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Title Page

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Title: The phenotype of axial spondyloarthritis: is it dependent on HLA-B27 status?

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Abstract (187 of 250 words)

Objective: To describe the radiographic phenotype of axial spondyloarthritis (axSpA) according to the carriage of HLA-B27.

Methods: An international collaboration compared the radiographic phenotype of axSpA according to HLA-B27 status. Patients with ankylosing spondylitis and axial psoriatic arthritis (PsA) were collected. Radiographs were read centrally, blinded to clinical details. The symmetry of the sacroiliac joints and lumbar syndesmophytes, the morphology of syndesmophytes (typical marginal vs atypical chunky) together with the modified Stoke Ankylosing spondylitis spinal score (mSASSS) and PsA spondylitis radiographic index (PASRI), were recorded.

Results: 244 PsA patients and 198 AS patients were included. In PsA, 60 (25%) were HLA-B27 positive while in AS, 148 (75%) were HLA-B27 positive. Patients with HLA-B27 were younger, more often male and had a longer duration of disease. In multivariable logistic regression HLA-B27 was significantly associated with syndesmophyte symmetry (OR 3.02 (95% CI: 1.38-6.61)) and marginal syndesmophytes (OR: 1.97 (95% CI 1.16-3.36)) but not with sacroiliac symmetry. Mean radiographic scores were higher for patients with HLA-B27.

Conclusions: HLA-B27 positive axSpA patients have more severe radiographic damage, more marginal syndesmophytes, and more frequent syndesmophyte symmetry compared to HLA B27 negative patients.

Significance and Innovations

1. HLA-B27 positive patients with aAxSpA have higher levels of radiographic damage, more symmetry and more marginal syndesmophytes.
2. Most patients with axial psoriatic arthritis are HLA-B27 negative and less frequently have sacroiliac joint involvement.
3. Existing classification criteria for axial spondyloarthritis may not be applicable to axial psoriatic arthritis

Introduction

Axial spondyloarthritis (axSpA) is an inflammatory disease of the spine and sacroiliac joints which leads to new bone formation and has the potential to cause total ankylosis of the spine. Ankylosing spondylitis,(AS) represents the classical manifestation of axSpA, and was the hallmark clinical manifestation of spondyloarthritis (SpA), first described in detail by Moll and Wright [1]. Psoriatic arthritis (PsA) is a common form of inflammatory arthritis affecting between 15 and 30% of people with psoriasis and is a member of the SpA group of conditions. The most common phenotype of PsA is predominant peripheral arthritis [2, 3] but up to 50% of patients with PsA develop inflammation in their axial skeleton (axial PsA), and a few (approximately 5%) have isolated axial inflammation [4].

Although axial involvement in PsA can be indistinguishable from axial disease in ankylosing spondylitis (AS), it can also differ in several respects, raising the question of whether axial PsA and AS, with or without psoriasis, are different clinical presentations of the same disease, axSpA, or whether they are separate diseases that have overlapping features [5]. Recent clinical [6] and genetic [7, 8] studies have shown that axial PsA is non-homogenous, based on the presence of HLA-B27, a result confirmed for early axSpA in the DESIR cohort [9].

Our study hypothesis was that the radiographic phenotype of patients with axSpA depends on the carriage of HLA-B27. We hypothesised that HLA-B27 positivity is associated with a more severe, classical ankylosing spondylitis phenotype: these patients have a more symmetrical appearance on the radiographs of both the spine and

the sacroiliac joints, and manifest classical syndesmophyte morphology with smooth, contiguous calcification between adjacent vertebral In contrast, HLA-B27 negative patients will represent an alternative phenotype, with less radiographic severity, less involvement of the sacroiliac joints and spine, less symmetry, and different morphology of syndesmophytes, with unusual shaped, bulkier, non-marginal syndesmophytes [10-12]. In order to achieve phenotypic diversity, we studied patients with PsA and axial involvement (a group of patients recognised to have less frequent carriage of HLA-B27), and AS, with patients being drawn from a number of geographically diverse populations.

Materials and Methods

Patients

Cross-sectional clinical, radiographic and laboratory data from several cohorts in Ireland, Canada, Italy, Germany, Russia and Spain were included. All sites have clinics dedicated to axSpA, with both PsA and AS. The data were extracted from existing databases and digital film archives. Patient consent was not sought specifically for this study although consent was collected within each existing cohort to study both clinical and radiographic data. Formal ethical review was not obtained.

The inclusion criteria were as follows:

- Age 18 or over

- Either: a clinical diagnosis of psoriatic arthritis and fulfilment of CASPAR criteria with a physician diagnosis of axial involvement; or a clinical diagnosis of ankylosing spondylitis and fulfilment of modified NY criteria
- HLA-B27 status available
- Plain radiographs of sacro-iliac joints, lumbar and cervical spines within the last 5 years

Minimal clinical data were collected including basic demographic data, a recent patient completed disease activity measure (the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[13]), and a recent C-reactive protein. In addition the presence/absence of diabetes mellitus was recorded, as there is an association between diabetes mellitus and diffuse idiopathic skeletal hyperostosis (DISH), the radiographic appearance of which may make interpretation of syndesmophyte morphology more difficult.[14]

Radiographs

The majority (>90%) of the images obtained were in the DICOM format: the rest were JPEG images. The images were read by consensus by two observers (LCC and PSH), blind to diagnosis.

The lateral spinal images were scored using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [15] and Psoriatic Arthritis Spondylitis Radiology Index (PASRI) [16] scoring systems. The mSASSS scores the corners of the vertebral bodies from lower border of C2 to upper border of T1, and from lower border of T12 to upper border of S1. At each vertebral corner scores range from 0 to 3 thus giving a total score range of 0 – 72. The PASRI also scores the vertebral bodies in a similar way to the

mSASSS but, in addition, scores the zygo-apophyseal joints at C2/C3, C3/C4, and C4/C5 for fusion, and the sacroiliac joints using the New York [17] criteria, with a score range for each joint of 0-4. These methods have been proven reliable in both AS and PsA[18].

Using further review of the lateral alongside the AP images, other features were recorded at each vertebral level: syndesmophyte morphology (marginal or non-marginal), Andersson lesions, zygo-apophyseal joint fusion in the cervical spine, and paravertebral ossification (ossification adjacent to, but separate from, vertebral body usually contiguous with syndesmophyte) at each level. Symmetry of sacroiliac joints was defined as a two-point difference in scores between each side. Symmetry of syndesmophytes was assessed on AP views and was determined from the ratio of the number of matched pairs of syndesmophytes to the total number of syndesmophytes; a ratio of 0.5 or above was deemed to indicate symmetry, as previously defined for peripheral joint involvement [19].

Statistical analysis

Summary statistics, according to data, are presented with appropriate univariate statistical tests. Logistic regression models were used to investigate the predictors of symmetry and syndesmophyte morphology using binary multivariable logistic regression models entering all independent variables together, assessing goodness of fit by the Hosmer Lemeshow method and percentage of accurate prediction. Independent variables were age, sex, HLA-B27 status, duration of disease, and diabetes status. Using the available data (radiographic scoring of sacroiliac joints, HLA-B27 status,

diagnosis of psoriasis, presence of inflammatory back pain, and elevated CRP) application of the ASAS criteria for axial spondyloarthritis [20] were applied.

Results

Eight sites contributed data on 244 PsA patients and 198 AS patients. In PsA patients, 60 (25%) were HLA-B27 positive, while in AS, 148 (75%) were HLA-B27 positive. Patients with HLA-B27 were younger, more often male and had a longer duration of disease. Patients with HLA-B27 had higher BASDAI, mSASSS and PASRI scores (Table 1). 54 patients in the PsA group did not have radiographic sacroiliitis. Of these, 33 also did not have syndesmophytes. In the AS group 13 patients did not have any syndesmophytes. In total 338 patients met either the clinical or radiographic arm of the axSpA criteria (n = 270 met the radiographic arm, n = 12 met the clinical arm, and n = 56 met both). Fulfilment of these criteria was significantly higher for those with HLA-B27.

Sacroiliac joint involvement

Patients who were negative for HLA-B27 were more likely to have bilateral normal (grade 0 or 1) sacroiliac joints, and less likely to have bilateral grade 4 sacroiliac joints (Table 2). However, there was no difference in symmetry of the sacroiliac joints according to HLA-B27 status, after exclusion of cases with bilateral normal sacroiliac joints. Multivariable logistic regression assessing predictors of sacroiliac symmetry found age (OR1.04 (1.01 – 1.06) to be the only significant predictor (Table 3).

Spinal involvement

Not all cases had syndesmophytes on the anterior-posterior view of the lumbar spine but, nevertheless, there was a clear difference between groups in terms of syndesmophyte symmetry, and in the presence of marginal syndesmophytes, particularly in the lumbar spine where these were more frequently seen in those who were HLA-B27 positive (Table 2). There were no differences in non-marginal syndesmophytes according to HLA-B27 status.

The only predictor of syndesmophyte symmetry was HLA-B27 positivity (OR 3.02 (1.38-6.61)). Presence of marginal syndesmophytes showed significant relationship with age (OR: 1.08 (1.05-1.10)), HLA-B27 status (OR: 1.97 (1.16-3.36)) and male sex (OR: 1.66 (1.04 – 2.66)). For non-marginal syndesmophytes only age (OR: 1.05 (1.03 – 1.07)) and male sex (OR: 2.55 (1.46 – 4.64)) were significant predictors (Table 3).

Discussion

In this observational cross-sectional study, differences in radiographic phenotype according to HLA-B27 status were largely as hypothesised. Thus, the HLA-B27 positive patients had more severe radiographic damage, as measured by mSASSS and PASRI, more bilateral fused sacroiliac joints, more typical marginal syndesmophytes and more symmetry in the spine. However, this study has shown no difference in sacroiliac symmetry, and no difference in non-marginal syndesmophytes, according to HLA-B27 status.

The strengths of this study are the large, international, sample size, with a mixed population of axial PsA and AS, and the blinded reading of the radiographs. The readers

were therefore not subject to bias due to knowledge of diagnosis which may have influenced the results, particularly with regard to 'subjective' interpretations, such as syndesmophyte morphology. This is the first study to describe the phenotype of established axSpA according to HLA-B27 carriage using a mixed population in which HLA-B27 carriage varied markedly. Unlike papers by Jadon et al [6], and Haroon et al [8], we did not focus specifically on disease status (axial PsA compared to AS) hypothesising that HLA-B27 status was the main influence of radiographic phenotype, as result largely confirmed by this study.

This study has some limitations. This study collected a large number of patients with axial PsA and AS from a number of cohorts in Europe and North America. Disease groups were not matched for age, sex and duration of disease, all of which may influence the phenotype (Table 3). Further, central reading was done by consensus, not independently, and the recognition of syndesmophyte morphology was subjective, as no standard definitions are available. As these participants were collected from existing cohorts, the study did not attempt to standardise case definition where currently no accepted criteria for axial PsA are available. Some differences may be due to case selection as it is possible that contributors 'hand-picked' the cases for inclusion.

The limitations noted above may reflect the discordance of results between this study and previous studies particularly with respect to sacroiliac symmetry. In a similar, but single centre study published in 1998, the proportion of symmetrical sacroiliitis in cases of AS and PsA were 0.85 and 0.74 respectively [11] compared to 0.88 for both conditions in this paper. Evaluation of the PsA cohort in Dublin found a proportion of

symmetrical sacroiliitis at 0.27, however this cohort evaluated all patients with PsA, rather than only those with physician diagnosed axial disease. In the latter study it was found that asymmetry was associated with HLA-B*08 and symmetry with HLA-B27 [8].

The patients included in this study had already been diagnosed with axial spondyloarthritis by the investigators, so that it can be assumed that cases of DISH had been excluded prior to referral. However, differentiating between non-marginal syndesmophytes and the appearances of DISH can be difficult, especially where the sacroiliac joints appear normal. DISH may co-exist with axSpA, and DISH may be found in approximately 8% of patients with psoriatic arthritis, according to one study [21]. We acknowledge that some cases of DISH may have been included inadvertently but were unlikely to influence the major findings in relation to HLA-B27 status and phenotype.

This, and other studies have implications for the diagnosis and classification of spondylitis in people with psoriasis. In AS, the prevalence of the MHC class I allele HLA-B27 is 85-90% but in PsA the prevalence is much lower at 20-50% [5, 22, 23] so it would be expected that the axial phenotype would differ between AS and PsA. The Assessment of Spodyloarthritis international Society (ASAS) classification criteria included patients with concomitant psoriasis and thus, by definition, psoriatic spondylitis, although it must be assumed that the majority of patients had non-psoriatic axSpA. The ASAS criteria include a clinical arm, which is dependent on HLA-B27 status, and a radiographic arm which includes imaging evidence of sacroiliitis [20].

Given the lower frequency of HLA-B27 in the spondylitis associated with psoriasis, and the lower frequency of sacroiliac involvement, PsA patients are less likely to fulfil both the clinical or the imaging arm of the classification criteria. It may be necessary to develop an alternative clinical and radiological definition of axial PsA, for classification. If this were to be done an entirely new classification study would be required, including cases of psoriatic spondylitis and classical AS, selecting consecutive cases attending out-patient clinics.

In summary, this analysis suggests less difference in radiographic phenotype between AS and axial PsA than previously found but emphasises the importance of HLA-B27 status in severity and the phenotypic expression of disease radiographically. Future studies, including those assessing classification criteria, should allow for the disparity in HLA-B27 frequency between AS and axial PsA.

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Table 1. Demographic details of cohort, fulfilment of ASAS criteria and radiographic damage scores

* mean (95% confidence intervals)

+ odds ratio (95% confidence intervals

~ median difference (range)

	HLA-B27 positive	HLA-B27 negative	Difference between B27+ and B27- (for continuous data). Odds ratios (for categorical data)	p value
n	208	234		
Age, y, mean (sd)	49.1 (14.2)	53.8 (13.8)	-4.7 (-7.4 – -2.1)*	< 0.0001
Males n (%)	152 (73)	138 (59)	1.9 (1.3 – 2.8)+	0.002
Duration of disease, y, mean (sd)	13.6 (11.9)	11.0 (10.2)	2.6 (0.5 - 4.7)*	0.02
Fulfils clinical arm of ASAS criteria	68 (33)	0	n/a	< 0.0001
Fulfils radiographic arm of ASAS criteria	177 (85)	149 (64)	3.3 (2.1 – 5.2)+	< 0.0001
mSASSS score median (range)	6 (0 – 72)	2 (0 – 72)	0.5 (0 – 3)~	0.04
PASRI score median (range)	12 (0 – 71)	6 (0 – 71)	5 (3 – 7)~	< 0.0001
BASDAI mean (sd)	4.1 (2.0)	3.5 (2.4)	0.6 (0.2 - 1.1)*	0.009

Table 2. Radiographic phenotype according to HLA-B27 status

OR: odds ratio

	HLA-B27 positive	HLA-B27 negative	OR (95% CI)	P (two way)
n	208	234		
N (%) with bilateral normal (grade 0 or 1) sacroiliac joints	11 (5)	39 (17)	0.3 (0.1 – 0.7)	< 0.0001
N (%) with bilateral grade 4 sacroiliac joints	82 (39)	37 (16)	3.5 (2.2 – 5.4)	< 0.0001
Symmetry at SIJ (Excludes bilateral zero) n/N (%)	175/193 (91)	169/194 (87)	1.4 (0.8 – 2.7)	ns
Symmetry syndesmophytes (lumbar spine) n/N (%)	88/113 (78)	50/86 (58)	2.5 (1.4 – 4.7)	0.003
Marginal syndesmophytes, n (%)	128 (62)	119 (51)	1.5 (1.1 – 2.3)	0.02
Marginal syndesmophytes: cervical n (%)	103 (50)	97 (42)	1.4 (0.9 – 2.0)	ns
Marginal syndesmophytes: lumbar n (%)	95 (46)	73 (31)	1.9 (1.3 – 2.7)	0.002
Non-marginal syndesmophytes, n (%)	46 (22)	53 (23)	1.0 (0.6 – 1.5)	ns
Non-marginal syndesmophytes: cervical n (%)	28 (14)	37 (16)	0.8 (0.5 – 1.4)	ns
Non-marginal syndesmophytes: lumbar n (%)	28 (14)	31 (13)	1.0 (0.6 – 1.7)	ns

Table 3. Predictors of radiographic phenotype (symmetry and syndesmophyte morphology)

OR: odds ratio

Multivariable logistic regression analysis	**OR (95% CI)**	**p**
Sacroiliac joint symmetry - chi-square = 7.9, p = 0.45, overall correct prediction = 88.8%		
Sex – male	0.81 (0.55 – 2.14)	ns
HLA-B27 positive	1.54 (0.72 – 3.28)	ns
Age (years)	1.04 (1.01 – 1.06)	**0.02**
Years of diagnosis	1.00 (0.96 – 1.04)	ns
Diagnosis of PsA	0.75 (0.36 – 1.59)	ns
Syndesmophyte symmetry - chi-square = 6.6, p = 0.59, overall correct prediction = 69.5%		
Sex – male	0.89 (0.41-1.95)	ns
HLA-B27 positive	3.02 (1.38-6.61)	**0.006**
Age	1.03 (0.99-1.06)	ns
Years of diagnosis	1.00 (0.97-1.03)	ns
Diagnosis of PsA	0.80 (0.39-1.67)	ns
Marginal syndesmophytes – chi-square = 8.77, p = 0.36, overall correct prediction = 70.2%		
Sex - male	1.66 (1.04 – 2.66)	**0.035**
HLA-B27 positive	1.97 (1.16-3.36)	**0.013**
Age	1.08 (1.05-1.10)	**<0.0001**
Years of diagnosis	1.02 (0.99 – 1.051.64)	ns
Diagnosis of PsA	0.80 (0.47-1.36)	ns
Non-marginal syndesmophytes – chi-square = 6.6, p = 0.58, overall correct prediction = 78.0%		
Sex - male	2.55 (1.46 – 4.64)	**0.001**
Presence of Diabetes	1.65 (0.73-3.76)	ns
HLA-B27 positive	1.20 (0.67-2.17)	ns
Age	1.05 (1.03 – 1.07)	**<0.0001**
Years of diagnosis	1.00 (0.98-1.03)	ns
Diagnosis of PsA	1.17 (0.66 – 2.10)	ns