current study was done during the COVID-19 pandemic period. Stressors (physical, mental, emotional and economic) are known to worsen FM symptoms. COVID-19-related stressors may similarly aggravate symptoms in FM patients.[17] In a study conducted with patients who had COVID-19 infection for 3 months or more, FM was detected in 30.7% of individuals, and it was emphasized that this rate was higher than the normal population.[18] In our study, the number of women and the percentage of patients with active disease were high. Depending on abovementioned reasons described above, the percentage of FM might be higher in our study.

In our study, there was no relationship between FM and age compatible with the literature, while the frequency of FM was higher in female patients. There are different results regarding the relationship between gender and FM in SpA patients. In the studies conducted by Magrey et al. and Sayin et al., the sex ratios were found to be similar in SpA patients with and without FM.[15,19] Similarly to our study, in a meta-analysis including 7 studies, the percentage of women was higher in SpA patients with FM.[20] This result is not surprising, since the frequency of women in FM, which is seen in the general population, is also high.

In our study, the percentage of FM was higher in nr-ax-SpA patients compared to the rad-ax-SpA patients. In the regression analysis, this relationship seems to have disappeared. In the study by Molto et al., the percentage of detection of sacroiliitis on X-ray in FM patients was lower than in those without FM.[3] Most of the patients in our study were in the rad-ax-SpA group (72.8%). 82.1% of the nr-ax-SpA group consisted of female patients. The higher frequency of FM in the nr-ax-SpA group might be related to female dominance.

In our study, the frequency of FM according to the 2016 ACR criteria was higher in patients with peripheral arthritis. According to the logistic regression analysis, the presence of history of peripheral arthritis increases the risk of FM 2.73 times. In the study by Molto et al. using the 1990 ACR criteria in ax-SpA patients, patients with FM had a higher history of peripheral synovitis and enthesitis than those without FM.[3] In a study conducted by Provan et al., high disease activity was found to be associated with FM development in ax-SpA patients.[21] The presence of peripheral arthritis in addition to low back pain may trigger the development of FM. Otherwise, patients with FM may have joint pain, tenderness, local soft tissue swelling complaints and may be confused with peripheral arthritis when questioned. The association between FM and peripheral arthritis association may be due to the abovementioned reasons.

One of the problems related to FM is that the disease activity might be overestimated due to FM and as a result, treatment might be intensified. In our study, the proportions of patients using biologic therapy were similar in the FM and non-FM groups. In a study conducted by Wolfe et al., they found a significant excess in the use of prednisolone and opioid analgesics, and a slight increase in the use of biological agents in RA patients with FM.[22] In a study by Almodóvar et al. in ankylosing spondylitis patients, similar to our study, the rate of biologic treatment was found to be similar in groups with and without FM.[14]

In our study, disease activity markers were statistically higher in patients with FM-ax-SpA, while CRP revealed no significant difference. According to the results of our study, the percentage of patients with active disease was high considering that more than half of the patients were on biologics. In our opinion, the high disease activity was associated with the high frequency of FM in the foreground. In the study by Wach et al. in SpA patients, BASDAI was higher in FM group, while ASDAS-CRP was evaluated as similar in FM and non-FM groups.[23] In the study by Salaffi et al. in patients with AS and PsA with axial involvement, they found that ASDAS was better in distinguishing disease activity than BASDAI in the presence of FM.[24] In other studies in the literature, similar to our study, both BASDAI and ASDAS-CRP were found to be higher in the FM group.[19,25] The ASDAS-CRP score includes subjective questions in addition to the objective parameter (CRP). These subjective parameters may also lead to high detection of disease activity, as in BASDAI. In a study conducted by Mulkoglu et al. in RA and PsA patients, disease activity was found to be higher in patients with FM.[26] Fibromyalgic pain might trigger or coexist with ax-SpA symptoms, while objective measures

are not affected by FM. Therefore, it is necessary to distinguish whether the increase in pain is related to disease activity or FM. At this point, besides history and physical examination, laboratory and imaging methods gain importance.

In our study, FIQ was used for the impact of FM on QoL and quantitative measurement of FM severity. Thus, the relationship between FM as a continuous variable with disease activity, functional disability and QoL was examined. Significant positive correlations were found between measurement of FM severity (FIQ) and disease activity markers, functional disability (BASFI), and QoL. We found weak-moderate positive correlations between measurement of FM severity (FIQ) and disease activity markers, functional disability (BASFI), and QoL. Besides the presence of FM, its severity was also correlated with activity indexes and functional status. In a study by Kancharla et al. in PsA patients, a significant positive association was found between FIQ and BASDAI.[27]

Evaluating the limitations of our study, we performed a single-center study with a relatively small number of patients. Consequently, the results of our study cannot be generalized to all ax-SpA patients. The strengths of our study are; we contributed to the literature by working with the 2016 ACR criteria in ax-SpA patients. We also examined the relationship between the degree of FM and disease activity, functional status, and QoL in patients with SpA.

In conclusion, the frequency of FM is increased in ax-SpA patients, more prominently in females. The COVID-19 pandemic may also have contributed to this frequent coexistence. The presence of peripheral arthritis might trigger the development of FM. Nevertheless, the presence of FM can be confused with the clinical features of the disease such as peripheral arthritis. Presence of FM may cause an overestimation of disease activity. In addition, since FM severity correlates with disease activity indices, it is very difficult to reach remission goal without FM treatment in patients with intense FM.

Funding source

There is no funding information.

Conflict of interest

There is no conflict of interest.

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