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A cross-sectional study on clinical characteristics of Saudi axial spondylarthritis: preliminary results

M.K. BEDAIWI, R.F. ALRASHEED, A. BIN ZUAIR, E.M. ALQURTAS, M.O. BAESHEN, M.A. OMAIR

Department of Medicine, College of Medicine, Rheumatology Unit, King Saud, University, Riyadh, Saudi Arabia

Abstract. – OBJECTIVE: To describe Spondyloarthritis (SpA) patients in a single center (preliminary phase), Build connections to establish local cohorts, Saudi Registry, and publication in Gulf and Arab database.

PATIENTS AND METHODS: This prospective observational cohort consists of patients with spondylarthritis (SpA) diagnosed by a rheumatologist. Patients with AS were defined as those who met the modified New York criteria for Ankylosing Spondylitis (AS) 1984. All other patients with axial SpA who did not meet the radiology criteria of modified New York criteria for Ankylosing Spondylitis were classified as having non-radiographic axial SpA based on Assessment of SpondyloArthritis International Society (ASAS) diagnostic criteria for axial spondyloarthropathy.

RESULTS: The study group comprised 106 patients with SpA (49 patients with AS and 57 patients with non-radiographic axial SpA). Patients with non-radiographic axial SpA and patients with AS who had previously been treated with biologic disease-modifying drugs (DMARDs) were 66.67 percent and 83.67 percent, respectively. In patients with AS, CRP and age significantly impact disease activities ($p<0.05$). The overall mean ASDAS score was 2.3 ± 0.7.

CONCLUSIONS: This study has shown a more detailed description of the largest Saudi cohort reported yet. Interestingly, both disease groups, Ankylosing spondylitis and non-radiographic spondyloarthritis showed a lower prevalence of HLA-B27 is lower in the general Saudi population compared to other nations including Caucasians, thus, limiting its use as a diagnostic tool. The majority of both groups, nearly three-quarters of all patients (74.53%) in biologic DMARD treatment, and only (22.64%) used csDMARD treatment, which may help control disease activity and showing easier access and availability of these therapies to the patient. Patients with non-radiographic axial SpA showed slightly higher Extra-articular Manifestations comparing with AS patients.

Key Words:
Spondylarthritis, Cohort, Ankylosing spondylitis, Saudi Arabia.

Introduction

Spondyloarthritis (SpA) is a group of diseases that share many clinical manifestations but are heterogeneous but interrelated. Ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, spondylitis associated with inflammatory bowel diseases, and undifferentiated SpA are examples of these diseases[1]. In this family, AS is characterized by universal involvement with sacroiliac joint inflammation or fusion, as well as more common spinal ankylosis[2]. Patients with axial SpA have already developed radiographic sacroiliitis, and patients with no evidence of radiographic structural damage are classified as non-radiographic axial SpA. In patients with non-radiographic axial SpA, structural damage might or may not develop over time[3]. However, radiographic sacroiliitis of this degree may take up to 10 years to develop from the onset of clinical symptoms, and therefore delays in diagnosis and care can occur[4].

The Assessment of SpondyloArthritis International Society (ASAS) recently developed criteria for AS based on the modified 1948 New York criteria, as well as patients with non-radiographic sacroiliitis (i.e., those who do not have sacroiliitis on radiographic images but may have evidence of sacroiliitis by magnetic resonance imaging [MRI]), or the presence of HLA-B27 plus two other clinical features[5,6].

Spinal stiffness and lack of movement are common symptoms of ankylosing spondylitis, which can be explained by spinal inflammation, structural damage, or both as long as the radio-

Corresponding Author: Mohamed Bedaiwi, MD; e-mail: dr.mkbedaiwi@gmail.com

logic criterion (radiographic sacroiliitis of grade 2 bilaterally or grade 3-4 unilaterally) are met. Bamboo spine and other structural changes are more prevalent in males[7,8]. The symptoms that best distinguished AS from NON-AS were back pain that woke the subject up at night and forced him to leave the bed, back pain that was not relieved by lying down but improved with exercise, back pain that lasted three months or longer, and morning stiffness lasting 0.5 hours or longer. Reduced lumbar spine lateral mobility, a total spinal extension of 20° or less, and a total spinal flexion of 40° or less were considered acceptable signs for the diagnosis of AS[9].

The spA has no specific diagnostic criteria. The initial diagnostic step remains a clinical examination in conjunction with an evaluation of radiological and laboratory findings[1]. There is a correlation between HLA B27 prevalence and the incidence and prevalence of this disease in a particular population[10]. The ASDAS is calculated using an algorithm that combines several questions from the BASDAI (assessment of back pain, peripheral pain/swelling, and duration of morning stiffness) and a patient-reported global assessment with objective laboratory measures of inflammation, either C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)[11]. The ACR panel made a conditional recommendation in favor of TNFi treatment over no treatment in adult patients with non-radiographic axial SpA. Consider and discuss the use of TNFi with patients who have active non-radiographic axial SpA and are not responding well to NSAIDs[1]. It is not recommended to use conventional synthetic DMARDs (csDMARDs) in patients with axial SpA who do not have peripheral arthritis[3].

Profile of Ankylosing Spondylitis in Saudi Arabia

Al-Arfaj[12] conducted a single study that described the profile of ankylosing spondylitis as seen at the King Khalid University Hospital in Riyadh, Saudi Arabia, over four years. Fifteen cases, eleven males and four females, were accumulated (M: F ratio 2.75:1). Thirteen of the patients were of Arab ancestry. The mean age of onset was 23.4 years, and all but one of the patients presented with subacute symptoms. Two patients (13%) had a positive family history, and eight of twelve patients had HLA B27 positivity (67%). All fifteen patients had symmetrical radiographic sacroiliitis, eleven (73%) had radiographic spondylitis, nine (60%) had enthesitis, and five had peripheral joint involvement (33%). Conjunctivitis and uveitis were observed in two (13%) and one (7%) patients, respectively. The majority of patients fell into ARA functional Class I or II.

The main objective of this cohort study was to provide a clinical description of SpA patients in the preliminary phase in the Kingdom of Saudi Arabia by examining the demographic, clinical, and treatment characteristics of patients with AS and patients with non-radiographic axial SpA at the time of enrollment in a Saudi-based registry. Because this study began in the Kingdom of Saudi Arabia, we hoped to establish local cohorts in other Gulf and Arab countries.

Patients and Methods

Study Design

This prospective observational study was carried out in King Saud University clinics. Patients with AS were identified as those who met the modified New York criteria for AS, 1984. Patients with non-radiographic axial SpA were defined as any other axial SpA patient who did not meet the radiology criterion. The spA was diagnosed by a rheumatologist in an independent, prospective, observational cohort of individuals. Data was gathered mostly from private clinics and academic practice sites in Riyadh and other locations in the kingdom. All patients diagnosed with axial SpA under 18 years of age were included in the current investigation and evaluated for demographic characteristics, clinical features, patient-reported outcome, and treatment characteristics. Patients diagnosed with psoriatic arthritis were excluded from the study. Data were collected using questionnaires from treating rheumatologists and patients at office visits, approximately every six months. Some patients were called by telephone to fill in missed data.

Statistical Package for Social Sciences (SPSS 22; IBM Corp., New York, NY, USA) was used for data entry and analysis. Descriptive statistics were presented as numbers and percentages for categorical data and mean and standard deviation for continuous data. Chi-square tests (χ^2) and Student's *t*-test were applied for categorical and to compare continuous variables, respectively. *p*-value equal to or less than 0.05 was considered statistically significant. Ethical approval was obtained from King Saud University College of Medicine and Medical City, Riyadh, Saudi Arabia, and consent was obtained from the patients before the enrollment into the study.

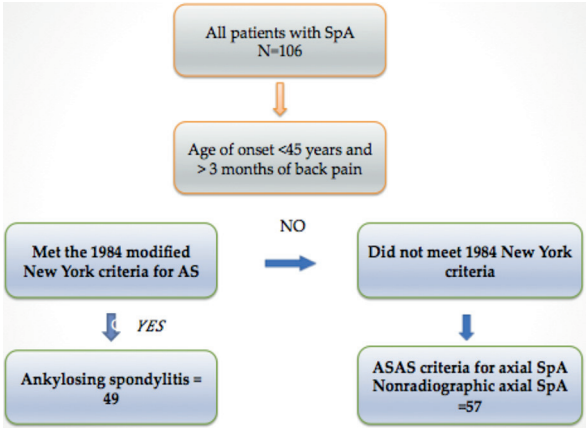

Figure 1. Flow chart of patients with ankylosing spondylitis (AS) and patients with non-radiographic axial spondyloarthritis from private clinics and academic practice sites mainly from Riyadh and partially from other cities in the kingdom of Saudi Arabia.

Results

Patient Baseline Characteristics

As of February 2019, there were 106 patients met the ASAS criteria for axial SpA in the SpA clinic. Our participants suffered from SpA with the age of onset less than 45 years and had complained of back pain for more than three months. Only 49 participants had AS who met the modified New York criteria for AS and 57 patients with non-radiographic axial SpA (Figure 1).

Demographics

Out of 106 participants, 57 (92.98%) patients with non-radiographic axial SpA were Saudi nationals, and 49 (87.76%) of patients with AS were non-Saudi nationals (Table I).

Characteristics of the Patients with AS and Those with Non-Radiographic Axial SpA

More than half of the participants were male (53.7%) and (46.23%) were females with a mean age of 39 ± 14.89 years. The mean symptoms duration and disease duration were 12.96 ± 9.3 years and 6.97 ± 5.8 years, respectively. The overall mean BMI was 27±5.3 kg/m^2, so the majority of patients were overweight (40.57%), (35.58%) within normal/underweight, and (23.58%) were obese (Table II).

HLA-B27 and Family History of SpA

Patients with non-radiographic axial SpA and those with AS were more likely to be HLA-B27-positive (66.67% and 61.22%, respectively). Family history of the disease is limited to (12.26%) out of all patients.

Current Medications Use in Both Subgroups

Near to three-quarters of all patients (74.53%) in both subgroups on biologic DMARD treatment, and only (22.64%) used csDMARD treatment. Biologic DMARD treatment was used more by AS patients (83.67%) than non-radiographic axial SpA patients (66.67%). NSAID and prednisone were used by a narrow section of patients in both subgroups (11.32% and 5.66%, respectively). Table III illustrates all medications used in both subgroups, whether used as monotherapy and/or combined.

Comorbidities in Both Groups

High cholesterol was common among patients in both groups (54%), followed by high triglycerides (40.3%), diabetes mellitus (23.7%), and hypertension (15.2%). Table IV shows the relationship between different diseases and the increase of inflammatory markers like CRP. Significant relation between neuropathy patients and high level of CRP (p=0.041). BMI played an important role in increasing the level of CRP, which overweight and obese participants had a significantly higher level of CRP (p=0.012).

Age is a remarkable factor when talking about disease activities in the human body. People aged forty and higher showed a significant ability to get fatty liver, DM2, osteoporosis, osteoarthritis, and hypertension than participants aged less than forty years with p-value (0.035, 0.002, 0.006,

Table I. Baseline demographics Patients with AS and Patients with Nonradiographic Axial SpA in the kingdom of Saudi Arabia.

	(N-106)	%	Nationality	N	%
Nonradiographic axial SpA	57	53.77	Saudi	53	92.98
AS	49	46.23	Non-Saudi	43	87.76

Table II. Characteristics of the patients with AS and those with non-radiographic axial SpA in the kingdom of Saudi Arabia.

Characteristic	Overall (n = 106)		
Gender	Male	57	53.77%
	Female	49	46.23%
Age	39 ± 14.89		
Symptoms (Mean, SD)	12.96 ± 9.3		
Disease duration (Mean, SD)	6.97 ± 5.8		
BMI	**BMI was 27.1 ± 5.3 kg/m^2**		
Normal/Underweight (< 25.0 kg/m^2)	38	35.88%	
Overweight (25.0 to < 30.0 kg/m^2)	43	40.57%	
Obese (≥ 30.0 kg/m^2)	25	23.58%	
Currently employed		91 (86.8%)	

0.004, and 0.002, respectively). However, depression increased significantly in participants aged less than forty years with a *p*-value = 0.026.

History of Extra-articular Manifestations

A lower percentage of subjects in the two groups suffers from Extra-articular Manifestations (uveitis, psoriasis, and Crohn's disease/colitis). Although, patients with non-radiographic axial SpA showed slightly higher Extra-articular Manifestations (uveitis 31.58%, psoriasis 14.03%, and Crohn's disease/colitis 8.77%) than AS patients (uveitis 28.57%, psoriasis 12.25%, and Crohn's disease/colitis 8.16%).

Disease Activity

Disease activity was measured through Ankylosing Spondylitis Disease Activity Score (ASDAS); the overall mean was 2.3±0.7, which is very close to the mean of the two subgroups separately. ASADS was an inactive disease in patients with AS (28.57%) and (21.05%) in non-radiographic axial SpA. Low disease activity was higher in patients with AS (32.65%) than non-radiographic axial SpA (29.82%). In contrast, high disease activity was more predominant in patients with non-radiographic axial SpA (31.58%) than AS patients (26.53%). Eventually, very high disease activity was not common within overall groups (15.09%), but it's higher in non-radiographic axial SpA patients (17.54%) than AS patients (12.24%).

Discussion

A cohort of individuals with AS and non-radiographic axial SpA enrolled in a longitudinal prospective study has been described. These findings add to the existing understanding of the SpA spectrum and cast doubt on the concept of nr-ax-SpA. Only a few clinical trials, registry reports, and observational studies have been published on patients with non-radiographic axial SpA, the majority of which were conducted outside of Saudi Arabia in Jordan, Egypt, Kuwait, and Qatar[13-15].

In our current study finding noted the lower prevalence of HLA B27 in patients with Ankylosing spondylitis and non-radiographic spondyloarthritis in the Saudi population compared to other nations, including Caucasians[16].

Our data support previous findings that relatively long mean symptoms duration (over 12 years) and disease duration mean near to 7 years. This is in ac-

Table III. Current medications used in both subgroups in the kingdom of Saudi Arabia.

	Overall (n = 106)		AS (n = 49)		Nonradiographic axial SpA (n = 57)	
NSAID only	12	11.32%	9	18.37%	3	5.26%
Biologic DMARD treatment	79	74.53%	41	83.67%	38	66.67%
cDMARD treatment	24	22.64%	10	20.41%	14	24.56%
Demographic of SpA patients in Saudi Arabian Prednisone	6	5.66%	2	4.08%	4	7.02%

Table IV. Relation between disease activities and increasing of inflammatory marker in the kingdom of Saudi Arabia.

Disease	Normal (83)		High (15)		*p*-value
	Number	%	Number	%	
Asthma	12	14.46	3	20.00	0.567
COPD	0	0.00	1	6.67	0.172
Neuropathy	35	42.17	4	26.67	0.041*
TIA	1	1.20	0	0.00	0.828
Serious infection	2	2.41	0	0.00	0.699
TB (Latent)	10	12.05	4	26.67	0.171
BMI					
Underweight	0	0.00	1	6.67	0.012*
Normal	26	31.33	1	6.67	
Overweight	29	34.94	4	26.67	
Obese	28	33.73	11	73.33	

*Significant *p*-value

cordance with a Canadian cohort study[17]. However, it's lower than the US-Based Corrona registry mean ± SD symptom duration was 17.3±12.5 years and disease duration 10.4±11.3 years[3].

A class 1 antigen with a major histocompatibility complex, the Human leukocyte antigen HLA-B27, is strongly related to ankylosing spondylitis (AS)[18]. Patients with non-radiographic axial SpA and those with AS were more likely to be HLA-B27-positive (66.67 percent and 61.22 percent, respectively). HLA-B27 is present in a higher percentage (90-95 percent of patients with ankylosing spondylitis) in the UK[19], but our findings are similar to those from Qatar: 69 percent of the people tested positive for HLA-B27. Positive responses were received by 49/66 Arabs (74%). The percentage of Asians who tested positive was 32/52 (61%)[15].

Although csDMARDs are not recommended for the treatment of patients with axial SpA, nearly three-quarters of all patients (74.53%) in both subgroups were on biologic DMARD treatment. However, only (22.64 %) used csDMARD treatment in the overall two groups. FDA-approved biologic DMARDs such as adalimumab, infliximab, golimumab, and etanercept used in our patients have demonstrated high efficacy. However, the positive treatment depends upon some predictors such as age, duration of disease, functional disability, and acute phase reactants[20].

A similar cohort study for characterization of patients with ankylosing spondylitis and non-radiological spondyloarthritis using Corrona Psoriatic Arthritis/Spondyloarthritis Registry in the United States noted no significant difference between patients who are on csDMARDS and biological DMARDs. These findings were indicative of most physicians treating all patients with axial SpA similarly irrespective of the presence or absence of radiological findings[21].

Evaluations of the ERS and C-reactive protein (CRP) validity and comorbidities in spondylitis ankylosing have already been conducted in previous studies[11,22]. In patients with AS, the levels of C-reactive protein (CRP) in comparison to the non-radiographic axial SpA were significantly higher. Therefore, the ASDAS was significantly higher for AS in patients 2 out of 4-time points[23]. The ASDAS (ASDAS) was significantly higher. Comorbid conditions contribute to the disease's prognosis and can either be related or independent. In the study, we found significant links between the age and disease with liver, DM2, osteoporosis, osteoarthritis, and hypertension ($p<.05$), as comorbidities increase with age (over 40 years). Recently there has been an increase in cardiovascular mortality and morbidity ratios and cardiovascular risk factors such as hypertension and type 2 diabetes mellitus in persons with AS[24].

In a significant number of patients, ankylosing spondylitis is accompanied by a variety of extra-articular manifestations. Crohn's disease, ulcerative colitis, psoriasis, and uveitis are examples of these manifestations[25]. Our findings revealed that in this sample, a lower percentage of comorbidities might be related to drug compliance.

Conclusions

Our study has the advantage of being the first cohort study conducted in the kingdom of Saudi Arabia to discuss the Characterization of

Patients with Ankylosing Spondylitis and non-radiographic axial SpA and to enable the establishment of further local cohort studies. However, the study had limitations as a cohort study; it is less suited to determining disease causes, whereas cohort studies follow exposure data and look for any emerging cases of the disease. Taking a long time is one of the disadvantages of the cohort study; in our study, it takes two years (2017-2018).

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *European Review for Medical and Pharmacological Sciences*.

Conception and Design of Study

Mohamed K Bedaiwi, Reema F AlRasheed, Amerah Bin Zuair, Eman M Alqurtas. Acquisition of data: Mohamed K Bedaiwi, Reema F AlRasheed, Moath O Baeten, Mohamed A. Omair. Drafting the manuscript: Mohamed K Bedaiwi, Reema F AlRasheed, Eman M Alqurtas, Moath O Baeten, Mohamed A. Omair.

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