Frequency of HLA antigens in patients with psoriasis or psoriatic arthritis

ROBERT J.R. MCKENDRY, MD, FRCP[C]
DHARMENDRA P.S. SENGAR, DVM, PH D
JEAN PIERRE DESGROSEILLIERS, MD, FRCP[C]
JAMES V. DUNNE, MB, FRCP[C]

A study of 138 patients with psoriasis — 74 with psoriasis alone and 64 with psoriatic arthritis — revealed a significantly increased frequency of the HLA antigens A1, A28, B13, DR7 and MT3 in those with psoriasis alone and of Bw39 in those with psoriatic arthritis. The frequency of B17 was higher in both patient groups than in a control group of healthy individuals. The frequency of DRw6 was slightly higher in the patients with psoriasis alone (17.8%) than in the controls (4.7%), and that of DR7 was higher in the patients with psoriatic arthritis (52.9%) than in the controls (32.6%). Elevated levels of serum IgG and IgA along with positive results of tests for antinuclear antibody or rheumatoid factor or both were present in less than a tenth of the patients with psoriatic rash alone and in up to a third of those with psoriatic arthritis. Psoriatic arthritis was found to be less likely to develop in patients with purely guttate psoriasis than in those with other types of psoriasis. Clinical subtypes of psoriatic rash or psoriatic arthritis were not associated with the presence of particular HLA antigens.

L'étude de 138 patients souffrant de psoriasis, 74 atteints de psoriasis simple et 64 atteints d'arthrite psoriasique, a révélé une augmentation significative de la fréquence des antigènes HLA A1, A28, B13, DR7 et MT3 chez ceux qui souffraient de psoriasis simple et de l'antigène Bw39 chez ceux atteints de l'arthrite psoriasique. La fréquence de l'antigène B17 était plus élevée chez les deux groupes de patients que chez un groupe témoin de sujets sains. La fréquence de l'antigène DRw6 (17,8%) était légèrement plus élevée chez les patients souffrant de psoriasis simple que chez les témoins (4,7%), alors que la fréquence de l'antigène DR7 était plus élevée chez les patients souffrant d'arthrite psoriasique (52,9%) que chez les témoins (32,6%). Chez moins du dixième des patients atteints d'éruption psoriasique simple et chez jusqu'au tiers de ceux atteints d'arthrite psoriasique on notait des taux élevés d'IgG et d'IgA sériques, de même que des résultats positifs de tests pour l'anticorps antinucléaire, le facteur rhumatoïde ou les deux. Il a été observé que l'arthrite psoriasique est moins susceptible à se développer chez des patients atteints de psoriasis en gouttes que chez ceux qui souffrent d'autres types de psoriasis. Des sous-types cliniques d'éruption psoriasique ou d'arthrite psoriasique n'étaient reliés à la présence d'aucun antigène HLA en particulier.

From the departments of medicine and pathology, Ottawa General Hospital, and the University of Ottawa

Reprint requests to: Dr. Robert J.R. McKendry, Director, Rheumatic diseases unit, Ottawa General Hospital, 501 Smyth Rd., Ottawa, Ont. K1H 8L6

Approximately 10% of patients with psoriasis have some form of psoriatic arthritis.[1] There is a family history of psoriasis in approximately 30% of patients with psoriasis, and various modes of inheritance have been suggested.[2,3] The previously observed association of HLA histocompatibility antigens with psoriasis and psoriatic arthritis[4-6] also emphasizes the etiologic role of genetics in these conditions.

Since the genetic predisposition to psoriasis or psoriatic arthritis seems to be multifactorial, we wondered whether certain clinical subtypes of these conditions would demonstrate more obvious associations with HLA antigens and modes of inheritance. We therefore performed a case–control study of patients with psoriasis alone or with psoriatic arthritis affecting the peripheral joints to determine if there were any differences in the frequency of HLA antigens between the two groups or if any of the subtypes of psoriasis or psoriatic arthritis were significantly associated with such antigens.

Patients and methods

We selected 138 unrelated consecutive patients who had psoriasis alone or psoriatic arthritis from the psoriasis day care centre of the Ottawa General Hospital and the rheumatic disease unit arthritis clinics serving eastern Ontario and western Quebec. The patients from the psoriasis day care centre had been referred there for PUVA therapy — photochemotherapy for the treatment of psoriasis, which involves the oral administration of a psoralen (P), a photoactive drug, followed by exposure to high-intensity, long-wave ultraviolet radiation (UVA). All the assessments for this study were done before the initiation of PUVA therapy. The controls included hospital staff and potential renal transplant donors living in the same area; the number of controls varied depending on the HLA antigen tested for: 370 controls were tested for A, B, Bw35 and Bw44, 185 for Bw38, Bw39 and Cw4, and 43 for all the DR and MT antigens.

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The duration, type and severity of the psoriasis and arthritis were determined by a dermatologist and a rheumatologist. Arthritis was defined as the presence of tenderness and swelling in at least one peripheral joint. Psoriatic arthritis was divided into four types: oligoarticular (fewer than five joints affected); distal interphalangeal; asymmetric polyarticular (five or more joints affected); and symmetric polyarticular. Pelvic x-ray films were not made for all the patients; therefore, the presence or absence of sacroiliitis could not be accurately determined. The types of psoriatic rash included plaque, erythrodermic, guttate and pustular.

Typing for HLA A, B, C, DR and MT antigens was performed by the standard microdroplet complement-dependent lymphocytotoxicity test with reagents supplied by Dr. Paul I. Terasaki. In all 138 patients typing was done for 12 A antigens (A1, A2, A3, A11, A25, A26, A28, A29, A30/31, A32, Aw23 and Aw24), 22 B antigens (B5, B7, B8, B12, B13, B14, B15, B17, B18, B27, B37, B40, Bw16, Bw21, Bw22, Bw35, Bw38, Bw39, Bw44, Bw45, Bw51 and Bw52) and 5 C antigens (Cw1, Cw2, Cw3, Cw4 and Cw5), and in 96 typing was done for 9 DR antigens (DR1, DR2, DR3, DR4, DR5, DR7, DRw6, DRw6Y and DRw8) and 3 MT antigens (MT1, MT2 and MT3). Owing to the unavailability of quality reagents, typing for the Cw6 antigen was not done in all the patients. Statistical analysis was done by the chi-square method with Yates's correction for continuity. The p values for the significance of differences in the frequencies of the HLA antigens in the two groups were not corrected for the number of antigens tested unless so specified.[7]

Testing for serum immunoglobulin levels (by radial immunodiffusion), antinuclear antibody (by indirect immunofluorescence), rheumatoid factor (by latex fixation) and the erythrocyte sedimentation rate (by the Wintrobe method) was done in 95 of the 138 patients.

Results

Of the 138 patients 74 had psoriasis alone and 64 had psoriatic arthritis. There were 73 women and 65 men. The mean age (± the standard deviation) at the onset of the psoriatic rash was 20.7 ± 10.9 years in the patients with psoriasis alone and 23.9 ± 12.1 years in those with psoriatic arthritis. The mean age at the onset of the psoriatic arthritis was 33.9 ± 10.7 years.

Table I shows that only 7% (1/15) of the patients with guttate psoriasis, compared with 51% (63/123) of the patients with other types of psoriasis, had arthritis. At the time of examination the patients with psoriasis alone had a more extensive rash than those with psoriatic arthritis, the average proportions of the total skin surface involved being 31% and 14% respectively. The clinical features of the patients with psoriatic arthritis are shown in Table II.

The patients with psoriatic arthritis were significantly more likely ($p < 0.01$) than those with psoriasis alone to have increased serum immunoglobulin levels (Table III). Five (31%) of the 16 patients with psoriatic arthritis who had a positive result of the antinuclear antibody test (a titre of 1:20 or greater) also had elevated serum IgG or IgA levels. Also, three (43%) of the seven patients with psoriatic arthritis who had a positive result of the rheumatoid factor test (a titre of 1:40 or greater) also had elevated serum IgG or IgA levels. None of the psoriasis or psoriatic arthritis subtypes or tissue types predominated in the patients with elevated serum immunoglobulin levels or antinuclear antibody titres. Increased serum immunoglobulin levels and antinuclear antibody and rheumatoid factor titres were not related to the activity of the arthritis, as measured by the erythrocyte sedimentation rate or the Lansbury Joint Index. For the Lansbury Joint Index, joints are considered "positive" if they are tender to palpation or movement, and each joint is numerically weighted according to its size.

Typing for HLA antigens revealed a marked increase in the

Table I — Clinical features of the rash in 138 patients with psoriasis

Type of psoriasis	No. of patients: With psoriasis alone	With psoriatic arthritis	Total
Plaque	45	42	87
Erythrodermic	0	1	1
Guttate	14	1	15
Plaque–erythrodermic	1	1	2
Plaque–guttate	14	11	25
Pustular	0	2	2
Unknown	0	6	6
Total	74	64	138

Table II — Clinical features of the 64 patients with psoriatic arthritis

Variable	No. of patients or mean ± standard deviation
Type of arthritis	
Oligoarticular	16
Distal interphalangeal	4
Polyarticular	
Asymmetric	21
Symmetric	10
Unclassified	13
Lansbury Joint Index (n = 49)	37.4 ± 37.1
No. of swollen joints (n = 47)	5.6 ± 5.8

Table III — Prevalence of elevated serum immunoglobulin levels and antinuclear antibody titres in the patients with psoriasis

Variable	No. of patients: With psoriasis alone	With psoriatic arthritis	Total
Serum immunoglobulin level (g/L)			
IgA > 3.8	2/34	9/42	11/76*
IgG > 17.6	0/34	2/42	2/76
IgM > 3.8	1/34	4/42	5/76
Antinuclear antibody titre ≥ 1:20	4/44	16/50	20/94*

*Only the initial patients were tested.

Table IV — Frequency of selected HLA antigens in the patients with psoriasis

HLA antigen	Frequency (%)* Control group (n = 370)	Patient group (n = 138)	Patients with psoriasis alone (n = 74)	Patients with psoriatic arthritis (n = 64)
A1	27.6	39.9	44.6†	34.4
A26	4.9	3.6	0.0‡	7.8
A28	5.6	12.3	16.2	7.8
B8	22.0	10.1	10.8	9.4
B13	5.4	12.3	19.9‡	4.7
B17	7.5	39.1	39.2‡	39.1‡
B27	10.5	13.0	10.8	15.6
Bw35	23.6	12.3	14.9	9.4
Bw38	4.4§	3.6	1.4	6.3
Bw39	4.9§	10.9	4.1	18.8‡
Bw44	27.0	15.9	17.6	14.1
Cw4	20.0§	22.5	29.7	14.1

*Certain frequencies were significantly higher at †$p < 0.01$ and ‡$p < 0.001$, although the p values were not corrected for the number of antigens tested.
§Only 185 controls underwent testing for these antigens.

Table V — Frequency of HLA-DR antigens in the patients with psoriasis

HLA antigen	Frequency (%)* Control group (n = 43)	Patient group (n = 96)	Patients with psoriasis alone (n = 45)	Patients with psoriatic arthritis (n = 51)
DR1	20.9	18.8	13.3	23.5
DR2	20.9	15.6	15.6	15.7
DR3	30.2	18.8	22.2	13.7
DR4	27.9	32.3	35.6	29.4
DR5	7.0	10.4	15.6	5.8
DR7	32.6	59.4	66.7†	52.9
DRw6	4.7	9.4	17.8	2.0
DRw6Y	9.4	13.5	13.8	13.7
DRw8	7.0	9.4	11.1	7.8
MT1	53.5	53.1	46.7	58.8
MT2	65.1	59.4	57.8	60.7
MT3	30.2	57.3	71.1‡	45.1

*Certain differences in frequency between the patients with psoriasis alone and the controls were statistically significant, with χ^2 = †8.914 and ‡13.115 ($p < 0.001$), although the p values were not corrected for the number of antigens tested.

Table VI — Effect of frequency of HLA antigens on relative risk* of psoriasis and psoriatic arthritis

HLA antigen†	Relative risk: Patients v. controls: All patients	Patients v. controls: Patients with psoriasis alone	Patients v. controls: Patients with psoriatic arthritis	Patients with psoriasis alone v. those with psoriatic arthritis	Patients with psoriatic arthritis v. those with psoriasis alone
A26					6.3
A28		3.3			
B13		4.1		4.7	
B17	7.9	7.9	7.8		
Bw39			4.5		5.5
DR7	3.0	4.1			
DRw6		4.4		10.8	
MT3	3.1	5.7		3.0	

*Calculated as follows: $\frac{\text{(no. of patients with antigen)(no. of controls without antigen)}}{\text{(no. of patients without antigen)(no. of controls with antigen)}}$.
†Only the antigens with which the relative risk was 3.0 or higher are listed.

frequency of B17 in both groups of patients compared with the control group. As well, there was a striking increase in the frequency of B13 in the patients with psoriasis alone and of Bw39 in those with psoriatic arthritis (Table IV). Although the frequencies of other HLA antigens were significantly increased, the p values were not corrected for the number of antigens tested.

The frequency of certain antigen pairs was also significantly higher in the patient groups than in the control group, perhaps partly because of the increased frequency of the antigens in the patient groups. The frequencies of the A1,B17 pair ($\chi^2 = 3.933$, $p < 0.05$) and the B17,Cw4 pair ($\chi^2 = 10.488$, $p < 0.005$) were increased in the patients with psoriasis alone, and the frequency of the B17,Cw4 pair ($\chi^2 = 17.684$, $p < 0.001$) was increased in those with psoriatic arthritis. In the latter group of patients the frequency of A26 was significantly increased ($p < 0.05$), and its association with Bw39 was significant ($\chi^2 = 5.269$, $p < 0.05$). The increased frequency of A1 in the patients with psoriasis alone was primarily due to a significant association between A1 and B17 in our patient groups. Contrary to the findings of Murray and colleagues[8] B13 was not significantly associated with A1 in our patients with psoriasis alone: only 2 of the 14 patients with B13 also had A1. Six of the 14 patients with psoriasis alone had A30/31. The frequencies of the A28,B17 and A30/31,B13 pairs were also slightly elevated in the patients with psoriasis alone, but not significantly so.

The results of testing for DR and MT antigens in an unselected subgroup of 96 patients is shown in Table V. The frequencies of the two B-cell antigens DR7 and MT3 were significantly higher in the total patient group ($p < 0.01$) and in those with psoriasis alone ($p < 0.005$) than in the controls. Similarly, the frequency of DRw6 was slightly higher in the patients with psoriasis alone than in those with psoriatic arthritis.

The effect of the presence of HLA antigens on the relative risk of psoriasis alone or psoriatic arthritis is shown in Table VI. The relative risk of either psoriasis alone or psor-

iatic arthritis is apparently greatly enhanced by the presence of HLA-B17. Although the DRw6 antigen increases the risk of psoriasis its presence may offer relative protection against the subsequent development of psoriatic arthritis. Conversely, the presence of the Bw39 antigen is associated with an increased risk of psoriatic arthritis.

Attempts to correlate the presence of particular HLA antigens with subtypes of psoriatic arthritis or psoriatic rash, age at onset and the presence of a family history failed to reveal any statistically significant associations.

Discussion

Our results suggest that patients with purely guttate skin lesions have a decreased risk of psoriatic arthritis. It has been noted that patients with pustular psoriasis are more likely to have arthritis;[9] however, the relative absence of arthritis in patients with guttate psoriasis has not been described previously. Although early studies failed to reveal differences in the frequency of HLA antigens between patients with psoriasis alone and those with psoriatic arthritis,[10] more recent studies of larger numbers of patients have shown a higher frequency of the HLA antigens A26, Bw38, Cw6 and DR4 in patients with psoriatic arthritis[8,11] than in those with psoriasis alone. Other studies have demonstrated an increased frequency of DRw6 in patients with symmetric polyarticular psoriatic arthritis and of DRw4 in those with oligoarticular psoriatic arthritis.[11] Our data failed to confirm these observations with Bw38 and DR4. We also found no relation between the presence of particular HLA antigens and any of the clinical subtypes of psoriatic arthritis or psoriatic rash. However, the small numbers of patients in some clinical subgroups would make it impossible to detect modest or moderate deviations in the frequencies of the antigens. The lack of such deviations among the clinical subtypes of psoriatic arthritis and psoriatic rash suggests that the variable clinical expression of the disease may not be genetically determined. Although a disease with a certain genetic predisposition should be more common in family clusters, there are two reasons why we could not show a correlation of HLA antigens with a positive family history of psoriasis. First, psoriasis is often mild, misinterpreted as dandruff or eczema and therefore overlooked by the patient and his or her relatives. Second, as the results of our study suggest, there are probably several HLA antigens and haplotypes that predispose individuals to psoriasis alone or psoriatic arthritis, and there may be different modes of inheritance and degrees of disease penetrance. Only careful family studies will resolve these difficulties.

Since HLA-B16 was divided into HLA-Bw38 and HLA-Bw39, several investigators have reported an increased frequency of HLA-Bw38 in patients with psoriatic arthritis.[8,12-14] Our data revealed no increase in the frequency of HLA-Bw38 in such patients but, rather, an increased frequency of HLA-Bw39, as reported by Hawkins and associates.[15] Arnett and Bias[13] found that the frequency of HLA-Bw38 was increased in their patients with peripheral joint disease plus sacroiliitis or spondylitis, or both. Since we did not routinely make x-ray films of the axial skeleton of all our patients with peripheral arthritis, our findings cannot be compared with those of Arnett and Bias.

Of the five patients in our series with HLA-A26 three had HLA-Bw39 and one HLA-Bw38. All five had psoriatic arthritis, but no subtype predominated. This observation supports the suggestion of Murray and colleagues[8] that certain factors linked to the HLA-A region could be involved in the pathogenesis of psoriatic arthritis. An increased frequency of HLA-DR7 in the total patient group compared with the control group (59.4% v. 32.6% in our series) has been found in most previous studies.[15-17] Others have shown an increased frequency of HLA-Cw6,[17] which is perhaps due to a strong linkage disequilibrium with HLA-DR7. We were unable to confirm this observation because antiserum for HLA-Cw6 was not available when the typing was done in our patients.

Our study population was different from that in most other North American studies only to the extent that approximately 60% of our patients and controls were French-Canadian.

Other investigators have also found high rheumatoid factor titres and elevated serum levels of IgG and especially IgA in patients with psoriatic arthritis.[18] However, no other studies have observed that antinuclear antibody and rheumatoid factor titres are more likely to be increased in patients with psoriatic arthritis who have increased serum immunoglobulin levels. In our study these patients had frequencies of HLA antigens similar to those of both patient groups.

Conclusions

The results of our study led to the following conclusions:

- Psoriatic arthritis is less likely to develop in patients with purely guttate psoriasis than in those with plaque, erythrodermic or pustular psoriasis.
- The frequency of HLA-A26 or HLA-Bw39 is more likely to be increased in patients with psoriatic arthritis than in those with psoriasis alone.
- Individuals with HLA-DRw6 or HLA-B13 are less likely to have psoriatic arthritis than those with psoriasis who do not have these antigens.
- Individuals with HLA-B17 or HLA-DR7 are more likely to have psoriasis, with or without peripheral arthritis, than those without these antigens.

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NEW BOOKS OF INTEREST

This list is an acknowledgement of the books received that we intend to send out for review.

BIOFEEDBACK. Principles and Practice for Clinicians. 2nd ed. Edited by John V. Basmajian. 390 pp. Illust. Williams & Wilkins, Baltimore, Maryland, 1983. $46.25 (US). ISBN 0-683-00356-9

CLINICAL BIOMECHANICS. Musculoskeletal Actions and Reactions. Edited by R.C. Schafer. 636 pp. Illust. Williams & Wilkins, Baltimore, Maryland, 1983. $78 (US). ISBN 0-683-07582-9

COMMUNICATION AND COUNSELING IN HEALTH CARE. Vincent M. Riccardi and Suzanne M. Kurtz. 248 pp. Illust. Charles C. Thomas, Publisher, Springfield, Illinois, 1983. $19.75 (US), paperbound. ISBN 0-398-04825-8

DEFINING HUMAN LIFE. Medical, Legal, and Ethical Implications. Edited by Margery W. Shaw and A. Edward Doudera. Published in cooperation with the American Society of Law & Medicine. AUPHA Press, Ann Arbor, Michigan, 1983. $30 (US). ISBN 0-914904-82-5

DEMENTIA: A CLINICAL APPROACH. Jeffrey L. Cummings and D. Frank Benson. 416 pp. Illust. Butterworths & Co. (Publishers), Woburn, Massachusetts, 1983. $34.95 (US). ISBN 0-409-95044-0