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HL-A-ANTIGENS AND PSORIATIC ARTHRITIS

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Abstract. A collaborative study of HL-A typing was carried out on 44 patients with psoriasis and sero-negative arthritis. Thirty-four of the patients had psoriasis vulgaris and 10 pustular psoriasis. The clinical, roentgenological, and serological data of the patients were in agreement with earlier studies on psoriatic arthritis. Thirty-seven patients had terminal interphalangeal joint involvement, 15 had sacro-ileitis and 6 had signs suggesting ankylosing spondylitis. HL-A27 was found in 6 of 34 patients with psoriasis vulgaris and arthritis (20.6%) and in 6 of 10 patients with pustular psoriasis and arthritis (60%) as compared with 8.2% of 2103 healthy controls. HL-A17 was present with an increased frequency in psoriasis vulgaris with arthritis (29.4% compared with 8.1% of controls), but was not found to be increased in patients with pustular psoriasis and arthritis. A low incidence of HL-A3 in psoriatic arthritis combined with psoriasis vulgaris was considered accidental. These findings support the theory of a close link between psoriatic arthritis and Reiter's disease. This seems especially true for psoriatic arthritis in patients with pustular psoriasis. The combination of pustular psoriasis and sero-negative arthritis may be a part of the Reiter spectrum. The present investigation demonstrates the value of tissue typing as a means of detecting pathogenetic relationships between different syndromes.

During recent years a great many studies have been carried out on relationships between HL-A-antigens and human diseases. Associations have been reported in multiple sclerosis (5), systemic lupus erythematosus (9), ankylosing spondylitis (3), psoriasis (13, 16) and Reiter's disease (17, 22). Among these the association between psoriasis and HL-A13 and 17, and that between Reiter's disease and HL-A27 are among the most well established, while no definite association has been established with rheumatoid arthritis (8).

In previous studies by our group it was found that pustular psoriasis differs from psoriasis vulgaris by having no relation to HL-A13 and 17 (14). In the same study we reported a significantly higher frequency of HL-A27 among patients with psoriatic arthritis. However, we found it difficult to evaluate the importance of this finding, as HL-A27 is found with a very high frequency in ankylosing spondylitis (3) and Reiter's disease (17, 22) and because these two types of sero-negative arthritis may often be confused with psoriatic arthritis.

In order to more firmly establish an association between HL-A-antigens and psoriatic arthritis we decided to proceed with our examination of the HL-A-phenotypes in this disease.

MATERIAL AND METHODS

All patients with the diagnosis of psoriasis arthritis, who have attended our clinics during 1973 have been studied. Although we find it reasonable to regard a sero-positive patient with the classical features of psoriatic arthritis as being truly psoriatic, rather than having rheumatoid arthritis, we excluded such patients from the study, as this concept remains controversial (20). Only patients having inflammatory polyarthritis associated with manifest psoriasis and having a negative sheep-cell agglutination test are included in this report.

The final investigations were carried out on 44 patients with psoriasis and arthritis; 22 of these were included in our previous report (14), 34 had psoriasis vulgaris and 10 pustular psoriasis. Eleven men and 21 women were patients from the departments of dermatology and physical medicine, Marselisborg Hospital and Aarhus Kommunehospital, University of Aarhus, and 9 men and 3 women from the department of dermatology, Rigshospital, University of Copenhagen. The patients were aged 13 to 77 years.

Roentgenographic studies were made on the bone changes of hands, feet, spine and the sacro-iliac joints. The type of psoriasis was classified and the patients examined for nail changes and rheumatoid nodules. All were questioned about age at onset of their psoriasis and arthritis. Sera were analysed for Rose-Waaler sheep-cell agglutination test, latex-fixation test (RAT), antinuclear factor (ANF) and erythrocyte sedimentation rate (ESR).

HL-A-typing was performed on freshly drawn blood samples by the method of Kissmeyer-Nielsen & Kjerbye (6) in the tissue typing laboratories of the blood-grouping depart-

Table I. *Clinical, roentgenological and laboratory findings*

Case no.	Sex, age		Joints involved[b]	Radiological changes	ESR	RAT	Rose-Waaler	ANF	HLA phenotypes	Family history of psoriasis	Treatment
1	♀ 34	v	To	+	38	0	0	0	1, 2, 5, 17	0	Analgetics
2	♂ 53	p	Mcp, S, To	+	16	0	0	0	2, 12, 27	(+)	Methotrexate
3	♀ 61	v	T	+	10	0	0	0	2, 17, 27 (AJ)	0	Methotrexate
4	♀ 24	v	T, F, To, Mtp	+	56	0	0		1, 28, 8, 27	0	Indomethacin
5	♀ 77	v	T, F	+	27	0	0	0	1, 11, W5	0	Methotrexate
6	♀ 44	v	T, F, S, Mtp, To	+	46	0	0	0	9, W26, W5, W16	0	Methotrexate
7	♂ 65	v	T, To	+	65	(÷)	0	0	1, 9, 8, 17	+	Analgetics
8	♀ 28	v	T, F, S, W, E, To	+	10	0	0	0	2, 7, W21	0	Methotrexate
9	♀ 46	v	T, F, Mcp, To	+	11	0	0	0	2, W26, 13	+	Methotrexate
10	♂ 61	v	T, F, Mcp, A–C, To	+	38			0	1, 2, 7, TY	+	Methotrexate
11	♂ 42	v	T, Mcp, S, To	+	15	0	0	0	2, W26, 8, W15	0	Analgetics
12	♀ 50	v	T, F, K	+	78	0	0	0	9, W19, 12, W16	0	Methotrexate
13	♀ 74	v	T, F, W, S, Mtp	+	65	0	0	0	1, 2, 12, TY	0	Methotrexate
14	♀ 42	v	T, F, Sh, To	+	13	0	0		1, W5, 8	0	Methotrexate
15	♂ 63	v	T, F, Sh	+	75	0	0	0	2, W19, 7, 8	0	Methotrexate
16	♀ 55	v	T, S, Sp, To	+	20	0	0	0	2, W19, 17	0	Methotrexate
17	♀ 74	v	T, K	+	72	0	0	(÷)	1, 2, W15, 17	0	Analgetics
18	♀ 75	v	T, F, Mcp, W, To	+	9	0	0	0	1, W19, 8, W21	0	Methotrexate
19	♀ 70	v	T, C–M, Sh	+	22	0	0		1, 2, 5, TY	0	Methotrexate
20	♂ 55	v	T, F, A–C	+	36	0		0	1, 2, 8, 13	+	Methotrexate
21	♀ 59	p	T, F, W	+	16	0	0	0	2, 3, W5, W16	0	Methotrexate
22	♂ 54	p	E, W, K	+	26	0	0		3, 11, 5, W5	0	Methotrexate
23	♂ 13	p	T, F, S, Sp, W, K, A	+	51	0	0	0	2, 9, W15	0	Methotrexate Azathioprin
24	♀ 31	v	T	+	42	0	0	0	9, W19, 17	+	Ibuprofen
25	♀ 61	v	Mcp, F, K	+	44	0	0	0	2, W19, W10, W18	+	Analgetics
26	♂ 61	p	T, F, S, Sp, To	+	110	0	0		9, W26, 12, 27	0	Methotrexate
27	♂ 42	v	T, F, Mcp, To, S	+	38	0	0	0	2, W26, W16, 27 (AJ)	+	Analgetics
28	♀ 59	v	T, F, Mcp, S	+	16	0	0		1, W19, 14, TY	+	Ibuprofen
29	♀ 59	p	T, F, Mcp, W, C–M, A–C, K	+ +	82	0	0	0	2, W5, 27 (AJ)	0	Analgetics
30	♀ 51	p	T, F, S, E, H	+	19	0	0	++	2, 3, 7, 27	+	Gold
31	♀ 21	v	Mcp, Mtp	0	10	0	0	0	1, 9, 7, 17	+	Ibuprofen
32	♂ 70	v	T, F, W	(÷)	16	0	0	0	2, 13, W10	+	Methotrexate
33	♂ 70	v	T, F, Mcp, S, To	+	38		0	0	1, 2, 7, 27	0	Methotrexate Idomet
34	♂ 63	p	T, F, Mcp, C–M, W, S, H, K, A, To, Mtp, Sp	÷	112	0	0	0	2, 27, 17	(÷)	Steroids system Methotrexate Indomethacin Phenylbutazone
35	♂ 67	v	T, F, A	+	43	0	0	0	2, 27	0	Methotrexate Phenylbutazone
36	♀ 39	p	T, F, Mcp, A, To	+	17	0	0	0	2, 3, 27, 14	0	Methotrexate
37	♂ 44	v	K, A, H, Sp, W	+	37	0	0	0	2, 9, 12, 13	+	Methotrexate
38	♂ 60	v	T, K, A, Sk	+	40	0	0	0	2, 3, 7, W5	0	Steroids system., Gold, Indomethacin
39	♂ 27	v	Mcp, Sk, A, K	–	23	0	0	0	1, 2, 8, 17	÷	Indomethacin Methotrexate
40	♀ 58	v	T, F, A, Sk	+	18	0	0	++	2, 10–2, 8, W16	÷	Indomethacin
41	♂ 61	v	T, F, Mcp, C–M, W, Sk, K, A, To, Mtp, S	+	44	0	0	0	1, 28, 27, 8	÷	Methotrexate Steroids system Indomethacin
42	♀ 53	p	T, F, S	÷	10	0	0	0	1, 11, 8, W5	0	Analgetics
43	♂ 70	v	T, F, Mcp, C–M, Mtp, Sp	+	57	0	0	0	2, 3, 7, 27	0	Gold
44	♂ 36	v	W, A, H, T, F, K	–	74	0	0	(+)	2, 11, 7	0	Indomethacin

[a] p = pustular psoriasis. v = psoriasis vulgaris.
[b] T = terminal interphalangeal joint; S = sacro-iliac joint; A = ankle; A–C = acromioclavicular joint; C–M = carpo-metacarpal joint; E = elbow: F = interphalangeal joints of fingers; H = hip; K = knee; Sh = shoulder; Sp = spinal joints; To = interphalangeal joints of toes; W = wrists.

Table II. *Frequencies (per cent) of HL-A-antigens in psoriatic arthritis*

Antigen	Psoriasis vulgaris and arthritis, $n = 34$	Pustular psoriasis and arthritis, $n = 10$	All patients, $n = 44$	Controls, $n = 2103$
HL-A1	52.9	10	43.2	32.1
2	67.6	70	68.2	51.9
3	5.9 (< 0.005)	40	13.6	28.1
9	17.6	20	18.2	16.9
10	11.8	10	11.4	8.7
11	5.9	20	9.1	10.8
28	5.9	0	4.5	9.8
W19	20.6	0	15.9	17.5
HL-A5	8.8	10	9.1	11.1
7	20.6	10	18.2	28.6
8	35.3	10	29.5	23.6
12	8.8	20	11.4	24.6
13	11.8	0	9.1	3.8
14	2.9	10	4.5	4.1
17	29.4 (0.0006)	10	25.0 (0.0014)	8.1
27	20.6	60 (0.0001)	29.5 (< 0.0002)	8.2
W5	8.8	40	15.9	13.0
W10	5.9	0	4.5	17.9
W15	5.9	10	6.8	17.5
W16	11.8	10	11.4	5.1
W18	2.9	0	2.3	7.1
W21	5.9	0	4.5	2.8
W22	0	0	0	3.4

Figures in parentheses are p-values obtained from the chi-square test on Fisher's exact test when comparing the patient group with controls. Only p-values less than 0.01 are given.

ments, Aarhus Kommunehospital and Rigshospital, Universities of Aarhus and Copenhagen. The equality of the typing in the two laboratories has been established by extensive exchange of cells during the cooperation of the Scandiatransplant project (7). All individuals were investigated for the antigens HL-A1, 2, 3, 9, 10, 11, 28 and W19 of the LA-series and HL-A5, 7, 8, 12, 13, 14, 17, 27, W5, W10, W15, W16, W18, W21 and W22 of the FOUR series. Controls consisted of 562 blood donors from Aarhus and 1541 healthy volunteers from Copenhagen.

RESULTS

The clinical roentgenological and serological results of the study are summarized in Table I. These data are in agreement with earlier studies on psoriatic arthritis (2, 12, 20, 21). Thirty-seven patients had terminal interphalangeal joint involvement and 15 had sacro-ileitis, 6 patients had roentgenological signs of spinal involvement. Thirty-one patients had psoriasis of their nails, while no patients showed rheumatoid nodules. The average age at onset was 29 years for psoriasis and 45 years for arthritis. Fourteen patients with psoriasis vulgaris and 2 patients with pustular psoriasis had a positive family history of psoriasis. The treatment of our patients is set out in Table I.

HL-A13 was present in 4 of 34 unrelated patients with psoriasis vulgaris (11.8%) as compared with 3.8% of the controls (Table II). HL-A17 was present in 9 of the same patients (29.4%) compared with 8.1% of the controls, while HL-A27 was found in 6 patients (20.6%) compared with 8.2% of the controls.

In patients with pustular psoriasis and arthritis the pattern was different. HL-A13 was not found among these patients and HL-A17 was demonstrated in only one patient. Six patients had HL-A27 (60%) compared with 8.2% in controls.

The frequency of HL-A17 in psoriatic arthritis in the psoriasis vulgaris group was significantly increased ($p = 0.006$). The finding of 6 patients with HL-A27 among 10 with pustular psoriasis and arthritis was significantly higher than the frequency in controls ($p = 0.0001$). The tissue antigen HL-A3 was found less frequently in patients with psoriatic arthritis and psoriasis vulgaris than in the controls (5.9% compared with 28.1% ($p < 0.005$)). It appears from Table I that among 12 patient swith HL-A27, 7 had a sacro-ileitis and 3 ankylosing spondylitis.

DISCUSSION

These findings confirm our earlier findings that HL-A13 and 17, although commonly found in psoriasis vulgaris, is not associated with pustular psoriasis. The study establishes that patients with pustular psoriasis and arthritis have an increased frequency of HL-A27. Although patients with psoriasis vulgaris and psoriatic arthritis also had an increased frequency of HL-A27, the difference between this group of patients and the controls was not statistically significant. These patients have an increased frequency of HL-A17. They showed a low incidence of HL-A3; in our opinion, this is probably accidental.

Our findings may have a direct bearing on the relationship between psoriatic arthritis and Reiter's disease. Various authors have hinted at a very definite link between psoriatic arthritis and Reiter's disease (11, 19). This link seems especially close, when the psoriasis is pustular. The histopathological appearance of the cutaneous lesions in these two entities is in reality indistinguishable. Furthermore, when chronic and progressive, the articular involvement in Reiter's disease presents a picture which cannot be distinguished from that of destructive psoriatic arthritis, and it has been shown as far back as in 1959 by Wright (18) that pustular psoriasis is significantly more common in patients with psoriatic arthritis who have severe joint disease than in those with uncomplicated psoriasis.

Conjunctivitis and urethritis are classical components of true Reiter's disease. Both symptoms may be mild, however, and thus escape the patient's notice. None of our patients complained initially of ocular inflammation or urethral discharge, but one patient treated by us for several years for psoriatic arthritis, developed renewed activity of his arthritis during our study, and although he had no subjective complaints his conjunctivae were found to be irritated. On rectal examination he was also found to have an irregularly enlarged and tender prostata.

Circumstantial evidence indicates that Reiter's disease is caused by infective agents, some of which can be treated with antibiotics. This is also the case in certain patients with different types of pustular psoriasis (4, 10, 15). The presence of HL-A27 in patients with pustular psoriasis might imply that early treatment with broad-spectrum antibiotics is indicated in these cases as the patients might be in great danger of developing arthritis. Pustular psoriasis with sero-negative arthritis may be a part of the Reiter spectrum.

It is also possible that the demonstration of HL-A27 in diseases such as ankylosing spondylitis (3), Yersinia arthritis (1), Reiter's disease (17, 22), and certain types of psoriatic arthritis, suggests a common pathogenesis for these entities. In all the groups mentioned, sacro-ileitis is a common finding. HL-A27 may therefore be linked closely to a certain type of reactive arthritis with involvement of the sacro-iliac and spinal joints.

The present study indicates the value of tissue typing as a means to establish pathogenetic relations between different syndromes. The study further supports our previous observation (14) of a genetic distinction between psoriasis vulgaris and pustular psoriasis. The indication of a linkage between Reiter's syndrome and psoriatic arthritis with pustular cutaneous lesions has, as stated, a possible bearing on therapy.

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