Differences between familial and sporadic early spondyloarthritis: results from the ESPERANZA cohort

R. Almodóvar[1], V. Navarro-Compán[2], C. Fernández-Carballido[3], A. Hernández[4], E. De Miguel[2], P. Zarco[1], and the ESPERANZA Study Group.

[1]Rheumatology Unit, Hospital Universitario Fundación Alcorcón, Madrid, Spain;
[2]Rheumatology Unit, Hospital Universitario La Paz, Madrid, Spain;
[3]Rheumatology Unit, Hospital Universitario de Elda, Alicante, Spain;
[4]Rheumatology Unit, Hospital Universitario Virgen de la Salud, Toledo. Spain.

Abstract

Objective

To describe and evaluate clinical and imaging differences between patients with familial and sporadic early spondyloarthritis (SpA).

Methods

This was a cross-sectional study analysing the baseline dataset from ESPERANZA, a national programme developed for the early identification of patients with SpA. Patients fulfilling SpA ASAS classification criteria were included. Familial SpA was defined according to the ASAS/ESSG criteria as the presence in first- or second-degree relatives of any of the following: ankylosing spondylitis, psoriasis, uveitis, reactive arthritis, and inflammatory bowel disease. Socio-demographic and disease characteristics, disease activity, metrology and laboratory and imaging data were compared by descriptive and bivariate statistics.

Results

A total of 377 patients were included – 64% men, mean age 32, and mean disease duration 12 months. Out of these, 132 (35%) patients (101 axial and 31 peripheral SpA) were familial forms. In patients with axial SpA, statistically significant differences ($p<0.05$) were found between familial and sporadic forms regarding age at symptoms onset (29.4±9.2 vs. 31.5±10 years), HLA B27 positivity (83% vs. 71%), BASMI (1.2± 13 vs. 1.6 1.2) and sacroiliitis on magnetic resonance imaging (36% vs. 47%), respectively. In patients with peripheral SpA, there were no significant differences for any of the variables analysed.

Conclusion

Familial axial SpA presents symptoms at a younger age, is more frequently HLA-B27 positive and shows better spinal mobility than sporadic axial SpA; this latter presenting sacroiliitis on MRI more frequently than familial axial SpA. Apparently, no differences exist in the expression of familial or sporadic peripheral SpA.

Key words
spondyloarthritis, familial forms, sporadic, disease expression

Raquel Almodóvar
Victoria Navarro-Compán
Cristina Fernández-Carballido
Azucena Hernández
Eugenio De Miguel
Pedro Zarco

Please address correspondence to:
Dr Raquel Almodóvar,
Rheumatology Department,
Hospital Universitario Fundación Alcorcón, Avda. Budapest s/n,
28922 Madrid Spain.
E-mail: ralmodovar@fhalcorcon.es

Received on April 21, 2015; accepted in revised form on November 2, 2015.

Funding: V. Navarro-Compán received one of the ASAS research grants on call 2013 to perform this study.
The Spanish Foundation of Rheumatology received funding from Pfizer to develop the Esperanza Programme.
At present, the programme is supported by a restricted grant of the Institute Carlos III (FIS PI13/02034).
The sponsor had no role in the study design, the collection, analysis or interpretation of the data, in the writing of the report, or in the decision to submit the article for publication.

Competing interests: none declared.

Introduction

Familial aggregation or clustered incidence in the group of spondyloarthritis (SpA) has been known for many years (1-4), especially in relation to ankylosing spondylitis (AS) (5-11). In fact, familial history is one of the features included in most of the classification criteria for SpA (12-14).

This familial clustering is determined by and large genetically and it is considered as multigenic (15, 16). About 10%–40% of AS patients have been reported as familial cases in the literature (17-19). The risk of AS is higher in familial cohorts than in sporadic cohorts or in the general population, where the prevalence lies between 0.2 to 0.9%; and the risk is generally higher in first degree relatives (5.9%–15%) than in other family members, and is higher in monozygotic twins than in dizygotic twins (15, 20). Moreover, first-degree relatives of patients with AS who are HLA-B27 positive have been estimated to have a 10-fold increased risk to develop AS compared to HLA-B27 positive individuals without a family history (19).

As different studies pointed out, there might be phenotypic differences between familial and sporadic cases of SpA or AS (1, 3, 5-9, 21). However, discrepancies have been found among studies, probably related to different methodologies and definitions. Some authors have reported a milder form of the disease in familial AS compared to sporadic AS (5), while others did not find any difference in phenotype expression (7). We previously observed a younger age at symptom onset and higher disease activity scores in patients with familial AS compared to sporadic cases (8). In addition, we suggested that the familial cases were more often women, and had uveitis, positive HLA-B27, and hip prostheses more frequently, and showed a better response to NSAID than sporadic cases. Another report showed arthritis and uveitis in association to familial forms of AS but no association with psoriasis and inflammatory bowel disease (1), and a Korean study reported lower frequency of oligoarthritis, lower BMI, lower ESR and CRP at diagnosis and higher presence of HLA-B27 in familial cases compared to sporadic (6).

With the new ASAS criteria, patients are classified as axial (including non-radiographic and AS subgroups) or peripheral SpA (12). Furthermore, these criteria have involved for the first time the use of magnetic resonance imaging (MRI) to detect inflammatory changes at sacroiliac joints at early stages of the disease. It is yet unknown whether or not the expression of familial disease in patients fulfilling ASAS criteria differs from previous results. If we were able to identify phenotypic differences between familial and sporadic cases according to the new criteria, we could tailor screening and ascertainment strategies that may differ between forms of disease; in addition, this knowledge might contribute to a better understanding of the disease.

Our objective was thus to analyse clinical and imaging differences between familial and sporadic SpA cases in patients with disease of recent onset and classified as SpA by the ASAS criteria.

Methods

We performed a cross-sectional study by using the baseline data of the ESPERANZA cohort. This ongoing early SpA cohort was created from the homonymous programme, which has been described in detail elsewhere (22). Briefly, patients with predefined referral criteria are referred to 25 early SpA units distributed nation-wide and are attended in the programme under specific protocols, their data are entered into a web-based system that allows monitoring the quality of care, as well as conducting research. The programme was reviewed and approved by the Research Ethics Committee of Hospital Reina Sofia, Cordoba, Spain, and all patients were informed and consented to participate in the cohort.

Patients and definitions

The study is based on the patients recruited in the Esperanza programme between April 2008 and June 2011. Patients were eligible for the programme if they were under 45 years of age, had experienced symptoms from more than 3 months and less than 2 years, and had

at least one of the following situations: (i) inflammatory back pain (IBP), (ii) asymmetrical arthritis, predominantly in lower limbs, or (iii) back pain or arthralgia with psoriasis, inflammatory bowel disease (IBD), uveitis, radiographic sacroiliitis, positivity for HLA-B27 or a family history of SpA. Patients were referred to the programme by primary or specialised care (rheumatology, gastroenterology, ophthalmology, orthopaedics and emergency services).

For this study, patients fulfilling ASAS classification criteria were included. (12) For analysis of the axial SpA subgroup we considered only patients referred by back pain and for the peripheral criteria only those patients referred by peripheral symptoms in the absence of axial pain. We thus prevented the same patient from being classified as both an axial and a peripheral case.

A patient was considered a familial SpA if he or she answered positively to whether any first or second degree relatives (father, mother, brother, sister, son, daughter) had any of the following: AS, psoriasis, uveitis, reactive arthritis or IBD (12-14), although the diagnosis in the relative was not further investigated. These diseases were chosen as they are part of the ESSG/ASAS criteria. All other cases were considered as sporadic.

Variables and data collection

Variables that were studied in relation to the phenotype were: sociodemographic (age, sex and work status), symptoms duration (time from the onset of symptoms to first visit of the Programme); the presence of lumbar morning stiffness, IBP, alternating buttock pain, peripheral arthritis, peripheral enthesitis, psoriasis, dactylitis, IBD, uveitis, diarrhea, cervicitis, urethritis; number of swollen joints; night pain, physician and patient's global assessment of disease activity using a 0–100 visual analogue scale (VAS); the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (23); the Ankylosing Spondylitis Disease Activity Score (ASDAS) (24, 25); functional capacity scored with the Bath Ankylosing Spondylitis Functional Index (BASFI) (26) and Bath Ankylosing Spondylitis Metrology Index (BASMI) (27). Laboratory tests evaluated included erythrocyte sedimentation rate (ESR, reference range 0–20 mm/h), C-reactive protein (CRP, reference range 0–5 mg/l) and HLA-B27. Quality of life was additionally evaluated with a specific 18-item questionnaire on quality of life in AS (ASQoL) (28), where lower values indicate a better quality of life. Structural damage was locally assessed with the Bath Ankylosing Spondylitis Radiology Index (BASRI) (29) by trained rheumatologists. The decision to perform an MRI of the sacroiliac joints with STIR images was performed at the discretion of each rheumatologist. The definition of positive MRI was based on the ASAS group definition for active lesion on MRI (30).

For additional description of the patients, we collected current treatments including non-steroidal anti-inflammatory drugs (NSAIDs), corticoids, disease-modifying anti-rheumatic drugs, and biologic therapies, as well as exercise and physical activity.

Statistical analysis

We used descriptive statistics adequate to the distribution of each variable to describe the patients in each group (familial versus sporadic, stratified by axial and peripheral SpA). Chi-square test was used to compare categorical and dichotomous variables between groups, and *t*-test and Mann-Whitney U-test to compare continuous with normal or not normal distribution variables, respectively. Missing data was not imputed. A two-tailed *p*-value of <0.05 was considered significant. All tests were performed using the SPSS statistical package, v. 20.0.

Results

A total of 377 patients with early SpA were included in this analysis. Seventy seven percent were classified as axial SpA (182 non-radiographic SpA and 109 AS) SpA and -and 23% as peripheral SpA. Sixty four percent were men, mean age was 32, and mean disease duration 12 months. One hundred thirty two patients (35%) were familial cases of SpA. The differences between patients of both familial and sporadic forms, stratified by type of SpA, axial or peripheral are presented in Table I. The number of patients for whom an MRI of sacroiliac joints was available follows: in axial SpA, 109 in sporadic cases and 58 in familial cases, and in peripheral SpA, 15 sporadic cases and 6 familial cases.

Table I. Baseline characteristics of the sample: Patients fulfilling ASAS classification criteria in the ESPERANZA cohort (n=377).

Characteristic	Parameter
Age (years), m ± SD	32.2 ±7.2
Male sex, n (%)	241 (63.9)
Symptoms duration (months), m ± SD	12.1 ±6.8
Inflammatory back pain (ASAS definition), n (%)	112 (29.7)
Peripheral arthritis, n (%)	136 (36.1)
Enthesitis, n (%)	100 (26.5)
Psoriasis, n (%)	61 (16.2)
Dactylitis, n (%)	44 (11.7)
Inflammatory bowel disease, n (%)	19 (5.0)
Uveitis, n (%)	24 (6.4)
Diarrhoea, cervicitis, urethritis, n (%)	16 (4.2)
Family history, n (%)	132 (35.0)
HLA-B27, n (%)	247 (66.2)
CRP (mg/L), m ± SD	11.5 ±20.3
ESR (mmHg), m ± SD	13.7 ±13.5
SJC (0-68), m ± SD	0.5 ±1.7
Physician's VAS (0-100), m ± SD	2.8 ±2.2
Patient's VAS (0-100), m ± SD	3.4 ±3.0
BASDAI (0-10), m ± SD	4.0 ±2.7
BASFI (0-10), m ± SD	3.7 ±2.3
ASQoL (0-18), m ± SD	3.7 ±2.3
Fulfillment of axial ASAS criteria, n (%)	200 (53.1)
Fulfillment of peripheral ASAS criteria, n (%)	86 (22.8)
Fulfillment of axial and peripheral ASAS criteria, n (%)	91 (24.1)

m: mean; SD: standard deviation; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SJC: swollen joint count; VAS: visual analogue scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life.

In patients with early axial disease, familial cases were significantly younger at symptoms onset (30 vs 33 years), presented more frequently HLA-B27 positivity (83.2% *vs*. 71.1%), had significantly lower BASMI (1.2 *vs*. 1.6) and less sacroiliitis on MRI (35.6% *vs*. 46.8%). No other differences were found in sociodemographic and clinical variables. In the group of patients with early peripheral SpA, no differences were found in any variable between familial and sporadic groups.

Discussion

In the present study we have compared patients with familial and sporadic axial and peripheral SpA in early stages of the disease. To our knowledge, this is the first report to analyse familiarity in very early SpA patients classified according to new ASAS criteria.

In the ESPERANZA programme, 35% of the patients had a familial SpA, similar to earlier reports (17-19), regardless being classified as axial or peripheral SpA. In patients with axial SpA, familial cases were younger at symptoms onset compared with sporadic cases. This finding has also been described in studies with AS patients (3, 8, 31), but not in others (1, 5, 6). It may suggest that patients with mild symptoms and a 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. This could even lead to a better response to treatment in the incident cases among family members, as it may be the explanation in the case-series by Caso *et al*. (32). Nevertheless, the contribution of a genetic component to an earlier disease onset should not be ignored. In fact, a study on women with familial AS reported younger age at onset (3), and another report found that the average age at disease onset was lower in HLA-B27 positive patients compared to HLA-B27 negative patients (33).

We found no sex differences as in other studies (1, 6); however, others found more women among familial cases of AS than in sporadic AS (8). In this latter case, the authors hypothesised that women with a family history of SpA were more closely assessed than those without a history, thus enabling more patients to be diagnosed in the first group, since AS in women is usually less symptomatic at axial level, what can lead to underdiagnosis (34).

As we expected, the prevalence of HLA-B27 positive was statistically higher in patients with familial axial SpA, the same as previous reports (6, 8). But in contrast to previous studies, no differences were observed for arthritis, uveitis, enthesitis, IBD or psoriasis between sporadic and familial patients (1, 6). Very likely, the definition of familiality and the extent of proband patients were different between studies. Moreover, previous studies were based on patients with established AS and we have only analysed patients with early disease. Thus, we consider that this picture might change in the long term, as some of our patients will probably develop extra-articular manifestations. There were significant differences in BASMI scores, patients with familial axial SpA had better spinal mobility than sporadic axial SpA patients. These results are similar to those reported in previous publications (5, 8). Nevertheless, we found no differences between groups in BASRI score, probably, at

Table II. Differences in early axial and peripheral spondyloarthritis according to family history.

	Axial spondyloarthritis (n=291)			Peripheral spondyloarthritis (n=86)		
	Sporadic n=190 (65%)	Familial n= 101 (35%)	*p*-value	Sporadic n=55 (64%)	Familial n=31 (36%)	*p*-value
Age, m (SD)	32.6 (6.9)	30.8 (7.1)	0.04	33.5 (8.0)	31.6 (7.3)	0.3
Age at symptoms onset, m (SD)	30.3 (6.9)	29.7 (7.2)	0.04	32.5 (7.8)	30.2 (7.1)	0.3
Men, n (%)	124 (65.3)	67 (66.3)	0.9	35 (63.6)	15 (48.4)	0.2
Work disability, n (%)						
Absent	170 (89.5)	90 (89.1)	0.7	40 (72.7)	27 (87.1)	0.3
Temporary	16 (8.4)	10 (9.9)		14 (25.5)	4 (12.9)	
Permanent	4 (2.1)	1 (1.0)		1 (1.8)	0	
Months with symptoms, m (SD)	12.8 (6.8)	13.4 (6.5)	0.5	10.0 (6.6)	8.0 (5.2)	0.2
Lumbar morning stiffness, n (%)	126 (66.3)	72 (71.3)	0.4	5 (9.1)	1 (3.2)	0.3
Inflammatory low back pain, n (%)	72 (37.9)	40 (39.6)	0.8	-	-	-
Pain in buttocks, n (%)	81 (42.6)	42 (41.6)	0.9	-	-	-
Peripheral arthritis, n (%)	38 (20.0)	15 (14.9)	0.3	53 (96.4)	30 (96.8)	0.9
Swollen joints, m (SD)	0.3 (1.5)	0.2 (1.1)	0.7	1.2 (2.0)	1.7 (2.8)	0.3
Peripheral enthesitis, n (%)	36 (18.9)	21 (20.8)	0.7	31 (56.4)	12 (38.7)	0.1
Psoriasis, n (%)	23 (12.1)	10 (9.9)	0.6	18 (32.7)	10 (32.3)	0.9
Dactylitis, n (%)	11 (5.8)	5 (5.0)	0.8	21 (38.2)	7 (22.6)	0.1
Inflammatory bowel disease, n (%)	6 (3.2)	3 (3.0)	0.9	7 (12.7)	3 (9.7)	0.7
Uveitis, n (%)	11 (5.8)	12 (11.9)	0.07	1 (1.8)	0	0.5
Diarrhoea, cervicitis, urethritis, n (%)	9 (4.7)	2 (2.0)	0.2	2 (3.6)	3 (9.7)	0.3
HLA-B27 positive, n (%)	135 (71.1)	84 (83.2)	0.02	18 (32.7)	10 (32.3)	0.9
Ankylosing spondylitis, n (%)	78 (41.1)	31 (30.7)	0.09	-	-	-
Sacroiliitis on MRI, n (%)	89 (46.8)	36 (35.6)	0.01	-	-	-
Total BASRI, m (SD)	1.9 (1.9)	1.6 (1.5)	0.2	-	-	-
CRP (mg/L), m (SD)	11.1 (15.3)	10.3 (15.1)	0.7	15.3 (36.0)	11.0 (20.2)	0.6
Night pain (0 – 10 VAS), m (SD)	3.9 (2.9)	3.7 (3.0)	0.6	1.3 (2.2)	2.2 (3.3)	0.2
Physician's global (0–10 VAS), m (SD)	2.9 (2.1)	3.0 (2.4)	0.8	2.5 (2.3)	2.3 (2.0)	0.7
Patient's global (0–10 VAS), m (SD)	4.2 (2.7)	4.0 (2.7)	0.6	3.2 (2.5)	3.0 (2.4)	0.8
BASDAI, m (SD)	3.9 (2.3)	3.6 (2.1)	0.3	3.7 (2.3)	3.0 (2.1)	0.2
BASDAI >4, n (%)	102 (53.7)	48 (47.5)	0.4	26 (47.3)	11 (35.5)	0.5
ASDAS-CRP, m (SD)	2.3 (1.1)	2.1 (1.0)	0.1	2.1 (1.1)	1.9 (1.1)	0.5
BASFI, m (SD)	2.5 (2.4)	2.2 (2.2)	0.3	1.7 (2.0)	1.7 (1.8)	0.9
BASMI, m (SD)	1.6 (1.2)	1.2 (1.3)	0.03	-	-	
ASQoL, m (SD)	6.1 (5.0)	5.5 (4.4)	0.5	4.5 (4.9)	4.2 (5.1)	0.8
Exercise, n (%)	83 (43.7)	44 (43.6)	1.0	9 (16.4)	6 (19.4)	0.7
NSAID, n (%)	164 (86.3)	83 (82.2)	0.3	31 (56.4)	23 (74.2)	0.1
Response to NSAID, n (%)	141 (74.2)	75 (74.3)	0.9	-	-	
Glucocorticoids, n (%)	11 (5.8)	2 (2.0)	0.1	12 (21.8)	5 (16.1)	0.5
DMARD, n (%)	36 (18.9)	15 (14.9)	0.4	30 (54.5)	18 (58.1)	0.8
Anti-TNF therapy, n (%)	12 (6.3)	5 (5.0)	0.6	6 (10.9)	2 (6.5)	0.5

m: mean; SD: standard deviation; MRI: magnetic resonance imaging; SpA: spondyloarthritis; VAS: visual analogue scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS-CRP: Ankylosing spondylitis disease activity index with CRP; BASMI: Bath AS Metrology Index; BASRI: Bath Ankylosing Spondylitis Radiology Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ASQoL: Ankylosing Spondylitis Quality of Life; NSAID: non-steroidal anti-inflammatory drugs; DMARD: disease-modifying anti-rheumatic drugs; TNF: tumour necrosis factor.

least in part, because we included patients with early disease. On the other hand, the rate of patients with positive sacroiliitis on MRI was significantly higher in the sporadic axial SpA subgroup. This could explain the worse spinal mobility on average in patients with sporadic axial SpA compared to familial cases. In addition, it might pose MRI more helpful in sporadic than in familial cases. Besides, this might reflect what it has been suggested, that familial SpA is less severe than sporadic SpA (5).

Interestingly, there were no clinical differences between familial and sporadic peripheral SpA. Although more studies are necessary to elucidate the possible role of familial clustering in peripheral SpA, taking into account that in patients with familial AS no clear association with peripheral arthritis has been reported (6-8), it might be considered that familial aggregation is mainly associated with axial disease. Additionally, it could be due to the smaller sample size in this group.

Next, it has been shown a major genetic contribution to disease severity in AS (21), being sporadic cases more severe (5). We only analysed patients with early SpA, therefore, it was impossible to establish robust prognostic conclusions.

As in most studies like this one, a potential limitation is that the classification of sporadic and familial SpA is based on patient's information. As a consequence, there could be patients unaware of cases of the disease in relatives and therefore a misdiagnosis of familial cases. However, most AS patients are correct in their statements, as previously shown (35). Additional limitations are the evaluation of images at the local level, instead of a centralised reading, what could increase the noise in the imaging variables, and thus reduce the detection level, as well as a notable number of missing values for many variables, especially MRI. Also, prognostic implications cannot be concluded due to the cross-sectional design of this analysis.

In conclusion, in this group of patients with early disease, axial familial SpA presents an earlier onset of symptoms, but less activity on MRI at sacroiliac joints and better mobility, suggesting that could be a milder disease compared with sporadic axial SpA, or that the cases were spotted at an earlier stage due to awareness of the disease in the family. We did not see any major differences between familial and sporadic peripheral SpA. Sporadic axial SpA should not be neglected and considered a less severe disease than familiar SpA. Prospective studies are needed to confirm whether prognosis differ between forms.

Key messages

- We can expect the onset of symptoms of axial SpA to happen in younger individuals in families with SpA-related diseases.
- Peripheral and axial SpA differ regarding the presentation of familial and sporadic cases; differences occur only among axial SpA cases.
- MRI seems to help identifying axial SpA in sporadic cases; this observation warrants confirmation.

Acknowledgements

The authors would like to thank all patients participating in the Esperanza Programme as well as all members of the Esperanza Study Group.

The members of the Esperanza Study Group are as follows.

Coordinators: E. Collantes, H. Reina Sofía, Córdoba; L. Carmona and M. Gobbo, Research Unit, Sociedad Española de Reumatología (SER), Madrid.

Scientific commitee: J. Mulero, H. Puerta de Hierro, Madrid; E. de Miguel, H.U. La Paz, Madrid; S. Muñoz-Fernández, H. Infanta Sofía, Madrid; P. Zarco, F.H. Alcorcón, Madrid;

Collaborators: J. Rivera, H. Gregorio Marañón, Madrid; J.C. López Robledillo, H. Niño Jesús, Madrid; C. Castillo Gallego, H.U. La Paz, Madrid; J. Rosas, G. Santos, H. Marina Baixa, Villajoyosa; J.L. Fernández Sueiro, J. Pinto Tasende, E. González Díaz de Rabago, H.U. Juan Canalejo, La Coruña; C. Montilla, S. Gómez Castro, López R, J. del Pino Montes, H.U. de Salamanca, Salamanca; I.P. Granados Bautista, A. Hernández Sanz, H. Virgen de la Salud, Toledo; J. Sanz Sanz, H. Puerta de Hierro, Majadahonda, Madrid; M. Fernández Prada, J. Tornero, H.U. de Guadalajara, Guadalajara; C. Campos, J. Calvo, H.G.U. de Valencia, Valencia; X. Juanola, V. Ríos, H.U. de Bellvitge, Barcelona; E. Moreno, M.I. Rotés, H. de San Rafael, Barcelona; I. Ibero, C. Fernández Carballido, V. Jovaní, N. Martínez Alberola, H.G.U. de Elda, Alicante; L.F. Linares, M.J. Moreno Ramos, A. Uceda, M.J. Moreno Martínez, M.D. Beteta, H.U. Virgen de la Arrixaca, Murcia; J.C. Quevedo, C. Rodríguez Lozano, H.U. Dr Negrín, Las Palmas de Gran Canaria; E. Trujillo, S. Bustabad, H.U. de Canarias, Santa Cruz de Tenerife; J.A. Román Ivorra, S. Muñoz Gil, H.U. Dr Peset, Valencia; A. Juan Mas, I. Ros Vilamajó, M. Ibáñez Barceló, H. Son Llatzer, Mallorca; M.C. Castro Villegas, H.U. Reina Sofía, Córdoba; J. Gratacós Matmija, M. Moreno Martínez-Loza, H. Sabadell Corp. Parc Taulí, Barcelona; R. Almodóvar, H. Fundación Alcorcón, Madrid; E. Rejón, S. Rodríguez Montero, H.U. Virgen de Valme, Sevilla; T. Ruiz Jimeno, H. Sierrallana, Torrelavega; J.J. Aznar, E. Chamizo Carmona, N. Garrido Puñal, H. de Mérida, Mérida; P. Fernández Dapica, H. 12 de Octubre, Madrid; E. Brito Brito, H. Ramón y Cajal, Madrid; E. Pérez Pampín, H. Clínico Universitario de Santiago, Santiago de Compostela.

References

1. SAID-NAHAL R, MICELI-RICHARD C, BERTHELOT JM *et al*.: The familial form of spondylarthropathy: a clinical study of 115 multiplex families. Groupe Francais d'Etude Genetique des Spondylarthropathies. *Arthritis Rheum* 2000; 43: 1356-65.
2. BREBAN M, SAID-NAHAL R, HUGOT JP, MICELI-RICHARD C: Familial and genetic aspects of spondyloarthropathy. *Rheum Dis Clin North Am* 2003; 29: 575-94.
3. KENNEDY LG, WILL R, CALIN A: Sex ratio in the spondyloarthropathies and its relationship to phenotypic expression, mode of inheritance and age at onset. *J Rheumatol* 1993; 20: 1900-4.
4. LECLERCQ SA, CHAPUT L, RUSSELL AS: Ankylosing spondylitis: a family study. *J Rheumatol* 1983; 10: 629-32.
5. CALIN A, KENNEDY LG, EDMUNDS L, WILL R: Familial versus sporadic ankylosing spondylitis. Two different diseases? *Arthritis Rheum* 1993; 36: 676-81.
6. KIM HW, CHOE HR, LEE SB *et al*.: Phenotype difference between familial and sporadic ankylosing spondylitis in Korean patients. *J Korean Med Sci* 2014; 29: 782-7.

7. PAARDT M, DIJKMANS B, GILTAY E, VAN DER HORST-BRUINSMA I: Dutch patients with familial and sporadic ankylosing spondylitis do not differ in disease phenotype. *J Rheumatol* 2002; 29: 2583-4.
8. ALMODOVAR R, FONT P, ZARCO-MONTEJO P *et al*.: Phenotypic differences between familial versus sporadic ankylosing spondylitis: a cross-sectional Spanish registry of spondyloarthropathies (REGISPONSER). *Clin Exp Rheumatol* 2011; 29: 822-7.
9. LIU Y, LI J, CHEN B, HELENIUS H, GRANFORS K: Familial aggregation of ankylosing spondylitis in Southern China. *J Rheumatol* 2001; 28: 550-3.
10. GEIRSSON AJ, KRISTJANSSON K, GUDBJORNSSON B: A strong familiality of ankylosing spondylitis through several generations. *Ann Rheum Dis* 2010; 69: 1346-8.
11. UDDIN M, MAKSYMOWYCH WP, INMAN R *et al*.: UGT2B17 copy number gain in a large ankylosing spondylitis multiplex family. *BMC Genet* 2013; 14: 67.
12. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
13. VAN DEN BERG R, VAN GAALEN F, VAN DER HELM-VAN MIL A, HUIZINGA T, VAN DER HEIJDE D: Performance of classification criteria for peripheral spondyloarthritis and psoriatic arthritis in the Leiden Early Arthritis cohort. *Ann Rheum Dis* 2012; 71: 1366-9.
14. DOUGADOS M, VAN DER LINDEN S, JUHLIN R *et al*.: The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218-27.
15. BROWN MA, KENNEDY LG, MACGREGOR AJ *et al*.: Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. *Arthritis Rheum* 1997; 40: 1823-8.
16. AMOR B, FELDMANN JL, DELBARRE F, HORS J, BEAUJAN MM, DAUSSET J: Letter: HL-A antigen W27--a genetic link between ankylosing spondylitis and Reiter's syndrome? *N Engl J Med* 1974; 290: 572.
17. BREWERTON DA, HART FD, NICHOLLS A, CAFFREY M, JAMES DC, STURROCK RD: Ankylosing spondylitis and HL-A 27. *Lancet* 1973; 1: 904-7.
18. SCHLOSSTEIN L, TERASAKI PI, BLUESTONE R, PEARSON CM: High association of an HL-A antigen, W27, with ankylosing spondylitis. *N Engl J Med* 1973; 288: 704-6.
19. VAN DER LINDEN SM, VALKENBURG HA, DE JONGH BM, CATS A: The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum* 1984; 27: 241-9.
20. BROWN MA, LAVAL SH, BROPHY S, CALIN A: Recurrence risk modelling of the genetic susceptibility to ankylosing spondylitis. *Ann Rheum Dis* 2000; 59: 883-6.
21. HAMERSMA J, CARDON LR, BRADBURY L *et al*.: Is disease severity in ankylosing spondylitis genetically determined? *Arthritis Rheum* 2001; 44: 1396-400.
22. MUNOZ-FERNANDEZ S, CARMONA L, COLLANTES E *et al*.: A model for the development and implementation of a national plan for the optimal management of early spondyloarthritis: the Esperanza Program. *Ann Rheum Dis* 2011; 70: 827-30.
23. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
24. LUKAS C, LANDEWÉ R, SIEPER J *et al*.: Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 18-24.
25. VAN DER HEIJDE D, LIE E, KVIEN TK *et al*.: ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 1811-8.
26. CALIN A, JONES SD, GARRETT SL, KENNEDY LG: Bath Ankylosing Spondylitis Functional Index. *Br J Rheumatol* 1995; 34: 793-4.
27. JONES SD, PORTER J, GARRETT SL, KENNEDY LG, WHITELOCK H, CALIN A: A new scoring system for the Bath Ankylosing Spondylitis Metrology Index (BASMI). *J Rheumatol* 1995; 22: 1609.
28. DOWARD LC, SPOORENBERG A, COOK SA *et al*.: Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Ann Rheum Dis* 2003; 62: 20-6.
29. MACKAY K, MACK C, BROPHY S, CALIN A: The Bath Ankylosing Spondylitis Radiology Index (BASRI): a new, validated approach to disease assessment. *Arthritis Rheum* 1998; 41: 2263-70.
30. RUDWALEIT M, JURIK AG, HERMANN KG *et al*.: Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009; 68: 1520-7.
31. DINCER U, CAKAR E, KIRALP MZ, DURSUN H: Diagnosis delay in patients with ankylosing spondylitis: possible reasons and proposals for new diagnostic criteria. *Clin Rheumatol* 2008; 27: 457-62.
32. CASO F, COSTA I, DEL PUENTE A *et al*.: Effects of tumour necrosis factor-α inhibitors in mothers and daughters concordant for HLA-B27-positive ankylosing spondylitis. *Clin Exp Rheumatol* 2015; 33: 411-3.
33. FELDTKELLER E, KHAN MA, VAN DER HEIJDE D, VAN DER LINDEN S, BRAUN J: Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003; 23: 61-6.
34. CALIN A, BROPHY S, BLAKE D: Impact of sex on inheritance of ankylosing spondylitis: a cohort study. *Lancet* 1999; 354: 1687-90.
35. CALIN A, ELSWOOD J: Relative role of genetic and environmental factors in disease expression: sib pair analysis in ankylosing spondylitis. *Arthritis Rheum* 1989; 32: 77-81.