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Disease impact in axial spondyloarthritis: Divergent roles between family history of disease and HLA-B27?

Impacto de la enfermedad en la espondiloartritis axial: ¿papel divergente entre los antecedentes familiares de la enfermedad y el HLA-B27?

Dear Editor,

Spondyloarthritis (SpA) is a group of interrelated processes with a strong genetic component.[1,2] A positive family history of SpA has been reported in up to 40% of axial SpA (axSpA) patients and the risk to develop SpA in HLA-B27-positive first-degree relatives of HLA-B27-positive SpA patients has been estimated to be 16-times higher than that of HLA-B27-positive individuals in the general population.[3] This has led to assume that both family history and HLA-B27 positivity are factors whose weight in the genesis and evolution of these diseases is interchangeable.[4] Herein, we explore the relationships between HLA-B27, family history, and disease impact, in axSpA.

Post hoc analysis of a study in which we evaluated the construct validity of the Assessment of SpondyloArthritis international Society-Health Index (ASAS-HI) in patients with axSpA.[5] The optimal criterion for detecting the high/very high disease activity ASDAS category was an ASAS-HI > 6, area under the ROC curve

Table 1
Univariate regression analysis of disease characteristics between patients with and without high disease impact.

Feature	ASAS HI ≤ 6 (*n*: 69)	ASAS HI > 6 (*n*: 42)	OR (95%CI)	*P*-Values
Age, yrs (SD)	42.7 (11.2)	44.3 (9.8)	1.01 [0.98–1.05]	.44
Disease duration, yrs (SD)	7.6 (7.5)	7.8 (5.2)	1.01 [0.94–1.08]	.88
Men, n (%)	49 (71)	25 (59.5)	0.6 [0.27–1.34]	.21
AS, n (%)	47 (68.1)	27 (64.3)	1.19 [0.53–2.67]	.67
Family history, n (%)	6 (8.7)	10 (23.8)	2.42 [0.83–7.07]	.10
HLA-B27, n (%)	62 (89.9)	26 (61.9)	0.18 [0.07–0.50]	.0008
Education level				
Primary, *n* (%)	25 (36.2)	18 (42.9)	Ref.	
Secondary, *n* (%)	20 (29)	14 (33.3)	0.97 [0.39–2.42]	.95
University, *n* (%)	24 (34.8)	10 (23.8)	0.58 [0.22–1.50]	.26
CVRF				
Smoking, *n* (%)	25 (36.2)	19 (45.2)	1.45 [0.67–3.18]	.34
Obesity, *n* (%)	8 (11.6)	10 (23.8)	2.38 [0.86–6.63]	.09
Diabetes, *n* (%)	3 (4.3)	3 (7.1)	1.69 [0.33–8.80]	.53
HBP, *n* (%)	9 (13)	5 (11.9)	0.90 [0.28–2.90]	.86
Dyslipidemia, *n* (%)	17 (24.6)	9 (21.4)	0.83 [0.33–2.09]	.69
Radiographic features				
Bilateral SI, *n* (%)	57 (82.6)	30 (71.4)	1.90 [0.76–4.74]	.17
Squaring, *n* (%)	13 (18.8)	9 (21.4)	1.17 [0.45–3.05]	.74
Syndesmophytes, *n* (%)	12 (17.4)	9 (21.4)	1.30 [0.49–3.40]	.59
SpA-associated features				
Enthesitis, *n* (%)	7 (10.1)	1 (2.4)	0.22 [0.03–1.82]	.15
Anterior uveitis, *n* (%)	12 (17.4)	2 (2.8)	0.24 [0.05–1.12]	.06
IBD, *n* (%)	2 (2.9)	4 (9.5)	3.53 [0.62–20.16]	.15
Fibromyalgia, n (%)	0 (0)	3 (7.1)	[a]	.99
Depression, n (%)	2 (2.9)	6 (14.3)	5.58 [1.07–29.09]	.041
Treatments				
NSAID, *n* (%)	50 (72.5)	39 (92.9)	4.94 [1.36–17.90]	.015
DMARDs, *n* (%)	4 (5.8)	2 (4.8)	0.81 [0.14–4.64]	.81
Biologic therapy, *n* (%)	40 (58)	27 (64.3)	1.38 [0.63–3.05]	.41

ASAS-HI: Assessment of SpondyloArthritis international Society-Health Index, yrs: years, SD: standard deviation, AS: ankylosing spondylitis, HLA: human leukocyte antigen, CVRF: cardiovascular risk factors, HBP: high blood pressure, SI: sacroiliitis, SpA: spondyloarthritis, IBD: inflammatory bowel disease, NSAID: non-steroidal anti-inflammatory drugs, DMARDs: disease modifying antirheumatic drugs.

[a] The OR for the variable referring to fibromyalgia cannot be calculated as there are no patients in the ASAS HI ≤ 6 column (the calculated ORs tend to infinite values).

0.86 (95%CI: 0.78–0.92), positive likelihood ratio (LR) 7.3 (95%CI: 3.1–17.1), $P < .0001$.[5] Then, a multivariate analysis (corrected by age, sex, and disease duration) was carried out to evaluate the disease factors associated with an ASAS-HI > 6 (regarded as a high impact status).

The average score for ASAS-HI was 5.4 ± 3.8.Among the study population, 69 patients had an ASAS-HI ≤ 6 while 42 showed an ASAS-HI > 6. Table 1 shows the univariate regression analysis between both groups. Upon multivariate regression analysis, HLA-B27 [OR 0.15 (95%CI: 0.05–0.48), $P = .001$], NSAID use [OR 5.4 (95%CI: 1.3–23.3), $P = .023$, and a family history of SpA [OR 3.1 (95%CI: 1.01–10.5), $P = .043$] were independently related to an ASAS-HI > 6, model fit: Cox-Snell's R^2: 0.244, Nagelkerke's R^2: 0.332.

We found a relatively high frequency of patients (37.8%) in the ASAS-HI high impact category. The factors independently associated with this category were HLA-B27, NSAID use, and a positive family history of SpA. The last two factors were positively associated with this state, while patients carrying HLA-B27 reduced the odds of being in a high impact category by 85%.

The HLA-B27 is the strongest known risk factor for axSpA.[1,2] Moreover, chronic back pain patients suspected of SpA with a family history of SpA are positively associated with HLA-B27 carriership.[6] However, when knowledge about HLA-B27 status is available, positive family history seems not to have further influence on axSpA diagnosis.[7] Anyway, both disease aspects are relevant. Our results confer divergent roles to both aspects. Thus, family history was associated with a worse impact of the disease, while HLA-B27 was protective against this outcome. Therefore, it seems that HLA-B27 has clear importance for the classification and diagnosis of SpA, while family history seems more relevant in terms of functional prognosis. In other words, disease susceptibility and adverse outcomes appear to be driven by different genes and other yet ill-defined factors. Our findings seem to be in line with recent observations that confer increasing importance to axSpA related family history burden on different phenotypes, including disease impact.[4,8]

Among the weaknesses of this study, it is worth mentioning that the original report from which the data of the present manuscript are derived had a cross-sectional design. Therefore, the direction of the associations found here is difficult to define. Moreover, the study sample was relatively small, which could introduce type II errors in the comparisons. In fact, there were few patients in the very high category of ASDAS. However, our findings regarding the associations between positive family history and worse disease impact appear to be in line with the results of recent studies.[8]

Family history and HLA-B27 contribute to the classification and diagnosis of SpA, but their roles on the impact of the disease seem to go in opposite directions. In any case, our findings should be endorsed by additional data obtained from larger SpA cohorts.

Data availability

All data from this study are available to third parties upon reasonable request.

Informed consent

This study was approved by the clinical research ethical committee of Hospital Universitario Central de Asturias (Oviedo-Spain).

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Conflict of interest

Authors declare no conflict of interests.

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