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


Servicio de Reumatología, Hospital Universitario Reina Sofía/IMIBIC/Universidad de Córdoba, Córdoba, Spain
Servicio de Reumatología, Fundación Hospital de Alcorcón, Alcorcón, Madrid, Spain
Servicio de Reumatología, Hospital Puerta de Hierro, Madrid, Spain
Servicio de Reumatología, Hospital Monte Naranco, Oviedo, Spain
Servicio de Reumatología, Hospital Parc Taulí, Barcelona, Spain
Servicio de Reumatología, Hospital Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain
Servicio de Reumatología, Hospital Virgen Macarena, Sevilla, Spain
Servicio de Reumatología, Hospital Doce de Octubre, Madrid, Spain
Servicio de Reumatología, Hospital Virgen de La Arrixaca, Murcia, Spain
Servicio de Reumatología, Hospital Ramón y Cajal, Madrid, Spain
Servicio de Reumatología, Hospital Universitario Príncipe de Asturias, Madrid, Spain
Servicio de Reumatología, Hospital General S. Jorge, Huesca, Spain
Servicio de Reumatología, Hospital Santa María del Rosell, Murcia, Spain
Servicio de Reumatología, Hospital Universitario Miguel Servet, Zaragoza, Spain
Servicio de Reumatología, Hospital Doctor Negrín, Las Palmas de Gran Canaria, Islas Canarias, Spain
Servicio de Reumatología, Hospital Central de Asturias, Oviedo, Spain
Servicio de Reumatología, Hospital San Rafael, Barcelona, Spain
Servicio de Reumatología, Hospital Virgen del Perpetuo Socorro, Albacete, Spain
Servicio de Reumatología, Hospital Fundación San Lázaro, Malcorra, Islas Baleares, Spain
Servicio de Reumatología, Hospital Internacional Mèrimar, Alicante, Spain
Servicio de Reumatología, Hospital Universitario Navarra, Pamplona, Navarra, Spain
Servicio de Reumatología, Hospital Universitario Virgen de La Vega, Salamanca, Spain
Servicio de Reumatología, Hospital Mutua de Terrassa, Terrassa, Barcelona, Spain
Servicio de Reumatología, Hospital de Palamós, Girona, Spain
Servicio de Reumatología, Hospital de Móstoles, Móstoles, Madrid, Spain
Unidad de Investigación de la Fundación Española de Reumatología, Madrid, Spain

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.
**Introduction**

Ankylosing spondylitis (AS) is the prototype of a group of diseases known as spondyloarthritides and, as most of them, is a chronic inflammatory disease that primarily affects the spine and sacrolilac joints and can affect peripheral joints and/or enthesis. It is 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). In addition, disease in women is not as benign as previously thought, and in many cases constitutes a recognized cause of functional limitation.

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

**Keywords:**
Ankylosing spondylitis
Bath Ankylosing Spondylitis
Radiographic Index Spine
Clinical differences
Sex
REGISPONSER

**Introduction**

Patients and methods: This is a transversal and observational study of 1514 patients with AS selected from 2367 spondyloarthritides 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, 1,131 (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.

© 2011 Elsevier España, S.L. All rights reserved.

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

**Resumen**

**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 el 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, 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 una posterior elección terapéutica.

© 2011 Elsevier España, S.L. Todos los derechos reservados.
have been published previously. To measure disease activity, patients were asked to complete the “Bath Ankylosing Spondylitis Functional Index” (BASFI). Each patient underwent anteroposterior pelvic X-ray, and were scored according to the “Bath Ankylosing Spondylitis Radiographic Index – Spinal” (BASRI-Spinal), 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 and systemic symptoms (cardiac, renal, neurological or pulmonary involvement, again categorized as yes or no). To measure disability, patients were asked to complete the “Bath Ankylosing Spondylitis Functional Index” (BASFI). 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). 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), which measures structural damage.

Radiographic Results

Radiological findings were more severe in men, with a mean score of 6.66 in BASRI – spinal (3.47) (95% CI, 6.45–8.68) vs 4.60 (2.67) (95% CI, 4.33–4.87) in women, P<0.001. 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. 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.
This discrepancy between radiological damage and functional outcomes is 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. This discrepancy between radiological damage and functional loss may be the result of women having more peripheral arthritis. Although radiographic damage is lower in women, this group exhibits greater functional loss. The prevalence of HLA B27 among women with AS is equivalent to that of men. 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.

**Acknowledgments**

This work was made possible through an unrestricted grant from Abbott, Schering-Plough (now MSD) and Wyeth Spain (now Pfizer), managed by the Spanish Foundation for Rheumatology (FER).
References


