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ORIGINAL ARTICLE

Prevalence of Axial Spondyloarthritis Among Patients With Fibromyalgia: A Magnetic Resonance Imaging Study With Application of the Assessment of SpondyloArthritis International Society Classification Criteria

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Objective. **To evaluate the prevalence of sacroiliitis, the radiographic hallmark of inflammatory spondyloarthropathy, among patients diagnosed with fibromyalgia syndrome (FMS), using the current Assessment of SpondyloArthritis International Society (ASAS) criteria and magnetic resonance imaging.**

Methods. **Patients experiencing FMS (American College of Rheumatology 1990 criteria) were interviewed regarding the presence of spondyloarthritis (SpA) features and underwent HLA–B27 testing, C-reactive protein (CRP) level measurement, and magnetic resonance imaging examinations of the sacroiliac joints. FMS severity was assessed by the Fibromyalgia Impact Questionnaire and the Short Form 36 health survey. SpA severity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index.**

Results. **Sacroiliitis was demonstrated among 8 patients (8.1%) and ASAS criteria for diagnosis of axial SpA were met in 10 patients (10.2%). Imaging changes suggestive of inflammatory involvement (e.g., erosions and subchondral sclerosis) were demonstrated in 15 patients (17%) and 22 patients (25%), respectively. The diagnosis of axial SpA was positively correlated with increased CRP level and with physical role limitation at recruitment.**

Conclusion. **Imaging changes suggestive of axial SpA were common among patients with a diagnosis of FMS. These findings suggest that FMS may mask an underlying axial SpA, a diagnosis with important therapeutic implications. Physicians involved in the management of FMS should remain vigilant to the possibility of underlying inflammatory disorders and actively search for such comorbidities.**

INTRODUCTION

Fibromyalgia syndrome (FMS) is a noninflammatory condition characterized by chronic, widespread musculoskeletal pain and tenderness; FMS is considered to be the result of increased processing of pain by the central nervous system, a situation described in recent literature as pain centralization (1). Axial spondyloarthritis (SpA) is an inflammatory joint disease involving the axial spine, sacroiliac joints, and peripheral joints. Although FMS and SpA differ vastly in their pathogenesis, a considerable clinical overlap may exist between these conditions. Both disorders typically cause chronic nocturnal back pain, morning stiffness, and disturbed sleep. Symptoms of FMS may also coexist with those of SpA; thus, we have previously described an increased prevalence of secondary FMS among female SpA patients (2). This overlap carries important clinical implications, since the presence of comorbid FMS may on the one hand mask SpA and on the other hand lead to increased severity results on commonly used instruments in the evaluation of disease activity in SpA, such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) (3).

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Significance & Innovations

- Magnetic resonance imaging findings consistent with sacroiliitis were found among a significant number of patients previously diagnosed and treated for fibromyalgia.
- Despite the difference in pathogenesis and treatment, fibromyalgia and inflammatory spondyloarthritis have overlapping clinical manifestations such as pain, stiffness, and fatigue.
- Clinicians treating patients with fibromyalgia should maintain a strong suspicion for the possibility of an unsuspected underlying inflammatory spondyloarthropathy.

In 2009, the Assessment of SpondyloArthritis International Society (ASAS) published updated classification criteria for axial SpA (4). These criteria are based on the evaluation of patients experiencing chronic back pain with an age at onset of <45 years. The objective of the current study was to evaluate the prevalence of underlying axial SpA, according to the ASAS criteria, among patients with a clinical diagnosis of FMS.

PATIENTS AND METHODS

Patients experiencing FMS, based on the 1990 classification criteria of the American College of Rheumatology (ACR), participated in the study (5). These criteria require the presence of widespread pain lasting over 3 months, as well as tenderness on at least 11 of 18 specified tender points. Patients were consecutively recruited from the fibromyalgia clinic as well as the general rheumatologic clinic of the Tel Aviv Sourasky Medical Center.

Patient evaluation. Patients underwent manual tender point examination, as well as dolorimetry in order to ascertain fulfillment of the ACR criteria. A detailed history was obtained regarding the presence of chronic back pain. All patients underwent HLA–B27 testing and C-reactive protein (CRP) level measurement. Radiologic evaluation included sacroiliac (SI) joint directed magnetic resonance imaging (MRI) evaluation. In accordance with the ASAS criteria for axial SpA, patients were interviewed regarding the following criteria: 1) presence of inflammatory back pain (IBP) according to the definition of the ASAS group, with 4 of 5 variables present (age at onset <40 years, insidious onset, improvement with exercise, no improvement with rest, and nocturnal pain); 2) arthritis, with past or present synovitis diagnosed by a physician; 3) psoriasis in the past or present, diagnosed by a physician; 4) inflammatory bowel disease, with Crohn's disease or ulcerative colitis, diagnosed by a physician; 5) dactylitis in the past or present; 6) enthesitis, defined as heel enthesitis (past or present spontaneous pain or tenderness at the site of insertion of the Achilles tendon, or plantar fascia of the calcaneus); 7) uveitis in the past or present; and 8) good clinical response to nonsteroidal antiinflammatory drugs (NSAIDS), defined as a significant improvement 24–48 hours after a full dose of NSAIDs. Patients not previously treated with NSAIDS were offered a course of standard NSAID treatment during 1 week according to the discretion of the attending physician.

FMS severity was documented using the following measures: the Fibromyalgia Impact Questionnaire (FIQ), a self-administered questionnaire that measures the FMS patient's status, progress, and outcomes over the last week (a validated Hebrew version of the FIQ was used) (6); the Brief Pain Inventory (modified Short Form), a self-reported scale measuring severity of pain and the effect of pain on function, with scores of 0–10 (where 0 = no pain and 10 = pain as bad as you can imagine); and the Short Form 36 health survey (SF-36) (7). In addition, patients were evaluated for severity of axial SpA using the BASDAI (8), a 1–10 scale (where 1 = no problem and 10 = the worst problem), with 6 questions pertaining to the 5 major symptoms of axial SpA: fatigue, spinal pain, joint pain/swelling, enthesitis, morning stiffness duration, and morning stiffness severity.

MRI examinations of the sacroiliac joints were performed on a 1.5T MRI unit (Signa, GE Excite2, Version 11) using semicoronal T1-weighted, STIR and FSPGR pre- and post-contrast injection sequences. All MRI examinations were evaluated by an experienced musculoskeletal radiologist (IE) blinded to the patient's clinical data. Findings in the SI joint were scored using the Berlin method (9), where each joint was divided into 4 quadrants, and each quadrant was scored for osteitis/bone marrow edema as 0 = absent (no osteitis), 1 = <33% of quadrant area, 2 = ≥33% to <66% of quadrant area, and 3 = ≥66% of quadrant area, with a maximum score of 24. Subchondral sclerosis was scored in the same way. The presence or absence of erosions or fatty replacement of the SI joint marrow, enthesitis, capsulitis, and joint fluid was also recorded. Additional pathologic pelvic findings, such as pathology in the symphysis pubis and femoral head, were also registered.

Variables were defined as suggested by the ASAS group (10). Bone marrow edema was categorized as a periarticular hyperintense signal on STIR or T2-weighted images and hypointense signal on T1-weighted images. Subchondral sclerosis was defined by low-intensity in all sequences that did not show signal enhancement after contrast administration. Erosions were characterized as cortical bony defects at the joint margin of low signal intensity on T1-weighted images and high signal intensity on STIR images, if active. Fat deposition was seen as a periarticular increased signal, on T1-weighted images, that is suppressed in fat-suppression sequences. Findings were further categorized into definite sacroiliitis using a composite evaluation of both structural and active findings and into ASAS-definite sacroiliitis according to the ASAS criteria (bone marrow edema highly suggestive of sacroiliitis in at least 2 consecutive slices or in 2 different areas) (10).

A second reading of all MRI examinations was performed by the same reader a minimum of 3 months after the first read. Intraclass correlation coefficients (ICCs) were calculated for intraobserver reliability by the analysis of variance 2-way random for absolute agreement. The 95% confidence interval for the ICC is presented, as is the *P* value for the ICC. *P* values less than 0.05 were considered statistically

Table 1. Demographic data, clinical characteristics, and C-reactive protein (CRP) levels of study participants (n = 99)*

Age, years	Female, no. (%)	FIQ	BASDAI	CRP, mg/liter	IBP, no. (%)
43.4 ± 13.3	83 (83.8)	63.3 ± 16.4	6.8 ± 1.7	5.2 ± 7.8	48 (50.5)

* Values are the mean ± SD unless indicated otherwise. FIQ = Fibromyalgia Impact Questionnaire; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; IBP = inflammatory back pain.

significant. ICC values were interpreted as follows: 0–0.2 = poor agreement, 0.3–0.4 = fair agreement, 0.5–0.6 = moderate agreement, 0.7–0.8 = strong agreement, and >0.8 = almost perfect agreement.

Statistical analysis. Continuous variables were compared by using the *t*-test with a level of significance set at 0.05. The evaluation of axial SpA among the cohort of FMS patients was done according to clinical variables and physician evaluation. Evaluation of the quality of life for these patients was done using the standard SF-36 health survey according to the recommended scoring guidelines.

The association between axial SpA and SF-36, as well as laboratory and clinical variables, was done by the nonparametric Mann-Whitney test. Variables that were associated with axial SpA were introduced into a logistic model, adjusted for age and sex. Finally, the fitting of this model was tested by receiver operating characteristic curve, based on the predicted values. The study was approved by the institutional ethics committee in both participating centers and all participants gave written informed consent.

RESULTS

A total of 99 unselected patients (16 men and 83 women) were recruited. The mean ± SD age of participants was 43.4 ± 13.2 years. Table 1 shows demographic data, clinical assessment (FIQ, BASDAI, and presence or absence of IBP), and CRP level results. As noted in the table, most patients were women; FIQ mean scores were relatively high (63.3), indicating significant impact of fibromyalgia symptoms. Mean BASDAI scores were 6.8, a result which would indicate moderate disease activity for patients with axial SpA.

Table 2 summarizes MRI findings, HLA–B27 results, and ASAS criteria positivity among FMS patients (n = 99). A total of 10 patients fulfilled ASAS criteria for the diagnosis of SpA; 8 patients fulfilled the criteria based on MRI findings diagnostic of sacroiliitis, while 2 patients with negative MRI results fulfilled ASAS criteria based on a positive HLA–B27 and the presence of SpA features.

The mean ± SD Berlin score was 2.15 ± 3.6 (range 0–23). Since ankylosis was not observed in any of the patients, the ICC could not be calculated for this variable. For the rest of the evaluated variables, intraobserver reliability was fair to strong (bone marrow edema 0.6, $P < 0.0001$; fat deposition 0.4, $P < 0.015$; erosions 0.5, $P < 0.001$; and sclerosis 0.8, $P < 0.0001$).

Testing for normality revealed the following variables to have a non-normal distribution: age, CRP level, FIQ score, BASDAI, role limitation due to emotional problems, role limitation due to physical health (SF-36 components), and general health. These variables were tested using the nonparametric Mann-Whitney test for continuous variables. Normally distributed variables were tested using the *t*-test for continuous variables. Table 3 shows the comparison between patients who were finally diagnosed with axial SpA (after testing for HLA–B27 and performing MRI of the SI joint) when compared with patients who were finally negative for SpA.

As noted in the table, only 2 variables, CRP level and the physical role limitation, were found to differ significantly between patients diagnosed with axial SpA compared with patients negative for axial SpA. The BASDAI was not significantly different between these groups. There was a trend toward increased levels of pain among patients who were diagnosed with axial SpA, but this trend did not reach statistical significance.

Dichotomous comparisons. We found that 50% of patients who were negative for axial SpA had IBP, whereas 50% did not. This ratio was identical among patients who were finally diagnosed as having axial SpA. Considering results by sex, we found 3 of 10 patients finally diagnosed as having axial SpA were male (30%), compared with 13 of 89 patients who were finally negative for axial SpA (14.6%). This difference did not reach statistical significance ($P = 0.15$). For axial SpA positivity by CRP level, 6 of 10 patients (60%)

Table 2. MRI findings, HLA–B27 results, and ASAS criteria positivity among fibromyalgia syndrome patients (n = 99)*

Sacroiliitis positive†	SpA positive‡	Bone marrow edema	Sclerosis	Fat deposition	Erosions	HLA–B27+	Elevated CRP
8 (8.1)	10 (10.2)	15 (17)	22 (25.0)	7 (7.9)	15 (17.0)	3 (3.2)	29 (31.5)

* Values are the number (%). MRI = magnetic resonance imaging; ASAS = Assessment of SpondyloArthritis International Society; SpA = spondyloarthritis; CRP = C-reactive protein.
† Composite score.
‡ ASAS criteria.

Table 3. Comparison between patients diagnosed as positive or negative for axial spondyloarthritis (SpA) according to the ASAS criteria*

Positive/negative for axial SpA	No.	Mean	*P* (2-tailed)
Age			
Positive	10	43.4	1.0
Negative	89	43.4	1.0
FIQ			
Positive	10	64.1	0.91
Negative	86	63.2	0.91
BASDAI			
Positive	9	7.0	0.82
Negative	82	6.8	0.82
PAIN			
Positive	10	34.7	0.38
Negative	84	26.0	0.38
CRP level			
Positive	8	7.7	0.047†
Negative	80	4.7	0.047†
Role-physical			
Positive	10	25.0	0.033†
Negative	84	10.9	0.033†
Role-emotional			
Positive	10	36.7	0.97
Negative	84	36.1	0.97
Energy/fatigue			
Positive	10	27.0	0.83
Negative	85	25.7	0.83
Social functioning			
Positive	10	46.2	0.36
Negative	84	39.4	0.36
General health			
Positive	9	35.6	0.98
Negative	85	35.4	0.98

* ASAS = Assessment of SpondyloArthritis International Society; FIQ = Fibromyalgia Impact Questionnaire; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; PAIN = Brief Pain Inventory; CRP = C-reactive protein.
† Significant.

finally diagnosed with axial SpA had elevated CRP level values on recruitment (>5 mg/dl), compared with 23 of 82 patients (28%) negative for axial SpA (Pearson's chi-square 2-sided significance = 0.04).

Logistic regression results. To evaluate the possibility of predicting a final diagnosis of axial SpA based on the clinical variables of patients with FMS, a logistic model was performed, in which variables found to be significantly associated with axial SpA were introduced. The following variables were entered into the regression: age, sex, CRP level, and limitation in activity due to physical cause (SF-36 component). The results of the regression indicated a positive correlation between CRP levels and a final diagnosis of axial SpA with an odds ratio of 5.1, after controlling for all other factors.

DISCUSSION

In the current study, we have demonstrated the presence of inflammatory active and structural changes indicative of axial SpA among a significant proportion of patients with a clinical diagnosis of FMS. The results indicate that axial SpA may need to be sought for more actively than commonly appreciated, among patients with such a condition.

FMS is classically considered a noninflammatory syndrome, thus differing in nature from most other rheumatologic disorders. Nonetheless, FMS clinically represents exactly what would classically be defined by the outdated term of rheumatism, i.e., a condition characterized by diffuse pain throughout the skeletal system. Thus, rheumatologists are called upon to perform the workup and differential diagnostic process necessary, both to establish the diagnosis of FMS and, equally importantly, for ruling out other possible explanations for the patient's symptoms. Recently published clinical guidelines (11–13) have described the basic diagnostic workup recommended for patients being evaluated for FMS. These guidelines stress the fact that once FMS is clinically identified, overzealous investigations should be avoided to limit discomfort, side effects, and cost. Nonetheless, this diagnostic frugality must be based on a careful clinical evaluation, which takes into consideration the range of differential diagnosis possibilities relevant for each patient. Recognizing the clinical overlap between FMS and inflammatory SpA is highly pertinent in this context, particularly since identifying SpA through imaging is not a trivial endeavor. Current ASAS criteria highlight the role of MRI in the identification of sacroiliitis (14); this modality is still a costly test, not readily available in many places, and requires highly qualified interpreters. Thus, careful clinical judgment and experience continue to constitute the most important tools in the hands of clinicians faced with the dilemma of differentiating truly inflammatory pain from centralized, FMS-like pain. In making this evaluation, clinicians must keep in mind that centralized pain is an important overlapping feature of many rheumatologic disorders, ranging from osteoarthritis (15) and rheumatoid arthritis (16) to systemic lupus erythematosus (17,18).

FMS has previously been demonstrated at rates ranging between 4.1% and 15% among SpA patients, with a significantly higher prevalence among females (19,20). Symptoms observed among female SpA patients, when compared with those of male patients, frequently appear to overlap significantly with classical FMS symptoms; thus, nocturnal pain, sleep disturbances, neck pain, and pain with pressure and fatigue were all more common among female SpA patients (while male patients more frequently reported joint pain) (21). Moreover, while radiographic severity indices have been reported to be worse among male SpA patients compared with females, women were found to report worse functioning than men, at any given level of radiographic damage (22). In another study, van der Horst-Bruinsma et al (23) were able to demonstrate that female SpA patients had a higher burden of disease and less improvement in SpA outcome measures compared with men. In a large epidemiologic study conducted in Spain, mean BASDAI scores were higher among female SpA patients compared with males, while both radiologic severity and response to NSAIDS were higher among males (24). Similarly, in a recent study conducted in France, Tournadre et al (25) demonstrated greater disease activity (when measured by the BASDAI) and worse

functioning among female early SpA patients compared to males, despite fewer radiologic abnormalities.

These findings may hint at the possibility of centralized symptoms exacerbating the functional consequences of inflammatory damage in female SpA patients, although other explanations may exist, such as an increased rate of enthesitis among female patients with axial SpA. While increasing attention is being focused on the clinical differences between women and men among SpA patients (26), relatively little attention has gone into analyzing the mechanisms underlying these different clinical manifestations. Bearing in mind the overwhelmingly higher prevalence of FMS among women compared to men (27) and the differences in pain processing mechanisms between the sexes (28), the above-mentioned observations, together with the results of the current study, raise the possibility that factors such as centralized pain (or fibromyalgianess) (29) may be responsible for part of this difference. More specifically, the effects of FMS on clinical indices commonly used for assessing disease activity in SpA are worth emphasizing. When assessed by BASFI, the decline in functional ability has been shown to be similar in patients with SpA and FMS, while the BASDAI was significantly higher in FMS patients (without SpA), thus casting doubt on the usefulness of the BASDAI in differentiating between symptoms related to the 2 conditions (30). Further adding to the potential confusion between axial SpA and FMS, considerable overlap has been described between sites of enthesitis and FMS tender points, in patients with IBP (31). Notably, centralized pain typically exhibits characteristic clinical features, which may alert the clinician to its existence. Thus, pain in many different body areas, a lifetime history of chronic pain, multiple somatic conditions, a family history of chronic pain, diffuse tenderness, and a female preponderance, are all clinical clues to the presence of centralized pain and can help with the differential diagnosis (1).

In the current study we have not dealt with the outcome of FMS symptoms once inflammatory SpA is diagnosed and treated. While it is tempting to assume that treating and removing the underlying inflammatory trigger for pain would improve FMS symptoms as well, this connection is not self-evident. Previous studies have shown on the one hand the persistence of chronic pain after joint replacement (32), while on the other hand centralized pain associated with osteoarthritis has been reported to improve after surgical joint repair (33,34). Thus, it is not obvious whether applying state-of-the-art antiinflammatory treatment to previously diagnosed FMS patients with a new ASAS-based diagnosis of SpA will in fact lead to a reversal of FMS symptoms, or indeed lead to clinically significant improvement. Further prospective research will be necessary to assess this intriguing issue.

When approaching the clinical conundrum of differentiating between pure fibromyalgia and those cases with an unsuspected underlying inflammatory disease, the physician must attempt to rely on clinical judgment and on available diagnostic tools. As demonstrated by our results, activity indices such as the FIQ and the BASDAI are not able to differentiate between the 2 groups. However, as demonstrated by our results, incorporating readily available data such as the CRP level may allow a relatively good prediction. Thus, inflammatory indices should be routinely measured among patients with fibromyalgia, and physicians should remain vigilant to the necessity of further diagnostic investigation.

An obvious limitation of the current study lies in the absence of a control group. Such a group, which could comprise either healthy asymptomatic individuals, or alternatively patients with back pain but not fulfilling FMS criteria, could add clinical utility to the current observations and may be valuable in future research. Previous research has demonstrated that MRI abnormalities, such as bone marrow edema, erosions, and fat infiltration, are not entirely specific, and erosions of the sacroiliac joints (according to the ASAS operational definition) can be found among 3.8% of patients with nonspecific back pain, as well as among 1.7% of healthy individuals (35). These figures appear to be lower than those reached in the current study (17%) among patients with a diagnosis of FMS. Notably, while the intraobserver reliability for MRI interpretation was relatively low regarding the fat-deposition criteria, it was higher regarding other criteria, such as bone marrow edema; thus, the overall results of the MRI interpretation were not compromised. One of the strengths of the current study lies in the systematic application of ASAS criteria, aided by both advanced MRI and HLA testing, to the evaluation of a substantial number of FMS patients recruited.

In conclusion, in the current study we have demonstrated the significant prevalence of ASAS-criteria–positive SpA among patients with a clinical diagnosis of FMS. These results underscore the importance of recognizing the overlap between inflammatory and centralized pain in each patient and call for increased clinical vigilance in the process of differential diagnosis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Ablin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ablin, Eshed, Elkayam.

Acquisition of data. Ablin, Eshed, Berman, Aloush, Wigler, Caspi, Likhter, Wollman, Paran, Anouk, Elkayam.

Analysis and interpretation of data. Ablin, Eshed, Berman, Likhter, Elkayam.

ROLE OF THE STUDY SPONSOR

AbbVie had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by AbbVie.

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