Phenotypic differences between familial *versus* sporadic ankylosing spondylitis: a cross-sectional Spanish registry of spondyloarthropathies (REGISPONSER)

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Abstract

Objective

To analyse potential differences in disease phenotype between patients with familial ankylosing spondylitis (AS) and sporadic AS.

Methods

A cross-sectional study was conducted on all patients with definite AS registered at the internet database REGISPONSER. Sociodemographic data, clinical features, spinal mobility measurements, the Bath AS disease activity index (BASDAI), functional index (BASFI) and radiology index (BASRI), laboratory data (ESR, CRP, HLA-B27), overall patient assessment of the disease (VAS), and treatments used were obtained. Familial AS was considered when the patient was confirmed to have first-degree relatives with spondyloarthropathy. The Chi-square test and Mann-Whitney U-test were used for the statistical analysis.

Results

A total of 1316 AS patients (990 males, 326 females; mean age 48.2±12.6 years), with mean age at symptom onset 26.1±8.5 years, were evaluated. The prevalence of familial AS was 20% (n=263). Familial and sporadic AS groups presented differences ($p<0.05$) in the following parameters: female (34.6% vs. 22%), mean age at symptom onset (25.0±9.2 years vs. 27.3±10.0 years), disease duration (23±13 years vs. 21±12 years), uveitis (27.5% vs. 19.3%), presence of HLA-B27+ (93% vs. 83%), VAS for overall patient assessment (5.0 cm vs. 4.4 cm), BASDAI (4.4 cm vs. 4.0 cm) and response to NSAID (82% vs. 74%).

Conclusion

Patients with familial AS were younger at symptom onset and had poorer VAS for overall patient assessment and BASDAI than the other group. There was a higher prevalence of females, uveitis, positive HLA-B27, hip prostheses and a better response to NSAID in the familial AS group.

Key words

ankylosing spondylitis, family, disease phenotype

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Introduction

Ankylosing spondylitis (AS) is a chronic and inflammatory arthritis and enthesitis involving the spine and peripheral joints (1, 2). The disease generally progresses to eventual fusion (*i.e.* ankylosis) of the affected spinal joints, resulting in reduced spinal mobility (3).

The strong association of HLA-B27 with AS and other spondyloarthropathies (SpA) has been known for some time, but it has been suggested that other genetic and environmental components also play a role in the development of AS (4). Familial studies show that the HLA region explains only a third of the genetic influence on AS, and that other genes linked to the major histocompatibility complex (MHC) are involved. Therefore, AS must be considered a multigenic disease (5).

At present, there are few publications on how genetic factors may influence phenotypic expression in familial and sporadic AS. There are only four studies that examine the differences between familial and sporadic AS (6-9). In the study by Calin *et al*., the comparison of familial *versus* sporadic AS revealed a milder form of the disease in patients with familial AS (6). In contrast, potential differences in genetic makeup were not reflected in differences in the phenotypic expression of familial and sporadic AS in the Dutch study by Paardt *et al*. (8).

To help physicians better understand AS, our group decided to analyse potential differences in disease phenotype between patients with familial and sporadic AS.

Patients and methods

In April 2004, the Spanish Spondyloarthropathies Study Group of the Spanish Society of Rheumatology (GRESSER) launched the National Spondyloarthropathies Registry (REGISPONSER) (10). The registry is available to all participating members through an Internet database (http://biobadaser.ser.es/cgi-bin/regisponser/index.html). Ten Spanish rheumatology departments were selected. All participating rheumatologists were required to include all patients who fulfilled the inclusion criteria up to a minimum of 100 patients per centre.

Patients

The inclusion criteria were: 1. Confirmed cases of ankylosing spondylitis (AS) as defined by the modified New York criteria (11); 2. Blood tests available within 15 days of the visit, and a complete radiographic study (lateral cervical, lateral lumbar and pelvic x-ray) within the previous year; and 3. Agreement to complete all self-administered questionnaires. Each patient was assigned a random code in the database to avoid the entry of personal data. Familial AS was considered when the patient-reported that they had one or more first-degree relatives (father, mother, brother, sister, son, daughter) being treated by a rheumatologist for Spondyloarthropathy (SpA), defined by ESSG criteria (12); all reports were subsequently confirmed in the medical records. The inclusion period was 12 months. All patients gave their informed consent to participate in the study, which was approved centrally by the Reina Sofia Hospital Ethics Committee.

Data collection

This was an observational, cross-sectional study. In each centre, all patients were evaluated by the same rheumatologist who had previously undergone a standardisation training session. The sociodemographic information recorded comprised patient age, gender, employment-related variables and habits, especially regular exercise. A considerable amount of the data collected were related to the diagnosis: time (year) of onset of AS, specific signs and symptoms (inflammatory back pain, peripheral arthritis, peripheral enthesitis, extra-skeletal symptoms), specific signs and symptoms that the patient experienced at the time of diagnosis, the involvement pattern of the disease (axial, mixed or enthesitic), and whether the patient had a family history of AS. To ascertain the degree of the disease, the number of inflamed peripheral joints, enthesitis according to MASES (Maastricht Ankylosing Spondylitis Enthesitis Score) assessment (13), and extra-articular disease manifestations were recorded by physical examination of the patient.

For the evaluation of disease status, the following anthropometrical measures

were used: occipital-to-wall distance, modified Schober test, lateral flexion of the lumbar spine, thoracic expansion, lateral cervical rotation and fingertip-to-floor distance. We decided not to include intermalleolar distance due to the difficulty in measuring this parameter and its low reliability (14).

As measures of disease status, we also included: nocturnal pain on a 0 (no pain) to 10 cm (maximum pain) visual analogue scale (VAS); physician and patient global assessments of disease activity, also on a 0 (very well) to 10 cm (very bad) VAS; the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) from 0 (no activity) to 10 cm (maximum activity) (15), and functional capacity as scored by the Bath Ankylosing Spondylitis Functional Index (BASFI) from 0 (no disability) to 10 cm (maximum disability) (16).

Damage was accrued by the radiological assessment valued by the Bath Ankylosing Spondylitis Radiology Index (BASRI) (17), both for spine and total joints (BASRI spine + BASRI hips). The x-rays were interpreted by the same rheumatologist trained in a standardisation session. The existence of erosions, osteophytes and protrusions in hips was also assessed.

Quality of life was additionally evaluated by a specific 18-item questionnaire on quality of life in spondyloarthritis (ASQoL) (18), where lower values indicate a better quality of life, and by the generic SF-12 physical and mental health survey questionnaire (19), in which higher values indicate a better quality of life.

Laboratory tests included erythrocyte sedimentation rate (ESR: reference range 0–20 mm/h), C-reactive protein (CRP: reference range 0–5 mg/l) and HLA-B27 status.

Current treatments including non-steroidal anti-inflammatory drugs (NSAIDs), corticoids, disease-modifying anti-rheumatic drugs (DMARDs), and biological therapies were also recorded. The effectiveness of NSAIDs in relieving pain was defined as a 50% reduction in pain within 48 hours after introducing the medication, or rapid worsening within 48 hours after discontinuing the treatment.

Table I. Demographic and clinical characteristics of probands with familial AS and sporadic AS.

Variables	Familial AS (n=263)	Sporadic AS (n=1053)	*p*-value
Age (years), m ± SD	48 ± 12	48 ± 12	0.9
Females, n (%)	91 (35%)	235 (22%)	0.0001*
Age at initial symptoms (years), m ± SD	25.0 ± 9.0	27.3 ± 10.6	0.004*
Disease duration (years), m ± SD	23 ± 13	21 ± 12	0.015*
Diagnosis delay (years), m ± SD	7.7 ± 9.0	7.8 ± 9.0	0.8
Work disability, n (%)	9 (3.5%)	48 (4.7%)	0.2
Exercise, n (%)	108 (41%)	453 (43%)	0.3
HLA-B27 +, n (%)	226 (93%)	775 (83%)	0.001*
Peripheral enthesitis, n (%)	66 (25%)	241 (23%)	0.3
Peripheral arthritis, n (%)	33 (12.5%)	122 (11.6%)	0.5
Psoriasis, n (%)	19 (7%)	94 (9%)	0.4
Inflammatory bowel disease, n (%)	14 (5%)	54 (5%)	0.5
Uveitis, n (%)	72 (27.5%)	202 (19.3%)	0.002*

AS: ankylosing spondylitis; m ± SD: mean ± standard deviation. *Probability value indicates statistical significance.

Statistical analysis

Descriptive statistics are presented as mean, standard deviation (SD) and range. The Chi-square test was used to compare the observed proportions between two or more groups and the non-parametric Mann-Whitney U-test to analyse the differences between two groups of qualitative variables. An odds ratio with 95% CI was used to predict the strength of association between a qualitative dependent variable, such as the presence or absence of a sign or symptom, and one or more independent variables. The Finner method was used to adjust multiple comparisons. A two-tailed *p*-value of <0.05 was considered significant. All tests were performed using the SPSS statistical package, version 13.

Results

A total of 1316 patients with AS responded to the invitation to participate, and were included in the study. There were 990 males (75%) and 326 females (25%), with a mean age of 48.2±12.6 years and disease duration of 22.0±12.5 years. Two hundred sixty-three (263) of 1316 (20%) AS patients self-reported a positive family history of SpA, defined by ESSG criteria, and were classified as familial AS. The remaining 1053 patients (80%) were classified as sporadic AS.

The sociodemographic and clinical characteristics of familial and sporadic AS, including the mean scores in disease measures, are presented in Tables I and II. The mean age was similar in both the familial and sporadic AS groups. The proportion of women was significantly higher in the familial AS group than in the sporadic AS group. A younger age at onset and longer disease duration were found in familial AS compared with sporadic disease. With regard to extra-articular manifestations, the study showed a higher prevalence of uveitis in patients with familial AS**.** The percentage of HLA-B27 positive individuals was higher in familial AS, as previously reported. The prevalence of peripheral arthritis and enthesitis between groups was similar. Familial AS showed significantly higher VAS values for global patient assessment and BASDAI, which indicated a poorer status, but the mean differences were very small [VAS: -0.53 (95% CI -0.89 to -0.16) and BASDAI:-0.34 (95% CI -0.59 to -0.03)] so they were probably not clinically relevant. Laboratory data were similar in both groups. There were no statistically significant differences between the groups with respect to diagnostic delay, work disability, exercise, metrology, BASFI and quality of life questionnaires (SF-12, ASQoL). These similarities were more evident after Finner correction.

The use of NSAIDs was similar in both groups, but the response to NSAIDs was better in the familial group than in sporadic AS (Table II). No differences were observed in the prevalence

Table II. Disease related scores in probands with familial and sporadic AS.

Measures	Familial AS (n=263)	Sporadic AS (n=1053)	*p*-value
VAS patient's global assessment (cm) m ± SD	5.0 ± 2.7	4.4 ± 2.6	0.008*
VAS physician's global assessment (cm) m ± SD	3.3 ± 2.0	3.1 ± 2.1	0.42
VAS of night pain (cm) m ± SD	4.4 ± 2.7	4.0 ± 2.6	0.07
BASDAI m ± SD	4.4 ± 2.2	4.0 ± 2.3	0.036*
BASFI m ± SD	4.0 ± 2.6	3.8 ± 2.6	0.16
Total BASRI m ± SD	7.4 ± 4.1	7.2 ± 4.0	0.3
Chest expansion (cm) m ± SD	3.8 ± 2.0	3.7 ± 2.0	0.6
Modified Schöber test (cm) m ± SD	2.9 ± 1.8	2.8 ± 1.7	0.4
Occipital-wall distance (cm) m ± SD	4.8 ± 6.6	4.3 ± 6.0	0.3
Finger-floor distance (cm) m ± SD	19.0 ± 14.0	18.6 ± 14.0	0.7
Lumbar lateral flexion (cm) m ± SD	21.4 ± 19.0	22.0 ± 19.5	0.6
ESR (mm/h) m ± SD	18.3 ± 15.0	18.4 ± 16.5	0.9
CRP (mg/dl) m ± SD	8.3 ± 11.6	9.4 ± 14	0.2
ASQoL m ± SD	7.0 ± 5.0	6.3 ± 5.0	0.07
SF-12: physical component m ± SD	35.0 ± 10.0	35.6 ± 10.0	0.6
SF-12: mental component m ± SD	48.7 ± 11.0	48.2 ± 12.0	0.6
NSAIDs, n (%)m ± SD	207 (79%)	798 (76%)	0.2
Response to NSAIDs, n (%)m ± SD	208 (82%)	748 (74%)	0.005*

VAS: visual analogue scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASRI: Bath Ankylosing Spondylitis Radiology Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASQoL: Ankylosing Spondylitis Quality of Life; SF-12: 12-Item Short-Form Health Survey; NSAID: non-steroidal anti-inflammatory drugs; m ± SD, mean ± standard deviation.
*$p<0.05$.

Table III. Radiographic sacroiliitis grade in familial and sporadic AS.

	Familial AS (n=255)	Sporadic AS (n=1031)	*p*-value
Grade II, n (%)	56 (22%)	213 (21%)	0.4
Grade III, n (%)	94 (37%)	350 (34%)	0.4
Grade IV, n (%)	105 (41%)	468 (45%)	0.3

of DMARDS and biologic therapies (adalimumab, etanercept and infliximab) between both groups (data not shown).

The BASRI index and degree of sacroiliitis detected on x-ray (Table III) did not show differences between groups. Nevertheless, there was a higher presence of erosions (8% *vs*. 4.8%, p=0.04) and hip prostheses (6.6% *vs*. 3.1%, p=0.01) in familial AS than in sporadic AS, respectively.

We further analysed the subgroup of patients with familial AS. Among them, 77 (29.3%, *i.e*. 5.8% of the total AS patients included in the study) reported a positive family history of AS only, defined by modified New York criteria (11); this subgroup did not include patients with a positive family history of other SpA. When we compared the full group of familial AS, there were more women in this familial AS subgroup (37.7% *vs*. 22.3%, p=0.003), the onset of symptoms was at a younger age (25.0±8.6 *vs*. 27.3±10.6 years, p=0.02), there was a higher proportion of HLA-B27+ (97% *vs*. 82.7% p=0.001) and a better response to NSAIDs (96% *vs*. 74%, p=0.001) than in sporadic AS, respectively. This subgroup of familial AS with family history of AS had higher modified Schober test (3.4±1.7 *vs*. 2.8±1.7 cm, p=0.005), a lower prevalence of psoriasis (4% *vs*. 9%, p=0.04) and greater use of NSAIDs (87% *vs*.76%, p=0.03). We did not find statistically significant differences between groups with respect to the other parameters studied.

Discussion

Few studies have been published on this topic and, to our knowledge, this study assessed the largest cohort of patients with AS. Twenty percent (20%) of our patients had familial AS, similar to that found in the study by Paardt *et al*. (8), but lower than the almost 40% found in the Belgian study (9).

In our study there were no large differences between groups, as has been observed in most previous studies. We found that patients with familial AS were younger at symptom onset and had poorer VAS for global patient assessment and BASDAI. Moreover, the percentage of women was higher and there was a higher prevalence of uveitis, HLA-B27+ and a better response to NSAID in the familial AS group than in the sporadic AS group. Calin *et al*. (6) found that there were no differences between the familial and sporadic AS groups with respect to age at onset, inflammatory bowel disease, use of NSAID, psoriasis and uveitis. Similarly, a recent Dutch study (8) showed that patients with familial and sporadic AS do not differ in disease phenotype. However, a Belgian study (9) observed that patients with familial AS were younger at onset of symptoms and had a higher prevalence of HLA-B27+, uveitis and psoriasis. These results are similar to our findings, except for psoriasis.

The age at symptom onset was younger in familial AS in our study. Interestingly, this difference was also present when there was a history of AS only, but not other SpA. Calin *et al*. (6) suggest that patients with mild symptoms and family history of AS would have greater awareness of the disease, and as such may be more likely to seek a diagnosis earlier than sporadic AS patients with the same level of symptoms. Dincer *et al*. (20) observed that Turkish patients with familial AS had a lower diagnostic delay, which highlights the significant contribution of disease awareness in early diagnosis. Kennedy *et al*. (7) observed a younger age at onset in women with familiar disease compared to the mean onset in sporadic disease. Two studies (21, 22) found that the age at disease onset was younger in HLA-B27 positive compared to HLA-B27 negative patients.

There were more women in the familial AS group in our study; this may be be-

cause they were more closely assessed as they had a family history of SpA, thus enabling more patients to be diagnosed, since AS in women is usually less symptomatic at axial level, which can lead to underdiagnosis (23, 24). Another explanation could be the influence of unknown genetic factors.

A higher prevalence of uveitis was also observed in the patient group with familial AS. These results are in concordance with the Belgian group (9). Calin *et al*. (6) also found more episodes of uveitis in patients with familiar AS, although the difference did not reach statistical significance. HLA-B27 is known to be associated with both AS and acute anterior uveitis (25-27). It seems reasonable then to suggest that the higher prevalence of uveitis observed in the familial AS group may be related to the higher prevalence of HLA-B27+ that also occurs in familial AS.

We found that the subgroup of patients with familial AS with family history of AS had higher Schober test; these results agree in part with Calin *et al*. (6), who observed that patients with familiar AS had better spinal mobility.

Regarding disease measures, we observed a higher global patient assessment VAS and BASDAI in familial AS. However, it should be taken into account that after analysing both groups, the mean difference was very small, so at clinical level it is probably not relevant. The familial AS group had a better response to NSAIDs, which may be explained by the higher axial activity found in this group, since the BASDAI and VAS were slightly higher.

We found that there were no differences between groups in the BASRI, except for the higher presence of hip erosions and prostheses in familial AS patients. Moreover, the "small" radiologic findings in joints may constitute an objective sign to explain, at least in part, the higher BASDAI and higher global patient assessment VAS found in familial AS. Hip involvement is generally recognised as a major predictor of severe disease and has been found to be associated with earlier onset of symptoms (28, 29); however, this may be a consequence of disease duration and should be taken into account in our study. Nevertheless, some authors have also found a correlation between HLA-B27+ and hip involvement (30, 31). As this feature is a poor prognostic factor in AS, and our familial AS group was found to have a higher prevalence of both these risk factors, these patients should be closely monitored.

Like most studies of this nature, a potential limitation is that information must be obtained from patients in order to classify them as sporadic or familial AS. Patients who are unaware of first-degree relatives with SpA, or indeed who present only early or mild symptoms and are as yet undiagnosed, could be classified incorrectly as sporadic rather than familial AS.

In conclusion, in our study, familial AS predisposes to earlier onset of symptoms, with hip involvement and hip prostheses. It is therefore important to closely monitor all patients with symptomatology and family history of SpA, in order to diagnose and treat them as soon as possible, due to the long-term implications of this disease.

Key messages:

- A family history of AS predisposes the individual to earlier onset of symptoms, with hip involvement and hip prostheses being poor prognostic factors.
- It is important to closely monitor all patients with symptomatology and family history of SpA.

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