HLA Antigens May Influence the Age of Onset of Psoriasis and Psoriatic Arthritis

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ABSTRACT. ***Objective.*** To analyze whether HLA antigens may influence the age of onset of both psoriasis and psoriatic arthritis (PsA).

Methods. One hundred thirty-five patients with PsA (77 men, 58 women, mean age 47 ± 12 yrs) were analyzed. All were studied with a standard protocol and consecutively recruited to evaluate the relative contribution of HLA-Cw and HLA-B27 alleles to PsA susceptibility. Fifty patients with psoriasis alone were also recruited to analyze the role of HLA-Cw genes on disease susceptibility. HLA-Cw antigens were investigated by DNA based methods (PCR-SSOP), while HLA-B27 antigen was studied using serological methods, and their frequencies were compared to 177 healthy controls.

Results. In PsA Cw6+ patients, the mean age at psoriasis onset was 23 ± 12 years compared to 32 ± 12 years in Cw6– patients ($p = 0.012$). Age of arthritis onset was 35 ± 13 years in Cw6+ patients versus 38 ± 12 years in Cw6– patients (p = NS). In patients with psoriasis alone, the age at onset was 18 ± 10 years in Cw6+ versus 30 ± 11 years in Cw6– patients ($p < 0.01$). Cw6 correlated well with a positive family history of psoriasis among first-degree relatives (64% of patients with family history were Cw6+, whereas only 30% of those without family history had this allele ($p < 0.05$). The onset age of psoriasis in HLA-B27+ patients was 24 ± 8 years vs 32 ± 14 years in B27– patients ($p = 0.026$), whereas onset age of arthritis was 30 ± 10 years in B27+ compared to an age of onset of 40 ± 12 in B27– patients ($p = 0.0056$).

Conclusion. Our results confirm the known association between Cw6, early onset psoriasis and positive family history (type I psoriasis). The association between HLA-B27 and earlier onset ages for both psoriasis and arthritis in PsA had not previously been emphasized. The HLA antigens may determine not only disease susceptibility, but also the age of disease onset in psoriasis and PsA. (J Rheumatol 2003;30:505–7)

Key Indexing Terms:
PSORIASIS HLA-CW*0602 HLA-B27 PSORIATIC ARTHRITIS ONSET AGE

The higher concordance of psoriasis among monozygotic twins has provided strong evidence for a genetic predisposition to psoriasis, but moreover, many other aspects of this entity (i.e., age of onset, distribution, severity) tend to be more similar in monozygotic than in dizygotic twins, revealing that genes are elements that further control disease expression[1].

On the basis of HLA studies, psoriasis has been divided into types I and II. Type I psoriasis defines patients with early onset disease and positive family history who carry the extended haplotype Cw6-B57-DRB1*0701-DQA1*0201-DQB1*0303 (EH57.1)[2]. Within EH57.1, HLA class I antigens (Cw6-B57) have been associated to a much higher extent with type I psoriasis than the HLA class II alleles[2]. Among patients with PsA, those who carry the HLA-Cw6 also show an earlier age of onset of psoriasis, although it is unclear whether this allele influences the age of onset of arthritis[3].

We analyzed the effect of some HLA genes not only on psoriasis and PsA susceptibility, but also on the expression of some aspects of both entities.

MATERIALS AND METHODS

Patient selection. One hundred thirty-five patients with PsA (77 men, 58 women, mean age 47 ± 12 yrs) according to Moll and Wright[4] were recruited consecutively for this retrospective cohort study. The main features of PsA in our context, as well as the study protocol used in this report, have been published[5]. At the end of the study, patients were classified according to our PsA classification system[5]. Distal interphalangeal (DIP) disease and mutilans form were initially recorded, but at the end of the study did not remain as independent models of PsA.

HLA antigens. HLA-B27 was investigated by serological methods, whereas HLA-Cw typing was performed by DNA based methods (polymerase chain reaction sequence-specific oligonucleotide polymorphism) in the whole cohort with arthritis, 50 patients with psoriasis alone, and 177 healthy blood donors. The control population was selected from the same geographic and racial origin as the study population.

Radiographic and laboratory assessments were as described[5]. Two senior

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rheumatologists read all radiographic films, and there was complete agreement in all except for 3 cases, in which a consensus was achieved.

Statistical analysis. Pearson's chi-square and Fisher's exact tests were used to analyze differences between categorical data, while Student's t proof was applied to test statistical differences between continuous data. ANOVA was used to establish comparisons between continuous data, when more than 2 groups were compared. The relative risk (RR) was calculated by Woolf's method[6]. P values were corrected (p_{corr}) by multiplying them by the number of comparisons at each locus (15 comparisons for the HLA-C locus).

RESULTS

Clinical, demographic, and epidemiological data are summarized in Table 1. Of the 15 HLA-Cw alleles detected, only Cw*0602 was found to be associated with disease. Twenty-seven out of 50 patients with psoriasis (54%, RR 5.3) and 79 of 135 with PsA (58.5%, RR 6.4) carried this antigen compared to a normal frequency of 18% in a control population ($p_{corr} < 0.00001$). This allele was equally distributed among the 3 articular categories found in the study. For PsA, the average age at the onset of psoriasis was 23 ± 12 years in patients carrying the Cw6 allele, and 32 ± 14 years in those who were Cw6 negative (p = 0.012). In patients with psoriasis alone, mean duration of disease was 16 ± 8 years, and the average age at the onset of psoriasis was 18 ± 10 years in Cw6 positive and 30 ± 11 years in Cw6 negative patients (p < 0.01). Age of onset of arthritis was 35 ± 13 years in Cw6 positive versus 38 ± 12 years in Cw6 negative patients (p = NS). Forty-seven of 180 patients (45 with psoriasis plus 135 with PsA) showed a positive family history of psoriasis among first-degree relatives (26%). Thirty of 47 (64%) patients with positive family history carried the HLA-Cw6 antigen compared to 40 of 133 (30%) without a family history (p < 0.05).

Table 1. Clinical, demographic, and epidemiological features of patients with PsA.

Variables	n = 135
Age, yrs	47 ± 12
Sex ratio, male:female	1.3
Psoriasis duration, yrs	17 ± 10
Arthritis duration, yrs	12 ± 6
Psoriasis onset age, yrs	28 ± 14
Arthritis onset age, yrs	35 ± 12
Psoriasis-arthritis latency, yrs	7 ± 7
Psoriasis first, %	75
DIP disease, %	33
Onychopathy, %	44
Enthesitis, %	30
Erosive disease, %	41
IOD, %	15
Oligoarthritis, %	40
Polyarthritis, %	23
Axial disease, %	37
ESR, mm/h	31 ± 20
CRP, mg/dl	12 ± 10

DIP: distal interphalangeal joint; IOD: inflammatory ocular disease; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; continuous data are expressed as mean ± standard deviation.

Fifty of 135 patients developed axial disease (37%), and 56% of them carried the HLA-B27 antigen (vs 7% in the control group, RR 17; p < 0.0001) compared to a frequency of 29.6% in the group with oligoarthritis and 16% in patients with polyarthritis (p = 0.015). In HLA-B27 positive patients, the mean age of onset of psoriasis was 24 ± 8 years versus 32 ± 14 years in HLA-B27 negative patients (p = 0.026), whereas average age at the onset of the arthropathy was 30 ± 10 years in B27 positive versus 40 ± 12 years in B27 negative patients (p = 0.0056).

DISCUSSION

Our analysis of this wide cohort of patients showed that the Cw6 antigen remains one of the major genetic factors contributing to psoriasis development, although its role in the appearance of PsA seems less impressive, if we consider that it was equally distributed among the 3 articular categories in the study. On the other hand, as expected, HLA-B27 contributed to axial disease development[7,8].

The interpretation of genetic studies in PsA has been more complex than in psoriasis alone, due in part to the heterogeneity of PsA clinical expression, which can cause confusion when comparing different studies that may have included different subtypes of patients[9]. Therefore many of the alleles associated with PsA relate to the coexistence of psoriasis rather than the arthritis itself. Indeed, the ancestral haplotypes, AH 13.1 (A30, B13, Cw6, DR7, DQ2), AH 57.1 (A1, B57, Cw6, DR7, DQ2), and AH 47.1 (A3, B47, Cw6, DR7, DQ2), related to psoriasis and PsA, share several alleles reported to be associated with both[10]. This has led to many errors in the past, not only when we analyze studies regarding the role of HLA genes on psoriasis or PsA susceptibility, but also when we try to interpret the supposed associations between HLA class I and II alleles and some aspects of disease, such as the age at disease onset[9]. For example, HLA-B17 and DR7 were found to be associated with earlier age of onset of skin lesions in patients with PsA, as well as in patients with uncomplicated psoriasis. HLA-B17 was also associated with an earlier onset of joint disease in patients with PsA, as was DR2[9]. However, there is now a clear notion that most of these genes are inherited in a linkage disequilibrium manner with HLA-Cw6[7,8]. Indeed, some have found that HLA-B and DR alleles do not contribute directly to disease susceptibility in psoriasis or PsA, and probably the associations between these genes and disease may be secondary to the linkage disequilibrium with Cw*0602 and psoriasis, and MICA-A9 and PsA[11].

With respect to the role of HLA-Cw6 on the age at disease onset and its correlation with a family history of psoriasis, we confirmed data previously reported[2,3]; however, the relationship between HLA-B27 and an earlier age of onset for both psoriasis and arthritis was previously unknown in our population. In this sense, Baek, *et al*[12] reported that in Korean patients with psoriasis, the ages of onset of psoriasis and arthritis in the spondylitic groups were significantly lower

than those of the nonspondylitic group. However, other authors have found HLA-B27 associated with a later onset of arthritis in patients with psoriasis[9].

Given the extensive stretches of polymorphism and the conservation of HLA haplotypes in populations, it remains difficult to implicate a single gene in both disease susceptibility and expression.

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