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Original Article

Comorbidities in Argentine patients with axial spondyloarthritis: Is nephrolithiasis associated with this disease?

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Abstract

Objective: The objective of this study was to compare the frequency of comorbidities among patients with ax-SpA in the general population and to evaluate the impact of these comorbidities on the functional status and quality of life.

Methods: Patients with ax-SpA fulfilling the modified New York 1984 criteria for Ankylosing Spondylitis (AS) and/or Assessment of SpondyloArthritis International Society (ASAS) 2009 criteria for patients with ax-SpA belonging to the ESPAXIA cohort (*"Estudio de eSPondiloartritis Axial Irep Argentina"*) were included. Data regarding sociodemographics, comorbidities, and disease characteristics were recorded. Statistical analysis included descriptive statistics using the student t-test, Chi-square, and Fisher's exact test. Multiple logistic regression analysis was performed. A p value <0.05 was considered significant.

Results: In total, 86 patients were included, 80% were males with a median age of 46 years (interquartile range [IQR]: 32-58) and a median disease duration of 19 years (IQR: 13-31). The most frequent comorbidities reported were hypertension (26.7%), gastritis (25.6%), dyslipidemia (24.4%), gallstone (12.8%), nephrolithiasis (11.6%), anemia (10.5%), hypothyroidism (7%), and type 2 diabetes (6%). The prevalence of these comorbidities in patients with ax-SpA was similar to that observed in the general population, with the exception of a higher frequency of nephrolithiasis among patients with ax-SpA (11.6% in ax-SpA vs 3.96% in the general population). We further categorized the study population into three groups: patients with no comorbidities, those with 1 or 2 comorbidities, and those with ≥3 comorbidities. The presence of ≥3 comorbidities was associated with older age, longer disease duration, worse disease activity, functional status, and quality of life as compared with the patients without comorbidities. In multivariate analysis, older age was the only variable independently associated with the presence of comorbidities.

Conclusion: The frequency of comorbidities in the ax-SpA cohort was high, and the only variable associated with a higher prevalence of comorbidities was older age. Nephrolithiasis was more frequent in the patients with ax-SpA than that reported in the general population.

Keywords: Hidradenitis suppurativa, inflammatory eye disease, uveitis, biologics

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Introduction

Ankylosing spondylitis (AS) is the prototype disease of axial spondyloarthritis (ax-SpA). It usually affects young adults aged 20-30 years, and it presents with the axial involvement of the sacroiliac joints and spine, which tends to progress to ankylosis. The most relevant immunogenic characteristic is the association with the histocompatibility antigen HLA-B27 and the family aggregation (1, 2).

The course of AS is variable, although patients most often tend to present with progressive disease and deterioration of the functional status because of axial ankylosis and hip involvement. The disease onset occurs during the most productive years of life; hence, AS impacts the patients' social, professional, and family life, with a major economic burden on both patients and society (3).

AS patients may present with extra-spinal manifestations, including acute anterior uveitis, aortic insufficiency, pulmonary fibrosis, and renal and neurologic involvement (4-7). In relation to renal disease, there are several reports concerning the development of immunoglobulin (Ig) A nephropathy and amyloidosis.

Several studies have described a higher association between certain comorbidities and AS, wherein osteoporosis, cardiovascular, and gastrointestinal involvement are most frequently reported (8-10). We have previously described a significantly higher frequency of comorbidities in AS patients than that in the gen-

eral population (78.7% vs. 31.5%, $p=1\times10^{-8}$) (3). Additionally, most studies have reported that the number of comorbidities increases with the patients' age (5-7).

The objective of the present study was to analyze the frequency of comorbidities in an ax-SpA cohort and compare this frequency with that observed in the general population and to evaluate the impact of comorbidities on the functional status and quality of life.

Methods

Patients aged ≥18 years, with ax-SpA according to the New York 1984 criteria for AS (11) and/or ASAS 2009 for ax-SpA (12) and belonging to the ESPAXIA cohort (*´Estudio de eSPondiloartritis Axial Irep Argentina´*) were included. ESPAXIA is a longitudinal ax-SpA cohort initiated in 2010; the patients are evaluated at least twice a year, and information is systematically collected, including clinical data (disease activity, functional capacity, and quality of life), genetics, and structural involvement by radiology and/or magnetic resonance imaging. Data are recorded in a central database for further analysis, and patients provided written consent to be included.

Sociodemographic data (age, sex, and employment status) and disease characteristics were collected from the database. The presence of comorbidities was evaluated through a direct interview with the patient and from medical records. Disease activity, functional capacity, and quality of life were assessed using the self-reported questionnaires BASDAI, BASFI, and ASQoL, respectively (13-16). Physical examination included 44 joint count and axial measures to calculate the BASMI score (17).

The prevalence of comorbidities in the general population of Argentina was obtained from two previously published studies (18, 24).

Statistical analysis included descriptive statistics. Continuous data are expressed as medians and interquartile range (IQR), whereas categorical data are expressed as frequencies and percentages. Categorical variables were compared using the Chi-square or Fisher's exact test and continuous data using student's *t*-test. Multiple logistic regression analysis was performed using the presence of comorbidities as the dependent variable and adjusting for age, sex, disease duration, and those variables with a p value <0.1 in the univariate analysis. A p value <0.05 was considered significant.

Results

In total, 86 patients were included with a marked male predominance (80%). Patients had a median age of 46 years (IQR: 32-58), median disease duration of 19 years (IQR: 13-31), and a median diagnosis delay of 74.5 months (IQR: 24-163).

At least, one comorbidity was reported in 53 patients (61.2%). The comorbidities most frequently described were hypertension (26.7%), gastritis (25.6%), dyslipidemia (24.4%), gallstone disease (12.8%), nephrolithiasis (11.6%), anemia (10.5%), hypothyroidism (7%), and type 2 diabetes (6%). The prevalence of these comorbidities was comparable to the general population (18-24) (Table 1), except nephrolithiasis which was more frequent in patients with ax-SpA (11.6% in ax-SpA vs 3.96% in the general population; Figure 1).

Table 1. Frequency of comorbidities in axial spondyloarthrtis compared to the general population

Comorbidity	Axial Spondyloarthritis	General population 18,24
Hypertension	26.7%	34.1%
Gastritis	25.6%	12%-30%
Dyslipidemia	24.4%	29.8%
Gallstone disease	12.8%	10%-15%
Nephrolithiasis	11.6%	3.96%
Anemia	10.5%	10%-20%
Hypothyroidism	7%	3%-5%
Type 2 diabetes	5.8%	9.8%
Acute myocardial infarction	2.3%	2.5%-4%
Upper gastrointestinal bleeding	1.2%	1%-2%

Ax-SpA: axial spondyloarthritis

Table 2. Comparison of sociodemographic and clinical data according to the number of comorbidities present

	Group 1	Group 2	Group 3
Variable	No comorbidities × (SD)	1-2 comorbidities × (SD)	≥ 3 comorbidities × (SD)
Age (years)	36.9*	48.2	58.3*
Disease duration (years)	17*	24.4	30.42*
BASDAI	3.3*	4.3	5.8*
BASFI	3.2*	4.5	5.2*

*p < 0.05 between group 1 and 3

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, SD: standard deviation

Table 3. Variables independently associated with the presence of comorbidities; multiple logistic regression analysis

				95% CI		
Variables	B	E.T	Exp (B)	Inferior	Superior	p
Age	0.083	0.031	1.087	1.023	3.007	0.007
Disease duration	0.001	0.003	1.000	0.995	1.154	0.919
BASDAI	0.203	0.158	1.225	0.899	1.006	0.199
BASFI	- 0.001	0.151	0.999	0.744	1.670	0.997

Dependent variable: presence of comorbidities

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, CI: confidence interval

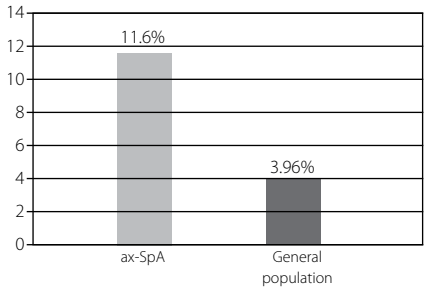

Figure 1. Prevalence of nephrolithiasis in patients with axial Spondyloarthritis vs the general population
ax-SpA: axial spondyloarthritis

The patients were further categorized into three groups according to the number of comorbidities present: patients with no comorbidities (38.8%), 1 to 2 comorbidities (45.9%), and ≥3 comorbidities (15.3%). Compared to the patients with no comorbidities, the presence of ≥3 comorbidities was associated with older age, longer disease duration, worse disease activity, functional status, and quality of life (Table 2). In multiple logistic regression analysis, the only variable independently associated with the presence of comorbidities was older age (Table 3).

Discussion

The frequency of comorbidities in our ax-SpA cohort was high. We have previously described that 78.7% of our patients have at least one comorbidity, unlike 31% of the general population (3). Other case series have found similar results; approximately 50%-80% of ax-SpA patients present with one comorbidity, which is more frequent than that in the general population (23).

Acute anterior uveitis, inflammatory bowel disease, and psoriasis are considered manifestations associated with ax-SpA, and we did not include them as comorbidities because they are contemplated in the ASAS classification criteria. Several studies have assessed the presence of comorbidities (23-25) in ax-SpA; however, as per our understanding, they focused erroneously on the extra-articular manifestations related to the disease.

Consistent with our results, other studies have observed that comorbidities negatively impact the prognosis of the disease and that they tend to increase in number with the increase in age (25-26).

The relationship between cardiovascular disease and inflammatory rheumatic conditions has been a matter of interest in the past years. Several authors found an increased cardiovascular risk in AS, which is associated with both dependent and independent risk factors. Han et al. (27), observed a higher frequency of hypertension, ischemic heart disease, congestive heart failure, atherosclerosis, diabetes mellitus, and cerebrovascular disease in patients with AS. However, in our study, we found that the frequency of hypertension, dyslipidemia, and diabetes in patients with ax-SpA was similar to that observed in the general population.

Our study has several limitations, including a small sample of patients and a referring bias, because our center is one of the reference locations for patients with SpA in Argentina.

A recent multicenter international study from the ASAS group (ASAS-COMOSPA study) found that the most frequent comorbidities were osteoporosis (13%) and peptic ulcer (11%), and the most frequent risk factors were hypertension (34%), smoking (29%), and hypercholesterolemia (27%) (28). The findings are similar to those found in our study. Nonetheless, a limitation of both studies is that the comorbidities were self-reported, which could include some forgetfulness bias. Another limitation to our study was that although the frequency of comorbidities was compared with that in the general population, we did not have a control group matched by age and gender. Moreover, an interesting finding was the high frequency of occurrence of nephrolithiasis. In a study by Spivacow et al, the prevalence of nephrolithiasis in the general population of the City of Buenos Aires was 3.96% (29). Interestingly, in our ax-SpA population, this frequency was 11.6%.

Whether urolithiasis is a comorbidity of ax-SpA or an extra-articular manifestation of ax-SpA is debatable. SpA and nephrolitiasis have genetic and biochemical mechanisms in common that could help us consider it as an extra-articular manifestation (30). Two studies exist in relation to nephrolithiasis in AS patients (31, 32). The first one included 83 AS patients who were compared with a group of patients with Behcet's disease and a healthy control group. Twenty-five percent of the patients with AS had nephrolithiasis compared to 5.5% of the Behcet's group and 3.3% of the healthy control group (30). The other study compared the frequency of nephrolithiasis between patients with AS and those with rheumatoid arthritis (RA). They described nephrolithiasis in 29% of AS patients and in 12.5% of RA patients (31). Although we performed an observational study, considering the two studies, future evaluation of nephrolithiasis as a related manifestation of AS is warranted.
In conclusion, the frequency of comorbidities in our ax-SpA cohort was high, and the only variable independently associated with a higher prevalence of comorbidities was older age. Nephrolithiasis was more frequent than expected in the general population. Further controlled studies are required to confirm this finding.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Instituto de Rehabilitación Psicofísica.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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