Histocompatibility Antigen Patterns in Dupuytren's Contracture

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Thirty-seven consecutive patients with Dupuytren's Contracture were investigated by tissue typing techniques to ascertain their HLA—A, B, C and DR antigen status. Whilst no definite HLA antigen was found in association with this disease, at least one possibly significant pattern of HLA DR antigens was found in these patients. This finding was also noted in patients with scleroderma, and the scleroderma-like syndrome induced by vinyl chloride exposure.

Interest in Dupuytren's Disease has increased in recent years. Research has shown (Bazin 1980) that the abnormal palmar fascia of the hand in Dupuytren's Contracture contains increased amounts of Type III collagen. In addition, microanatomical studies by McGrouther (1982) have delineated further the structure of the palmar fascia. However, the primary cause of the condition is still not known.

The disease has been related to a high alcohol intake and liver disease (Wolfe 1956), epilepsy (Hueston 1963), diabetes mellitus, tuberculosis, Peyronie's Disease (Billig 1975) and manual work, especially that associated with polyvinyl chloride (Bennett 1982), and these relationships may indicate the possibility of an environmental origin. It has been also recognised for many years that the condition may be familial (Manson 1931). Additional evidence of genetic implication stems from the fact that the disease is rare in certain racial groups, e.g. Negroes, Chinese (James 1974).

To assess the possibility of there being an HLA-DR marker for this disease of the superficial palmar fascia, we undertook a prospective survey of thirty-seven consecutive patients with Dupuytren's Contracture.

Patients

The thirty-seven patients in this series were seen in the Hand Clinic and Orthopaedic Out-Patients Department of Lewisham Hospital in 1982. All patients had undergone surgery or had recently been placed on the admission list. The average age of the group was fifty-nine years (range thirty-one to eighty-one). Twenty-nine of the patients had followed a manual occupation and nineteen patients out of the whole group of thirty-seven patients had both hands involved in Dupuytren's Contracture.

Fifteen patients in this series (Table 1) gave a history of high alcohol intake but the reliability of the negative history is questionable. No patient was found to have cirrhosis by clinical examination or biochemical investigations. Twelve patients had a positive family history of Dupuytren's Contracture and in three of these cases, a high alcohol intake was noted. Two patients suffered from diabetes mellitus, two from epilepsy and two from previous tuberculosis. A control group of normal Caucasian hospital workers was used.

TABLE 1
Numbers of Dupuytren's patients with associated conditions

Associated Condition	*Numbers*	*(Per Cent)*
Alcoholism	15	(40.5%)
Family History (Three also included in Alcoholism)	12	(33.0%)
Epilepsy	4	(10.8%)
Diabetes Mellitus	2	(5.4%)
Tuberculosis	2	(5.4%)

(Nine patients (i.e. 25%) in the study group with Dupuytren's Contracture had no associated illnesses)

Methods

All patients were typed for HLA A, B and DR locus antigens with sera standardised against the eighth histocompatibility workshop sera. Lymphocytes were prepared from ten millilitres of blood taken into an equal volume of 0.5% EDTA. Separation of B and T cells and the HLA typing methods used have been described previously (Walsh 1978). The statistical significance of the HLA associations with Dupuytren's Contracture were determined with the Chi square test with Yates' correction. Multiplication of the p value by the number of DR antigens tested for was used to allow for the possibility that the difference in DR 3 or DR 4 frequency between groups could have occurred by chance because of the number of observations made. This correction may not be necessary, however, because the DR 3 difference is paralleled by the B 8 difference, and these two antigens are in close linkage disequilibrium.

Results

In Table 2 the patients were grouped into three groups depending on DR antigen status. Group I contained all those who had DR 3 and of these patients almost all in addition exhibited A1 and B8 antigens. Twelve patients were in this group, and only two had a positive family

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TABLE 2
Histocompatibility antigens in the Dupuytren's patients

	Patients	*HLA-A*	*B*	*DR*
Group I	A.D.	1, 11,	8, 5,	3
	W.H.	1, 2,	8, 12,	3
	A.B.	1	8	3
	S.P.	1, 11,	8, 22,	3
	R.C.	1, 3,	8, 7,	3, ?2
	H.S.	1, 3,	8, 35,	3, ?2
	A.L.	9, 10,	8, 16,	3, 5
	V.P.	1, 9,	8, 16,	3, 5
	H.S.	2, 12,	40	3, 7
	J.R.	1, 31,	8, 14,	3, 9
	D.W.	1, 2,	8, 12,	3, 4
	F.G.	1, 2,	8, 27,	3, 4
GROUP II	H.P.	2, 3,	12, 35,	1, 4
	J.L.	2, 29,	12, 15,	2, 4
	L.R.	2, 3,	7, 12,	2, 4
	J.C.	3	12, 35,	4
	P.C.	1, 2,	12, 22,	4
	L.C.	2	7, 12,	4
	L.H.	9, 11,	18, 27,	4, 5
	O.B.	2, 11,	12, 22,	4, 6
	W.B.	2, 28,	5, 12,	4, 6
	H.B.	1, 3,	12, 17,	4, 7
	B.B.	1, 3,	17, 47,	4, 7
	H.S.	2	17, 21,	4, 7
	L.R.	2	13, 27,	4, 7
	R.L.	2, 32,	7, 12,	4, 8

Miscellaneous group, neither DR 3 or 4

	Patients	*HLA-A*	*B*	*DR*
GROUP III	D.C.	3, 11,	7	2, 1
	L.C.	10, 29,	12	2
	F.N.	2, 32,	15, 27,	2, 6
	D.F.	2, 28,	15, 40,	2, 6
	S.J.	2, 11,	7, 18,	1, 6
	L.R.	2, 9,	5, 27,	1, 7
	D.C.	3, 11,	7	6, 7
	P.K.	9, 28,	5, 13,	5, 7
	N.B.	1, 2,	5	5, 7
	D.K.	2, 3,	12, 22,	6, 7
	V.H.	1, 10,	8, 27,	6

history. The remaining patients with a positive family history were equally spread between the two remaining groups. Five patients in each of these three arbitrary groups admitted to a history of high alcohol intake.

In Group II there were fourteen patients with DR 4 and as can be seen from Table 2 seven of these patients also had A2 and B12 antigens in common. Two patients (included in Group I) had DR 3 as well as DR 4. Group III contained patients whose HLA DR-status was non DR 3 or 4. In Table 3 it can be seen, from analysis of the frequency of occurrence of individual HLA DR antigens in Dupuytren's Contracture patients and comparing them to controls, that DR 4, A1 and B8 occurred more frequently in our Dupuytren's patients. These findings were not, however, statistically significant.

In Table 4 we looked in more detail at the pattern of A1 B8 DR 3 antigens in our control patients, Dupuytren's patients and patients with scleroderma-like syndrome due to vinyl chloride exposure and scleroderma. The result of the linkage disequilibrium analysis is that very few patients with Dupuytren's Contracture, scleroderma-like syndrome and scleroderma who are DR 3 positive, do not also have A1 and B8 antigens, whereas in the control group a large number did, i.e. one third of patients who were DR 3 positive did not have B8 and one half did not have A1. Again because of the small number of Dupuytren's patients, the results did not quite reach statistical significance, but the

TABLE 3
Percentage of patients with HLA-DR antigens in Dupuytren's Contracture compared with controls

DR	*Dupuytren's Contracture Patients (37)*	*Normal Controls (148)*
1	10.8%	10.6%
2	21.6%	21.2%
3	32.4%	30.0%
4	43.2%	32.7%
5	13.5%	17.6%
6	21.6%	23.8%
7	27.0%	26.8%
8	2.7%	3.4%
9	2.7%	1.7%
A1	39.5%	22.8%
B8	31.6%	22.2%
A2	50.0%	54.3%
B12	34.2%	36.6%
A3	26.3%	28.8%
B7	18.4%	21.5%

TABLE 4(a)
Linkage disequilibrium (Δ) between B8 and DR3 in Scleroderma patients (S) Vinyl Chloride disease patients (VCD) Dupuytren's Contracture patients (DC)

Antigens	*Controls*	*S*	*VCD*	*DC*
B8+/DR3+	30	16	11	11
B8+/DR3−	8	0	0	1
B8−/DR3+	14	2	1	1
B8−/DR3−	96	32	12	24
Total number of patients	148	50	24	37
Δ	= 0.08*	= 0.13*	= 0.11	= 0.1

*p <0.05

TABLE 4(b)
Linkage disequilibrium between A1/DR in Controls

Antigens	*Controls*	*S*	*VCD*	*DC*
A1+/DR3+	20	14	11	10
A1+/DR3−	12	2	1	5
A1−/DR3+	20	2	1	2
A1−/DR3−	96	32	11	20
Total number of patients	148	50	24	37

pattern of the linkage disequilibrium was very similar to that of the patients with scleroderma-like syndrome due to vinyl chloride exposure and scleroderma. The twenty-four patients with vinyl chloride induced scleroderma used in this part of the study have not so far been noted to have evidence of Dupuytren's Contracture. In Table 4 the control group consisted of one hundred and forty-eight normal people.

Discussion

One third of cases of Dupuytren's Contracture are associated with a positive family history, and the disease is rare in certain racial groups. This implies a genetic predisposition but a chromosome associated with the transmission of Dupuytren's Contracture has not so far been identified; we undertook to study the HLA region markers of thirty-seven patients with Dupuytren's Contracture.

Tait (1982) and Hunter (1982) were unable to find an association between the disease and HLA—ABC and DR locus products but Tait (1982) did find an increase of HLA—B12 reminiscent of earlier reports on Rheumatoid Arthritis where the disease later turned out to be strongly associated with HLA—DR 4, (HLA-B12 is in weak linkage disequilibrium with DR 4). Our study in thirty-seven patients whose incidence of alcoholism and positive family histories was nearly the same as in the two studies mentioned above, does indeed show that the incidence of DR 4 is higher in disease patients than controls but the findings did not reach statistical significance (p value > 0.05 without Yates' correction). In Group II (fourteen patients) patients having the DR 4 antigen often also had an associated B12 antigen (ten cases).

In our Group 1 Dupuytren's patients having DR 3, the antigen almost invariably had associated A1 and B8 antigens. It is apparent that the incidence of HLA-DR3 is not raised in Dupuytren's patients whereas HLA—A1 and B8 are. Thus in Dupuytren's Contracture, scleroderma and scleroderma-like syndrome produced by vinyl chloride, the expected incidence of the A1 B8 DR 3 haplotype is raised but the incidence of DR 3 occurring without A1 B8 is lowered.

The A1 B8 DR 3 haplotype is a characteristic of autoimmune disorders (e.g. scleroderma (Black 1983), myasthenia gravis, chronic active hepatitis etc). In fact, on present evidence DR 3 alone i.e. not associated with A1 or B8, is possibly protective regarding the development of Dupuytren's Contracture, scleroderma-like syndrome induced by vinyl chloride and scleroderma.

Whilst we have not confirmed that the HLA system is responsible for the familial clustering of Dupuytren's Contracture patients, we have shown interesting patterns of HLA—DR antigens (Group I and II) in twenty-six of our thirty-seven Dupuytren's patients. In addition, the near absence of DR 3 unassociated with A1 or B8 in our patients and in patients with scleroderma-like syndrome due to vinyl chloride exposure and scleroderma is of some interest and deserves further investigation. Finally further work on HLA-DR antigen status is indicated in those patients with a positive family history of Dupuytren's Contracture.

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