Association of HLA class I and class II antigens with rheumatic fever in Turkish population

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The distribution of class I and class II HLA antigens of 100 Turkish patients with rheumatic fever, 77 of whom had cardiac involvement was examined. We compared the results with a control group of identical origin. The frequency of HLA A10 and HLA B35 antigens were found significantly higher in patients with rheumatic fever ($p<0.05$, $p<0.01$, respectively). The frequency of HLA A10 and HLA Dw11 in patients with cardiac involvement were significantly higher than those without cardiac involvement ($p<0.05$, $p<0.01$, recpectively). On the other hand, HLA Cw2 antigen frequency was found significantly higher in patients without cardiac involvement than those with rheumatic heart disease ($p<0.05$). We support the concept that rheumatic fever is an immunological reaction to group A, beta hemolytic streptococci in individuals who have genetic predisposition. [Turk J Med Res 1993; 11(1):11-14]

Key Words: Rheumatic fever, HLA antigens

Rheumatic fever is believed to develop as a consequence of the immune reaction initiated by group A beta hemolytic streptococci. But only a small number of subjects exposed to rheumatogenic streptococci develop the disease. Cheadle was the first to point out the familial incidence of rheumatic fever (1). Since then, several investigators have reported an increased familial incidence, suggesting a possible role of heredity in the susceptibility to rheumatic fever (2).

The HLA antigens are known to be important in controlling the immunological response. No consistent association between rheumatic fever and HLA antigens has been established in several studies (3-6).

In this study, we examined class I and class II HLA antigens of 100 Turkish patients with rheumatic fever and compared them with a control group of identical origin.

MATERIALS AND METHODS

100 patients attending to the immunology and cardiology departments of the University of Ankara, School of Medicine were included in the study. Seventy-seven of them had rheumatic heart disease and 23 had arthritis. The age and sex distribution of the patients are shown in Table 1. In patients presenting with polyarthritis, the diagnosis of acute rheumatic fever was made according to the modified Jones criteria (7). In patients presenting with rheumatic heart disease a diagnosis of rheumatic fever has been made 1-18.1 years previously. Detailed valvular deformities are recorded in Table 2. A female patient (17 years old) had chorea. We didn't observe erythema marginatum or subcutaneous nodules in any of our patients.

There were 100 healthy adults in the control group for HLA typing. 62 of them were females, 38 were males and the mean age was 30.2±5.4.

HLA-A, B, and C antigens were determined by the standard two-stage microlymphocytotoxicity technique (8). For HLA class II antigen analysis, B lymphocytes were separated by means of an immunomagnetic procedure with "Dynabeads® HLA class II". Acridin orange and ethidium bromide dyes were used and detected in immunofluorescence misroscope (9). Antisera were mainly from Behring and Biotest.

Statistical analysis: Relative risk (r.r.) was calculated with the method of Woolf (10). When the frequencies were sufficiently large, the classical chi square test was used to analyze contingency tables.

RESULTS

Detailed results are presented in Table 3, 4, 5 and 6. Rheumatic heart disease in the chronic phase was the

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Table 1. Age and sex characteristics of the patients

	Carditis (+)	Carditis (—)
Male :	29 (37.66%)	10(43.48%)
Female:	48 (62.34%)	13(56.52%)
TOTAL:	77	23
Mean age:	37.2±8.3	18.4±5.7

Table 2. The various valvular involvements of the patients with chronic valvular heart disease

Valvuler Involvements	Patient no.
Mitral stenosis and /or mitral insufficiency	41 (53.2%)
Mitral stenosis and aortic insufficiency	15(19.5%)
Mitral insufficiency and aortic insufficiency	10(13%)
Mitral stenosis and insufficiency and aortic insufficiency	11 (14.3%)

most common clinical manifestation, being present in 77% of the patients studied. There was no cardiac involvement in 23% of the patients, presented with acute arthritis.

The frequencies of HLA A10 (r.r.: 2.89, p<0.05) and HLA B35 (r.r.: 2.52, p<0.01) were found to be significantly increased in the patient group compared with controls (Table 3). The frequencies of HLA A10 and HLA DRw11 were found to be significantly higher in the patients who had cardiac involvement (respectively, r.r.: 3, p<0.05, r.r.: 5.3, p<0.01) (Table 5 and 6). On the otherhand, in patients without cardiac involvement, HLA Cw2 significantly increased, as compared with the patients with carditis (r.r.: —4.15, p<0.05) (Tablo 5).

DISCUSSION

Although an abnormal immune response following streptococcal infection has been accused to be a potential casue of rheumatic fever and rheumatic heart disease, the exact mechanism of this damage has not yet been clarified. Several investigators have attempted to establish an association of HLA antigens with rheumatic fever and rheumatic heart disease (3-6).

Falk and co-workers (11) investigated the association of class I HLA antigens with rheumatic fever and reported a decreased frequency of HLA A3 in Caucasians with rheumatic fever (Table 7). Caughey et al (6) studying rheumatic patients, found increased frequencies of HLA A3 and HLA B8 and a decreased frequency of HLA A10 antigen in Maoris, as well as a decreased frequency of HLA A28 with increased HLA B17 antigens in Europeans. Leirisalo et al (12) reported an increased frequency of HLA B35 phenotype in Finnish patients with rheumatic fever, but couldn't confirm this in a subsequent study (13). Murray's study revealed an increase in HLA B5 frequency in his patients with rheumatic fever, but this finding wasn't statistically significant (14). Yoshinoya and Pope (15) demonstrated that patients with rheumatic fever and HLA B5 antigen positivity had more pronounced immune responses as measured by circulating immune complexes.

The results of studies associated with class II HLA antigens in rheumatic fever are as follows; Ayoub et al (3) found that HLA DR2 and HLA DR4 antigens were significantly higher in Black and Caucasian patients when compared with race-matched controls. The

Table 3. Antigen frequency (HLA-A,B,C) %, relative risk and p values of the patient and the control group

	Patient n: 100	Control n: 100	r.r.	p values
A1	17.0	20.8	—0.77	NS
A2	41.0	38.2	1.1	NS
A3	11.0	15.4	—1.47	NS
A9	33.0	29.2	1.19	NS
A10	19.0	7.5	2.89	p<0.05
A11	6.0	11.1	—1.9	NS
A28	9.0	10.3	—1.16	NS
B5	27.0	30.0	—1.15	NS
B7	8.0	10.4	—1.32	NS
B8	15.0	7.8	2.07	NS
B12	15.0	12.4	1.24	NS
B13	7.0	8.3	—1.2	NS
B18	5.0	3.3	1.51	NS
B27	11.0	6.9	1.667	NS
B35	32.0	15.7	2.52	p<0.01
B40	16.0	9.1	1.88	NS
Cw2	12.0	6.4	1.99	NS
Cw3	11.0	6.3	1.83	NS
Cw4	28.0	31.2	—1.14	NS

NS: not significant

Table 4. Frequency of HLA Class II, relative risk and p values of the patient and the control group

	Patient	Control	r.r.	p values
DR1	10.0	5.0	2.1	NS
DR2	12.0	21.0	—1.94	NS
DR3	4.0	5.0	—1.28	NS
DR4	26.0	33.0	—1.4	NS
DR7	23.0	16.0	1.56	NS
DRw11	37,0	59.0	—2.45	NS
DRw52	62.0	54.0	1.38	NS
DRw53	37.0	48.0	—1.57	NS
DQw1	43.0	34.0	1.46	NS

NS: not significant

Table 5. Antigen frequency (HLA-A,B,C) %, relative risk (r.r) and p values of the patients with and without carditis

	Carditis (+) n: 77	Carditis (—) n: 23	r.r.	p values
A1	19.5	8.6	2.57	NS
A2	37.6	52.1	—1.8	NS
A3	9.0	17.4	—2.13	NS
A9	36.4	21.7	2.0	NS
A10	22.0	8.6	3	p<0.05
A11	6.5	4.3	1.54	NS
A28	9.0	8.6	1.05	NS
B5	27.3	26.0	1.06	NS
B7	6.5	13.0	—2.15	NS
B8	18.2	4.3	4.98	NS
B12	16.8	8.6	2.1	NS
B13	6.5	8.6	—1.35	NS
B18	3.9	8.6	—2.32	NS
B27	9.0	17.4	—2.13	NS
B35	31.2	34.7	—1.17	NS
B40	18.2	8.6	2.38	NS
Cw2	7.8	26.0	—4.15	p<0.05
Cw3	10.4	13.0	—1.13	NS
Cw4	24.7	39.0	—1.95	NS

NS: not significant

Table 6 Frequency of HLA Class II Antigen (%), relative risk, and p values of the patients with and without carditis

	Carditis (+)	Carditis (-)	r.r.	p values
DR1	9.0	13.0	—2.1	NS
DR2	20.7	13.0	1.74	NS
DR3	3.9	4.3	—1.28	NS
DR4	20.8	43.5	—1.4	NS
DR7	20.7	17.4	1.56	NS
DRw11	44.2	13.0	5.3	p<0.01
DRw52	58.4	74.0	—2.45	NS
DRw53	37.6	34.7	—1.38	NS
DQw1	45.5	34.7	1.57	NS

NS: not significant

Table7. Data from the literature related to HLA phenotypes in rheumatic fever and rheumatic heart disease

Publication	Decreased frequency	Increased frequency
Falk et ai, 1973	A3	
Caughey et al, 1975	A10	A3, B8 (in Maoris) B17 (in Europeans)
Leirisalo et al, 1977		B35
Murray et al, 1978		B5 (not statistically significant)
Ayoub et al, 1986		DR2, DR4
Monplaisir et al, 1986	B14, Bw42	B35, DR1
Jhinghan et al, 1986	DR2	DR3, Aw33
Rajapakse et al, 1987		DR4

frequency of antigen types in a group of 15 Saudi Arab patients with acute rheumatic fever was compared with those in a group of 100 healthy volunteers. Only the frequency of HLA DR4 was found significantly higher in the patient group (53% versus 12% control) (16). Jhingham et al (5) reported that in patients with rheumatic fever the frequencies of HLA DR3 and Aw33 antigens were significantly increased, while HLA DR2 was reduced. Monplaisir et al (4) showed a modest but significant reduction of HLA B14 and Bw42 antigens as well as an increase in HLA B35 and DR1 antigens.

In our study, the frequencies of HLA A10 and HLA B35 antigens were found significantly higher in patients with rheumatic fever. This finding is parallel to Leirisalo and Monplaisir's reports (12,4). In contrast with our results, Caughey et al reported decreased frequency of HLA-A10 in such patients (6). Moreover we found that the frequencies of HLA A10 and HLA DRw11 antigens were significantly higher in patients with carditis than those without cardiac involvement. On the other hand, the frequency of HLA Cw2 in patients without cardiac involvement was found higher than those with cardiac involvement. As mentioned above, class I and especially class II HLA antigen studies showed conflicting results in patients with rheumatic fever. Our results differ especially for class II antigens. The reasons for these discrepancies are probably related to geographical or racial differences in populations and different patterns of reactivity to alloantisera.

Patarroyo et al (17) identified a new B cell alloantigen called 883, which correctly identified 70-75% of all rheumatic fever subjects from different geographic areas. In the following studies, Zabriskie et al (18) confirmed these findings using two monoclonal antibodies with similar specificity as the 883 alloantiserum. Both the human antiserum and the monoclonal antibodies didn't react with the major histocompatibility complex (MHC) alleles of HLA-A, B,C and DR loci. These findings suggest that a new class of B cell alloantigens besides the MHC complex may have a role in the development of rheumatic fever after streptococcal infection.

HLA antigens help macrophages in presenting the rheumatogenic determinants of beta hemolytic streptococi to T lymphocytes. In accordance with several investigators (3,5,16), we also think that the differences in HLA antigen phenotypes may indicate a genetically controlled disorder in antigen presentation in rheumatic fever. An abnormal immunological response directed against connective tissue may be initiated by many factors. Certain HLA alleles increase the responsiveness to beta hemolytic streptococi (16). In addition, several streptococcal antigens cross react immunologi-

cally with human tissue antigens. As a result, eliminating the streptococcal infections becomes difficult for the immune system, since their antigens may be erroneously recognized as self by the lymphocytes. On the other hand, the response against microorganisms cause tissue damage in rheumatic fever, especially in rheumatic carditis due to the cross reaction of streptococcal antigens with heart antigens (19). Further studies may provide convincing evidence in the pathogenesis of the rheumatic fever and rheumatic heart disease.

Türk toplumunda akut romatizma ile
HLA sınıf I ve sınıf II antijenlerinin ilişkisi

77'sinde kardiyak tutulum olmak üzere akut romatizmalı 100 Türk hastada HLA sınıf I ve sınıf II antijenlerinin dağılımı incelendi. Sonuçları benzer orijinli kontrol grubu ile mukayese edildi. Akut romatizmalı hastalarda HLA A10 ve HLA B35 antigen sıklığı belirgin olarak yüksek bulundu (sırasıyla, p<0.05, p<0.01). Kardiyak tutulumu bulunan hastalarda HLA A10 ve HLA Dw11 sıklığı kardiyak tutulumu bulunmayanlardan belirgin yüksekti (sırasıyla, p<0.05, p<0.01). Diğer yandan, HLA Cw2 antijen sıklığı kardiyak tutulum bulunmayan hastalarda romatizma! kalp hastalığı bulunanlardan belirgin olarak daha yüksek bulundu (p<0.05). Biz, akut romatizmanın genetik predispozisyona sahip bireylerde grup A beta hemolitik streptokoka bir immünolojik reaksiyon düşüncesini desteklemiş olduk. [TurkJMedRes 1993; 11(1): 11-14]

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