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Relationship between human lymphocyte antigen-B27 and clinical features of in psoriatic arthritis

Yi-Giien Tsai[1], Deh-Ming Chang[2], San-Yuan Kuo[2], Wei-Ming Wang[3], Yi-Chueng Chen[4], Jenn-Haung Lai[2]

[1]Department of Pediatrics, Christian Hospital, Changhua; [2]Division of Rheumatology/Immunology and Allergy, Department of Internal Medicine and [3]Department of Dermatology, Tri-Service General Hospital; and [4]Armed Forces Sung Shan Hospital, Taipei, Taiwan, ROC

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Psoriatic arthritis is a chronic destructive joint disease. About 40% of psoriatic arthritis patients are positive for human lymphocyte antigens (HLA)-B27. This study investigated the relationship between HLA-B27 and clinical manifestations and prognosis in psoriatic arthritis patients. Demographic, clinical, and laboratory data were analyzed from 41 psoriatic arthritis patients with regular follow-ups. The mean percentage of HLA-B27 in psoriatic arthritis was about 39%. Positive HLA-B27 was associated with an increased risk of development of sacroiliitis (relative risk 8.75; $p<0.01$) but not peripheral arthritis ($p=0.925$). Psoriatic arthritis patients with psoriatic nail disease (41.5% vs 2.4%, $p<0.01$) and distal interphalangeal joints involvement (26.8% vs 3.4%, $p<0.05$) had significantly increased risk of developing deformed joints. Psoriatic arthritis patients with positive HLA-B27 tend to develop deformed joints ($p=0.068$) as well as having elevated levels of C-reactive protein ($p=0.072$), although these results did not attain significance. HLA-B27 antigen may serve as a useful predictive marker for the development of sacroiliitis in Taiwan.

Key words: Human lymphocyte antigen-B27, psoriatic arthritis

Psoriatic arthritis (PA) is an inflammatory arthritis associated with psoriasis. Psoriatic arthritis has been reported in 5% to 42% of patients with psoriasis [1,2]. Joint deformity and destruction as well as disability are frequent among patients with PA. The etiology and pathogenesis of psoriasis and PA remain unknown. It has been suggested that genetic, environmental, and immunological factors have significant influence on the susceptibility and development of the disease [3]. Although the presence of human lymphocyte antigens (HLA)-B27 has been shown to increase the frequency of PA in psoriasis patients as well as the development of psoriatic spondylitis [4], its association with important clinical subsets of PA patients in Taiwan remains unclear [5].

Since HLA antigens are molecules present before development of the disease, their presence may be a risk factor for disease progression [6]. It may also be possible to develop appropriate therapeutic approaches according to the presence or absence of HLA antigens for individual patients with PA [6,7]. The aim of this study was to investigate the relationship between HLA-B27 and the various clinical manifestations of PA. In addition, we tried to analyze whether the presence of HLA-B27 is a risk factor for poor prognosis as well as for developing deformed joints in PA patients.

Materials and Methods

Patients

Data from 41 PA patients diagnosed and regularly followed-up in Tri-Service General Hospital between 1991 and 2001 were analyzed. Skin manifestations of psoriasis were based on the findings of dermatologic examination [8]. Psoriatic arthritis was diagnosed according to the following criteria: the presence of one or more swollen joints for at least 3 months; radiologic changes compatible with PA, including erosions in peripheral joints or definite spinal changes; and past diagnosis of PA by a rheumatologist [4]. Patients with evidence of other joint diseases, such as typical rheumatoid arthritis, systemic lupus erythematosus, and gout, were excluded. Included patients were classified as having: (a) peripheral arthritis when one or more of the following joints was involved: elbows, wrists, knees, ankles, and metacarpophalangeal, proximal

Corresponding author: Dr. Jenn-Haung Lai, Division of Rheumatology/Immunology and Allergy, Department of Internal Medicine, Tri-Service General Hospital, 325, Section 2, Cheng-Kung Road, Taipei, Taiwan, 114, ROC. E-mail address: haungben@tpts5.seed.net.tw

interphalangeal and distal interphalangeal (DIP) joints of the hands and feet; and (b) spinal involvement in the presence of definite radiologic sacroiliitis and/or radiologic syndesmophytes involving the lumbar or cervical spines. At least grade II bilateral or grade III unilateral sacroiliitis by X-ray was considered as sacroiliac joint involvement [1].

Clinical and laboratory assessments

Careful history taking and examinations were performed with particular attention to symptoms of active arthritis. Disease severity and extent of joint disease as well as skin involvement was also assessed. The number of inflamed joints (stress pain, tenderness, effusion) was recorded. A rheumatologist without knowledge of previous medical records further evaluated the final deformed joints (ankylosis, subluxation, or decreased range of motion attributed to joint damage rather than inflammation).

A blood sample was taken at first visit for measurement of inflammatory parameters, including complete blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). HLA-B27 typing was performed by flow-cytometry with monoclonal antibody technology and the erythrocyte-lysed whole blood method [9].

Statistical analysis

The relationship between clinical manifestations at the initial visit and age at onset, psoriasis duration, arthritis duration, peripheral arthritic joints, DIP involvement, nail changes, radiological sacroiliitis, and laboratory findings such as ESR and CRP to HLA-B27 was evaluated. Moreover, all the above clinical parameters were correlated with the number of deformed joints at the final visit.

Data analysis was done using SAS system (Version 6.12, US). Mann-Whitney test was performed for comparing continuous variables related to HLA-B27. Chi-square analysis was used to compare the subgroups of PA related to HLA-B27 and deformed joints. Comparisons between groups (mean) were analyzed using a 2-tailed independent *t* test. A two-tailed *p* value of less than 0.05 was considered significant.

Results

Demographic data and clinical characteristics

All 41 PA patients (28 men, 13 women) registered at the hospital at the time of this analysis were included in the study. Their demographic characteristics are shown in Table 1. The age of onset of PA was 29.4 ± 16.3 years (range, 15-63 years). The mean duration of psoriasis and PA were 9.6 ± 8.5 years and 8.8 ± 8.4 years, respectively. Psoriasis was diagnosed before PA in 21 (51.2 %) patients. The mean number of arthritis cases was 5.2 ± 3.7. The mean number of deformed joint arthritis cases was 1.1 ± 2.7. Spondyloarthropathy with sacroiliitis occurred in 14 (34.1%) patients and only 1 of these had cervical joint involvement (2.4%). Distal interphalangeal involvement was found in 11 (26.8%) patients and nail changes in 17 (41.5%). The mean ESR and CRP were 29.7 ± 31.2 mm/h and 2.04 ± 2.8 mg/dL, respectively. Of these patients, 16 (39%) were HLA-B27 positive.

Table 1. Characteristics of patients with psoriatic arthritis attending the rheumatology department initially (n = 41)

Characteristic	No. of cases (%)
Sex	
Male	28 (68.3)
Female	13 (31.7)
Age, year	40.9 ±14.7
Age onset, year	29.4 ±16.3
Duration of psoriasis, year	9.6 ±8.5
Duration of arthritis, year	8.8 ±8.4
Psoriasis or arthritis diagnosed before	
Psoriasis	21 (51.2)
Arthritis	1 (2.4)
Psoriasis and arthritis at the same time	19 (46.3)
Deformed arthritis, no.	1.1 ±2.7
Peripheral arthritis, no.	5.2 ±3.7
Sacroiliitis	14 (34.1)
Cervical involvement	1 (2.4)
Nail involvement	17 (41.5)
DIP joints involvement	11 (26.8)
ESR, mm/h	29.7 ±31.2
CRP, mg/dL	2.04 ±2.8
HLA-B27	16 (39.0)

Abbreviations: DIP = distal interphalangeal; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein

Interrelationship between HLA-B27 and different arthritis subtypes

Patients were divided into clinical subsets according to the categories outlined above (Table 2). HLA-B27 positive patients have increased frequency of sacroiliitis when compared with the negative population (relative risk 8.75, p=0.006). However, there was no significant association between HLA-B27 status and peripheral arthritis (5.06 ± 4.4 vs 4.76 ± 3.56, p=0.925) as well as DIP involvement (37.5% vs 24%, p=0.485).

Interrelationship between clinical features and advanced joint destruction

HLA-B27 positive patients appeared to have a tendency

Table 2. Relationships between clinical manifestations and HLA-B27 and clinical subsets of psoriatic arthritis related to HLA-B27

	HLA-B27 (+)	HLA-B27 (–)	*p*
Onset age, year	30.19 ± 16.0	28.96 ± 16.7	0.947
Duration psoriasis, year	10.69 ± 9.6	8.84 ± 7.8	0.554
Duration arthritis, year	6.31 ± 4.4	5.37 ± 5.0	0.382
Peripheral arthritis	5.06 ± 4.4	4.76 ± 3.5	0.925
Arthritis no.	5.75 ± 4.2	4.92 ± 3.4	0.657
Deformed no.	2.25 ± 3.7	0.40 ± 1.4	0.068
ESR, mm/h	34.64 ± 45.0	27.45 ± 25.0	0.692
CRP, mg/dL	4.01 ± 4.1	1.05 ± 1.1	0.072
Sacroiliitis	10/16 (62.5%)	4/25 (16%)	0.006
Cervical involvement	1/16 (6.3%)	0/25 (0%)	0.39
Nail involvement	9/16 (56.3%)	8/25 (32%)	0.195
DIP involvement	6/16 (37.5%)	6/25 (24%)	0.485

Abbreviations: HLA = human lymphocyte antigens; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DIP = distal interphalangeal joint

to develop joint deformity (2.25 ± 3.7 vs 0.4 ± 1.4, p= 0.068), but this result did not attain significance. The CRP values in HLA-B27 positive patients revealed the same tendency (4.01 ± 4.1 vs 1.05 ± 1.1, p=0.072) (Table 2). Moreover, examination of the relationship between clinical manifestations at the initial visit and the final number of deformed joints after long-term followed-up revealed that only patients with DIP involvement (26.8% vs 3.4%, p=0.034) and psoriatic nail changes (41.4% vs 2.4%, p=0.001) had significantly increased numbers of deformed joints.

Discussion

Genetic factors play an important role in both psoriasis and PA. Psoriasis is a chronic scaling erythematosus skin disease, known to run in families, with a multifactorial pattern of inheritance. A previous study found a higher frequency of HLA- A1, A10, Bw4, Bw6, Bw38, and DR1 in Chinese psoriasis patients than in the general population [5]. It has been reported that HLA-Cw6 was associated with PA but this association is weak in psoriasis [10]. In addition, analysis of HLA antigen in psoriasis revealed that HLA-B27 was found with increased frequency in patients with PA [5,11]. In this study, the percentage of HLA-B27 in PA is about 39%, a result similar to reports from other countries [1].

A subset of PA patients in this study revealed that HLA-B27 was associated with the presence of sacroiliitis. It is well known that HLA-B27 was higher in various seronegative spondyloarthropathy, such as ankylosing spondylitis, Reiter syndrome, enteropathic arthropathy, and PA [1,12]. Previous studies of HLA antigens also showed that HLA-B27 is a good marker for spondyloarthropathy and the coexistence of HLA-B38, B39, and DR4 is associated with the development of peripheral arthritis [3,4]. Since patients with sacroiliitis were diagnosed by X-ray, the actual percentages may be underestimated due to the absence of obvious radiologic changes in sacroiliac joints in patients with subclinical spinal involvement. However, the association between HLA-B27 and radiologic sacroiliitis has been observed in most studies. [3-6,13-15].

It would be useful for clinicians to identify markers for detection of disease progression in PA patients. One potential marker is HLA-B27. Accordingly, patients can be classified at the time of diagnosis as being either at high risk or low risk for disease progression based on the number of damaged joints. Gladman *et al* [6] prospectively followed a PA cohort over a 14-year period and found that HLA antigens B27, B39, and DQw3 were associated with progression of damage to joints. Patients with HLA-B27 coexistence with DR7 carried a higher susceptibility to joint destruction. By contrast, HLA-B22 provided protection from disease progression in PA [7].

HLA-B27 positive patients in this study seemed to have the tendency to develop joint deformed after 10 years of follow-up. The results did not show significant difference due to several reasons. First, HLA-B27 testing should be combined with testing for other HLA molecules, such HLA-DR7, when evaluating patients. Second, larger data pools may provide a more powerful statistical analysis to reveal a significant difference.

C-reactive protein and ESR are acute-phase reactants that appear to induce inflammation. Both are clinically useful indicators to monitor the level of inflammation [16,17]. In this study, patients with high values of CRP, but not ESR, tended to develop greater deformity in a high number of joints. Helliwell *et al* [16] studied acute-phase reactants in PA patients with varying disease duration and severity. High CRP

concentrations seem to be associated with extensive joint destruction. Erythrocyte sedimentation rate was not more sensitive than CRP in measuring inflammation because it can be influenced by many factors like age, sex, and anemia [17].

Not much is known about the cutaneous pattern and regional involvement related to the severity of PA. Cohen *et al* [18] studied a group of 221 active PA patients and examined the baseline relationships between psoriasis and PA. Only DIP involvement and nail involvement were found to correlate with disease activity of arthritis. As expected, patients with the initial manifestations of DIP involvement and nail changes in our series often progressed to poor condition with joint deformities despite medical treatment.

This study showed that positive HLA-B27 status is related to inflammatory back disease, and may predispose to poor prognosis with high numbers of damaged joints. Further prospective studies are required to examine whether other HLA alleles are strong indicators for disease progression with destructive joints in Taiwan patients with PA. There is evidence to suggest that molecular mimicry may play a role in the pathogenesis of HLA-B27-related spondylo-arthropathies [19]. The role of the B27 molecule in PA remains to be clarified.

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