Ankylosing Spondylitis without Axial Progression: Analysis of Associated Factors

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ABSTRACT. ***Objective.*** To evaluate clinical factors associated with the absence of radiographic progression in patients with spondylitis.

Methods. The cross-sectional study included 672 patients. All patients presented a disease evolution of more than 15 years. Patients were classified as with radiographic spinal involvement versus without radiographic spinal involvement. We included clinical variables potentially related to null radiological progression.

Results. Seventy-five patients had no radiographic involvement. These patients were predominantly female, had a lower erythrocyte sedimentation rate (ESR), and a lower C-reactive protein level. Multivariate analysis showed an association with the female sex and low ESR.

Conclusion. Clinical factors associated with this lack of progression were female sex and low ESR.
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Key Indexing Terms:
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Ankylosing spondylitis (AS) is a chronic inflammatory disease that predominantly affects the axial skeleton. In this disease, increased bone proliferation causes the formation of enthesophytes and syndesmophytes, contributing to ankylosis. Although bone progression is a phenomenon partly associated with disease progression time, great variability exists among patients with the same disease duration.

Therefore, it is not uncommon to find patients in clinical practice with mild radiographic progression despite long periods of disease development. Research has been conducted for years on the factors that influence the heterogeneity in the appearance of syndesmophytes in patients with spondylitis. One of the main difficulties in studying this process is measuring structural radiographic changes in the spine of these patients. The first of the methods used to quantify the damage was the Bath AS Radiological Index (BASRI)[1] method. Other measurement methods have been validated subsequently, among them the Stoke Ankylosing Spondylitis Spine Score (SASSS)[2] and the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)[3]. Currently, it is mSASSS that is more frequently used, given its greater sensitivity to change in comparison with the other two[4]. With either method, several studies have suggested the existence of a relationship between clinical variables and radiological damage. The patients' sex, age at onset of symptoms, hip involvement, uveitis, smoking status, and acute-phase reactants have been associated, among other factors, with greater radiographic damage in patients with AS[5,6,7,8,9,10,11,12,13]. However, given the absence of previously published data about the factors related to lack of radiologic damage in patients with AS, we decided to conduct our study using data from the Spanish Registry of Spondyloarthritis (REGISPONSER).

MATERIALS AND METHODS

Data were obtained from REGISPONSER, which is a registry of patients with spondyloarthritis according to the European Spondyloarthropathy Study Group[14] classification criteria. The registry is available through a

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computerized Internet database accessible by all participating members (biobadaser.ser.es/cgi-bin/regisponser/index.html). Methodological and organizational details of the project have been described[15,16]. For all patients included in the registry and during a followup period of 6 years, the following variables were recorded at study entry and every 2 years: clinical activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[17] and nocturnal pain by visual analog scale, patient and physician global assessment of disease], biological variables [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], vertebral mobility (occipital-to-wall distance, modified Schober's test, lateral flexion of lumbar spine, thoracic expansion, cervical rotation), and disability [Bath Ankylosing Spondylitis Functional Index (BASFI)][18]. Health assessment questionnaires (such as Medical Outcomes Study Short Form-36) were completed 3 times during followup, and the assessment of radiologic damage by the BASRI[1], for both spine and total (BASRI spine + BASRI hips), was conducted at study entry and at the end of followup.

For the purpose of our study, REGISPONSER patients who met the modified New York criteria for AS and presented at least 15 years of disease evolution according to the onset of symptoms were selected. Patients were classified into 2 groups according to radiographic changes: (A) lack of radiological changes and (B) presence of radiographic changes. We defined lack of radiographic changes as patients who, after 15 years of disease evolution, did not show any radiographic changes in the BASRI measurement of the cervical or lumbar spine. As a cutoff point, we used a BASRI score equal to 3 that resulted from moderate sacroiliitis in the group of patients that did not have radiographic damage, and a BASRI greater than 3 resulting from moderate sacroiliitis plus lumbar and/or cervical spine. Indeed, to simplify the study, and as the spinal BASRI includes radiographic damage of the sacroiliac joints, both groups included only patients with definitive radiologic sacroiliitis (criteria of AS), with or without radiographic axial damage. We believe that dividing the spinal BASRI measure into axial and sacroiliac damage would have been artificial and harder to understand.

All the radiographs were evaluated by the same investigator (CM), and we did not perform any intrareader or interreader agreement assessments.

To assess the potential clinical variables associated with lack of radiographic changes, we decided to include all the variables previously related to radiographic progression as recorded in the univariate analyses of REGISPONSER: presence of uveitis, sex, involvement of the hips, age at disease onset, dactylitis, use of nonsteroidal antiinflammatory drugs (NSAID), HLA-B27, and biological variables of inflammation (ESR and CRP). Use of NSAID was recorded only as yes (continuous or by demand) or no (does not use). Given the about equal time of determination intervals, the overall mean of the inflammation markers was used instead of time-individual values[19]. Smoking, despite being a variable included in the registry, had an irregular recruitment (below 50%), and was therefore not included in the analysis. The statistical analysis was performed using SPSS version 20 (IBM Corp.). Variables were examined by testing frequency dispersion and normality criteria. Categorical variables were tested using the chi-square test, and quantitative variables by the Student t test. The influence of each variable was measured in univariate regression tests. Finally, the variables that were significant in the univariate analysis were weighted using logistic regression with conditional forward stepwise (forward step) methods.

RESULTS

Of the 1281 REGISPONSER patients, 672 had over 15 years of disease progression. Of these, 75 presented no radiographic changes (11.16%). The clinical characteristics of the patients in both groups are shown in Table 1.

In the regression testing, we found that only female sex and decreased levels of ESR were associated with a BASRI score equal to 3 (Table 2).

DISCUSSION

In our study, we found that 15 years after onset of the disease, 10% of patients show no radiological axial progression. Factors associated with this lack of progression were female sex, and low ESR and CRP levels. Multivariate analysis showed that female sex and low biological activity of the disease independently justify up to 15% of the lack of radiographic progression in patients with spondylitis (Nagelkerke R^2 of 0.157). We found no relationship with other variables such as age of onset of the disease, associated musculoskeletal manifestations (hip involvement, dactylitis), uveitis, spondylitis activity index (BASDAI), or HLA-B27. In our study, the use of NSAID (on demand or continuously) did not influence the lack of radiographic progression. Nonetheless, given the low accuracy of the collection of this measurement, we cannot definitively rule out its influence. This is something that has been pointed out in other studies[5], given that 70% of our patients report taking NSAID regularly.

With methodological limitations, the group of Amor, *et al* conducted the first study that attempted to associate clinical factors with radiographic progression in patients with spondyloarthropathies[6]. The authors found that none of the variables analyzed had enough weight to properly classify patients into any of the proposed groups, but they found that poor prognostic factors were hip arthritis, ineffective treatment with NSAID, dactylitis, oligoarticular involvement, sedimentation rate above 30, limitations in the range of motion of the lumbar spine, and onset of the disease before the age of 16, with the presence of hip involvement being the most influential.

In later years, several groups tried to correlate radiographic progression with clinical factors. In most cases, the authors concluded that male sex and increase in acute-phase reactants (particularly CRP) correlated with a greater radiographic progression of the disease. These results are in line with those we have obtained in our study using an inverse methodology. Most studies used a cross-sectional design, except Poddubnyy, *et al*[20]. In the German cohort, the authors measured radiographic progression over 2 years using the mSASSS method. Radiographic progression was defined as an increase of 2 points in the mSASSS or the formation of a new syndesmophyte. Clinical variables associated with radiographic changes were the presence of a syndesmophyte at the start of followup, CRP, and smoking. The authors found no association with age, disease duration, BASDAI, BASFI, presence of arthritis, enthesitis, or treatment with NSAID. It is important to note that our work includes the evaluation of the Nagelkerke R^2. This constant measures the proportion of variation in the response that is explained by the mathematical model. In the study by

Table 1. Summary of the clinical characteristics of patients in relation to the BASRI.

Clinical Characteristics	BASRI Spine ≤ 3	BASRI Spine > 3	p
Women, n (%)	29 (38.66)	128 (21.44)	0.001
Hip involvement, n (%)	2 (2.66)	23 (4.12)	0.546
Dactylitis, n (%)	4 (5.33)	20 (3.59)	0.443
No NSAID, n (%)	20 (26.66)	114 (19.07)	
Yes NSAID, on demand, n (%)	5 (6.66)	31 (5.19)	0.594
Yes NSAID, continuous, n (%)	50 (66.66)	413 (69.17)	
HLA-B27, n (%)	56 (78.87)	430 (83.82)	0.297
Uveitis, n (%)	20 (26.66)	137 (24.72)	0.716
Age at onset, mean (SD)	23.76 (7.71)	24.26 (8.34)	0.713
ESR, mm/h, mean (SD)	12.58 (11.41)	19.39 (16.42)	0.001
CRP, mg/l, mean (SD)	5.93 (11.28)	10.08 (14.07)	0.007
BASDAI, mean/SD	4.12 (2.34)	4.44 (2.29)	0.514

BASRI: Bath AS Radiological Index; AS: ankylosing spondylitis; NSAID: nonsteroidal antiinflammatory drugs; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath AS Disease Activity Index.

Table 2. Logistic regression. Nagelkerke R^2 of 0.157.

Variables	p	OR	95% CI
Female	0.0001	3.94	2.139–6.669
ESR	0.001	0.963	0.942–0.985

ESR: erythrocyte sedimentation rate.

Poddubnyy, *et al*, the presence of a syndesmophyte at the beginning of the analysis, and the increase in CRP and smoking explain over 40% of radiographic progression[20]. In other words, there are other variables, possibly of genetic origin[21], that could explain almost 60% of radiographic progression.

The originality of our study was in the inverse analysis of radiographic progression. Indeed, to the best of our knowledge, there are no previous studies linking clinical prognostic variables with a lack of axial progression in patients with longstanding disease. This different approach to radiographic progression reinforces the importance of sex and inflammation in this process. Thus, the results of our study are consistent with much of the previously published data that identify male sex as a predictor of poor radiographic outcome[10,13,21]. Similarly, other studies have correlated acute-phase reactants with radiographic progression in spondylitis[9,11,20].

As limitations, we must emphasize that this is a cross-sectional study, the radiographs were evaluated by a single observer, the method used in measuring radiographic progression was BASRI, and smoking was not included among the predictor variables for radiographic progression. To overcome some of these limitations, we proposed very strict inclusion criteria (patients with no axial involvement 15 yrs after disease onset, and the modified New York AS criteria). We believe that the use of these criteria define, unambiguously, the lack of radiographic progression much better than can be explained by the different methods used in other studies to define "rapid progression". Consequently, we believe that the methodology used, at the expense of losing sensitivity and power, allowed us to prove that sex and disease activity are unambiguously associated with no radiographic progression.

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