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Original Article

Different Clinical Expression of Patients With Ankylosing Spondylitis According to Gender in Relation to Time Since Onset of Disease. Data From REGISPONSER☆

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ABSTRACT

Objective: To describe the differential characteristics by gender and time since disease onset in patients diagnosed with ankylosing spondylitis (AS) attending the Spanish rheumatology clinics, including those on the "Spanish Registry of spondyloarthritis" (REGISPONSER), as well as the diagnostic and therapeutic implications that this entails.

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Patients and methods: This is a transversal and observational study of 1514 patients with AS selected from 2367 spondyloarthritis cases included in REGISPONSER. For each patient, the demographics, epidemiology, geriatric, clinical, laboratory, radiological, and therapeutic aspects were evaluated and comprehensively recorded under the aegis of REGISPONSER, constituting the Minimum Basic identifying data for the disease. Physical function was assessed by Bath Ankylosing Spondylitis Functional Index (BASFI). Clinical activity was evaluated using erythrocyte sedimentation rate, C reactive protein and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Each patient underwent pelvic anteroposterior, anteroposterior and lateral lumbar spine as well as lateral cervical spine X-ray; they were scored according to the Bath Ankylosing Spondylitis Spine Radiographic Index, which measures structural damage.
Results: Of the 1514 patients screened, 1131 (74.7%) were men. We found significant differences in age at onset of symptoms as well as in the day of inclusion, between the two groups, being lower in men. We also obtained differences in the duration of the disease, which was lower in women. As for the existence of a history of AS among first-degree relatives, family forms were more common among women. The mean BASDAI score was also higher in women, regardless of time since onset of disease. In contrast, the improvement of pain with the use of NSAID's and radiological severity were higher in men, both reaching statistical significance.
Conclusions: Among the Spanish AS patients, there are some differences in the clinical manifestations, even when the time since onset of disease was controlled; we also found radiological differences by gender; men showing more structural damage, while women were more active. These data suggest that the phenotype of AS differs between genders. This can influence the subsequent diagnostic approach and therapeutic decisions.

Diferente expresión clínica de los pacientes con espondilitis anquilosante según el sexo en función del tiempo de evolución. Datos de REGISPONSER

Palabras clave:
Espondilitis anquilosante
Bath Ankylosing Spondylitis
Radiographic Index Spine
Diferencias clínicas
Sexo
REGISPONSER

R E S U M E N

Objetivo: Establecer las características diferenciales según el sexo y el tiempo de evolución de la enfermedad en aquellos pacientes diagnosticados de espondilitis anquilosante (EA) asistidos en consultas de reumatología de toda España, incluidos en el Registro Español de Espondiloartritis (REGISPONSER), así como la repercusión diagnóstica y terapéutica que ello conlleva.
Pacientes y métodos: Estudio transversal y observacional de 1.514 pacientes con EA seleccionados de entre 2.367 con espondiloartritis incluidos en REGISPONSER. En cada paciente se evaluaron y registraron de modo exhaustivo los datos demográficos, epidemiológicos, sociosanitarios, clínicos, analíticos, radiológicos y terapéuticos previstos en el protocolo de REGISPONSER que componen el Conjunto Mínimo Básico que identifica la enfermedad. La función física se evaluó mediante «Bath Ankylosing Spondylitis Functional Index». La actividad clínica mediante velocidad de sedimentación globular, proteína C reactiva y «Bath Ankylosing Spondylitis Disease Activity Index» (BASDAI). A cada paciente se le realizaron radiografías anteroposterior de pelvis, anteroposterior y lateral de columna lumbar y lateral de columna cervical, y se puntuaron según el índice «Bath Ankylosing Spondylitis Radiographic Index Spine» (BASRI-Spine), que mide el daño estructural.
Resultados: De los 1.514 pacientes seleccionados, 1.131 (74,7%) eran hombres. Encontramos que existen diferencias significativas en la edad tanto al inicio de los síntomas como en el día de la inclusión entre ambos grupos, siendo menor en los hombres. También obtuvimos diferencias en el tiempo de evolución de la enfermedad, que fue menor en el grupo de las mujeres. En cuanto a la existencia de antecedentes de EA entre los familiares de primer grado, las formas familiares fueron más frecuentes entre las mujeres, también resultó superior en éstas la puntuación media del BASDAI, con independencia del tiempo de evolución. Por el contrario, la mejoría del dolor con la toma de antiinflamatorios no esteroideos fue mayor en el caso de los hombres, así como la severidad radiológica, ambas de forma significativa.
Conclusiones: Entre los pacientes con EA españoles existen algunas diferencias en las manifestaciones clínicas y cuando se controló según el tiempo de evolución, también encontramos diferencias radiológicas según el sexo; los hombres muestran más daño estructural, mientras que las mujeres presentan mayor actividad. Estos datos sugieren que el fenotipo de EA difiere entre géneros, lo que puede influir en el manejo diagnóstico y posterior elección terapéutica.

Introduction

Ankylosing spondylitis (AS) is the prototype of a group of diseases known as spondyloarthritis and, as most of them, is a chronic inflammatory disease that primarily affects the spine and sacroiliac joints and can affect peripheral joints and/or enthesis[1,2]; it a potentially serious disease that can cause significant functional disability and ultimately axial skeletal fusion (Ankylosis). Although considered a disease that mainly affects men, both in frequency and intensity, recent studies show that a significant proportion of AS patients are women (2–3 males per female)[3–6]; in addition, disease in women is not as benign as previously thought, and in many cases constitutes a recognized cause of functional limitation.[7] The frequent delay in diagnosis of AS may be due in large part to the lack of recognition of the presence of this disease in women.[8]

In April 2004 the Spanish Task Force for the Study of Spondyloarthritis of the Spanish Society of Rheumatology (GRESSER), launched a project to create a national registry of spondyloarthropathies called REGISPONSER, through a computerized central database (SQLserver) and shared via the internet http://biobadaser.ser.es/cgi-bin/regisponser/index.html. So far 31 rheumatology departments have participated in 31 hospitals in

19 provinces covering the spectrum of the Spanish population both from the demographic, social, labor and economic viewpoint. Today, it has more than 2000 patient's data regarding disease characteristics, clinical and radiological presentation and therapeutic response. This registry has been the basis for describing the clinical, demographic, analytical, radiological and metrological parameters of patients with spondyloarthritis in Spain.[1,9]

This article establishes the differential characteristics by gender and duration of disease of patients diagnosed with AS, as well as the diagnostic and therapeutic implications that this entails. To do this we compared the clinical, radiographic and functional outcomes and possible differences in severity considering gender and time since onset of disease.

Patients and Methods

Patients

For this study we selected 1514 of 2367 patients with AS composing the REGISPONSER database, of which 1131 (74.7%) were men and 383 (25.3%) women. The full details on the methodology and comprehensive compilation of the data included in REGISPONSER[1,9] have been published previously.

Compiled Data

Each center had a trained rheumatologist who was responsible for patient assessment, data collection and compliance with the inclusion criteria. For our study we considered the following variables: age (years), gender, ethnicity (caucasian/other), first-degree family history (yes, no), smoking status (smoker or former smoker/non-smoker), marital status (married/single), type of work (sedentary, moderate, severe), SA disability and presence of human leukocyte antigen HLA-B27. Likewise, we collected the prior and current medications used by each patient (including the use of methotrexate, sulfasalazine, leflunomide, infliximab and etanercept) and improvement in pain with nonsteroidal antiinflammatory drugs (NSAIDs). Other data collected included the presence of symptoms such as peripheral arthritis, enthesitis, uveitis and coxitis, the presence of hip affection and systemic symptoms (cardiac, renal, neurological or pulmonary involvement, all categorized as yes or no). To measure disability, patients were asked to complete the "Bath Ankylosing Spondylitis Functional Index" (BASFI).[10] To measure disease activity, we considered the following quantitative variables: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the self-completion of the "Bath Ankylosing Spondylitis Disease Activity Index" (BASDAI).[11] Each patient underwent anteroposterior pelvic X-ray, anteroposterior and lateral lumbar spine and cervical spine X-ray, and were scored according to the "Bath Ankylosing Spondylitis Radiographic Index – Spinal" (BASRI-Spinal),[12] which measures structural damage.

Statistical Analysis

We performed a descriptive analysis of the clinical, epidemiological, radiographic and laboratory variables by gender and duration of disease. To do that, variables were stratified into 4 groups (0–9 years, 10–19, 20–39 and 40 years or more of disease progression). Subsequently, the first subgroup was analyzed by creating a new variable (0–4 years, 5–7 and 8–10 years). We calculated the mean and standard deviation for quantitative variables and absolute frequencies and percentages for qualitative variables. A bivariate test was performed using the Student's t test for independent data for quantitative variables and the chi-square test for qualitative variables. The values of "*P*" were adjusted by the Finner test. Subsequently, we performed a univariate factorial ANOVA with a Sidak adjustment for multiple comparisons to establish the differences in BASDAI, BASFI, BASRI, ESR and CRP by gender and duration of disease.

All contrasts were bilateral and those considered significant had a $P<0.05$.

Results

Demographic and Clinical Characteristics

Table 1 shows the sociodemographic and clinical differences between men and women with AS of the 1514 patients selected. We found that there were significant differences between both groups in the mean age and the onset of symptoms at inclusion, being lower, in both cases, in men. There were also significant differences in the mean duration of disease, again lower in women. Regarding the existence of a history of AS among first-degree relatives, family forms were more frequent in the female group. For other sociodemographic characteristics there were no differences between the two groups, as occurred in the clinical expression, except for the presence of low back pain, which was more common among men.

Regarding treatment, there was no significant differences between genders in the drugs used previously. At the onset of the disease, the proportion of men using sulfasalazine was greater 87.9% than women (95% CI, 86.26–89.54) vs 83.3% (95% CI, 81.73–84.87), $P=0.03$. The improvement in pain of those patients taking NSAIDs was significantly more favorable in men.

Disease Activity

To assess disease activity we considered BASDAI, ESR and CRP. Compared to men, women had a higher average BASDAI score, regardless of the time of disease progression, with significant differences in all cases, except in those patients whose disease had a mean time interval of 20–39 years. This difference was accentuated in the group of 40 or more years of disease progression, where we observed that both the average score of the BASDAI as well as ESR and CRP levels were significantly higher in the women than in the men: BASDAI (cm) 5.25 (2.06) (95% CI, 4.18–6.32) vs 4.01 (2.39) (95% CI, 3.62–4.40), $P=.033$; ESR (mm/h) 36.56 (26.37) (95%, 29, 14–43.97) vs 17.85 (17.08) (95% CI, 15.01–20.70), $P<.001$, and CRP (mg/l) of 19.60 (30.44) (95%, 13.39–25.81) vs 8.42 (10.69) (95% CI, 6.03–10.81), $P=.001$.

Both the average BASDAI score and CRP levels were significantly increased in the men related to the years of disease progression.

Radiographic Results

Radiological findings were more severe in men, with a mean score of 6.66 in BASRI – spinal (3.47) (95% CI, 6.45–6.87) vs 4.60 (2.67) (95% CI, 4.33–4.87) in women, $P<.001$. Adjusting for the duration of the disease, we found that the mean score of BASRI – spinal worsened significantly in both groups over the years, resulting in all cases in worse outcomes in men. In the subgroup of 0–10 years we saw that BASRI – spinal significantly increased over the years in men. When comparing both groups we confirmed that, from the early stages of the disease, the mean BASRI – spinal score was higher in men, except in the group of 5–7 years where there were no differences.

Functional Disability

Globally, the BASFI increased significantly with time of disease progression although we cannot say that there were gender differences.

Table 1
Sociodemographic and Clinical Data of 1514 AS Patients by Gender.

	Men (n=1131)	Women (n=383)	P[a]
Sociodemographic			
Age, years	48.6 (13.2)	46.7 (11.7)	0.017
Age at onset of symptoms, years	26.7 (10.6)	28.2 (10.3)	0.017
Age at diagnosis, years	34.6 (12.1)	35.5 (11.3)	n/a
Time since onset, years	21.9 (13.5)	18.5 (11.7)	0.007
SA Family history, %	17.9	27.7	0.007
Smoking, %	8.7	8.5	0.007
Married, %	77.6	77.6	n/a
Type of work, %			
Sedentary	31.0	31.3	n/a
Moderate	52.4	55.8	n/a
Intense	16.7	12.9	
Occupational disability due to EA, %	66.2	54.1	n/a
HLA B 27 positive, %	83.2	80.3	n/a
Clinical			
Lumbalgia, %	72.4	66.1	0.017
sacroiliac syndrome, %	42.1	45.4	n/a
Cervicalgia, %	11.6	9.1	n/a
peripheral arthritis, %			
LL	16.9	17.2.	n/a
UL	4.0	6.0	n/a
Enthesitis, %	7.3	7.3	n/a
Uveitis, %	20.5	24.0	n/a
Coxitis, %	4.6	2.3%	n/a
Hip prosthesis, %	4.5	2.4	n/a
Cardiac involvement, %	2.2	1	n/a
Renal involvement, %	2.6	0.3	n/a
neurological involvement, %	1.1	0.5	n/a
Pulmonary involvement, %	1.7	0.8%	n/a

The data show the mean±SD for quantitative variables and absolute frequencies (%) for qualitative variables.
AS: Ankylosing spondylitis; HLA: human leukocyte antigen; LL: lower limbs; UL: upper limbs; NS: not significant.
[a] Student *t* test for independent data and chi-square, '*P*' test corrected by the Finner test.

Discussion

The review of previously published studies showed that women have more peripheral arthritis and less axial radiographic changes. In our study, we found no differences in relation to the presence of peripheral involvement by gender, although it did occur relative to axial involvement, being higher in men with a better response to NSAID use. Although our study confirms that men have greater radiographic damage than women, there seems to be an apparent contradiction, since although the structural damage was significantly higher in men functional outcomes are the same in both groups. The study of Grand et al.[3] showed no gender differences in mobility of the spine. Furthermore Dagfinrud et al.[13] found that changes in the mobility of the spine did not explain the observed differences in function; furthermore, the relationship between the radiographic structural damage and loss of function remains unknown. Even in the rheumatoid arthritis studies that have examined this question more fully, the nature of the relationship between the radiographic damage and functional loss is controversial, and may vary over the time course of the disease.[14–16] This discrepancy between radiological damage and functional loss may be the result of women having more peripheral arthritis. The prevalence of HLA B27 among women with AS is equivalent to that of men.[4] From the data obtained in our study of the Spanish population we can conclude that there are differences in the clinical and radiographic findings of SA by gender. We observed that men show more structural damage than women with similar time since onset of the disease. Damage also increases with the progression of the disease regardless of gender. Although radiographic damage is lower in women, this group exhibits greater activity. These data suggest that the AS phenotype differs between genders and may influence the subsequent diagnostic and therapeutic choices. Regarding genetic data, there were no differences in the presence of positivity for HLA-B27, although women had more first-degree family history, which may suggest a different type of inheritance pattern in relation to gender

Ethical Responsibilities

Protection of People and Animals. The authors declare that procedures conformed to the ethical standards of the committee responsible for human experimentation and were in accordance with the World Medical Association Declaration of Helsinki.

Data Confidentiality. The authors declare that they have followed the protocols of their workplace regarding the publication of data from patients and all patients included in the study have received sufficient information and gave their written informed consent to participate in this study.

Right to Privacy and Informed Consent. The authors have obtained informed consent from patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Conflict of Interest

The authors have no disclosures to make.

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