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HLA and Rheumatic Fever in Turkish Children

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SUMMARY. **We report the results of research on human leukocyte allo-antigen (HLA) and rheumatic fever (RF), the first published study to be carried out among Turkish children with RF. Ninety-three Turkish children, aged between 6 and 16 years (mean: 8 ± 2.6), with RF participated in the study. Of the total, 26 patients had their first attack and 39 had acute rheumatic activity at the time of registration. The results demonstrate (1) negative but not significant association between HLA-A2 and RF; (2) a positive association between HLA-DR4 and RF ($p < 0.001$); (3) a significant association between HLA-DR4 and carditis, but not with isolated arthritis. These results corroborate the concept of race-specific genetically determined familial susceptibility to the development of rheumatic heart disease.**

KEY WORDS: **HLA — Rheumatic carditis — Rheumatic fever**

The association between several autoimmune diseases and HLA-DR, an immune-response gene product, has been well documented in the literature. There is a general acceptance that rheumatic fever (RF) is related to familial susceptibility (i.e., genetically influenced). Its pathogenesis is thought to be influenced through human leukocyte allo-antigen (HLA) produced by closely arranged genes on the sixth chromosome. This may explain the high familial incidence of RF and has much to do with the immune response evoked by group A streptococci.

However, because of a contradictory relationship between RF and class I HLA antigens (A, B, and C) and also limited available data concerning the RF and class II antigens, we performed HLA typing to determine the role of genetic factor(s), predisposing to the development of RF, among Turkish children.

Patients and Methods

We investigated 93 Turkish children, aged between 6 and 16 years (mean: 8 ± 2.6) (male/female ratio: 44/49), who had RF. The modified Jones' criteria [1] were used in the diagnosis, 26 patients had their first attack and 39 had acute rheumatic activity at the time of enrollment in the study. Seventy children had carditis and 18 isolated arthritis. The control group consisted of unrelated subjects who were selected randomly from healthy donors of the Bone Marrow Transplantation Center of the Gülhane Military Medical Academy, Ankara. There were 218 subjects for HLA A, B, and C typing and 80 for HLA-DR. The standard microtoxicity technique of Terasaki and modified NIH methods were used for determination of class I and II antigens [3, 29]. Student's t test, chi square, and Fisher's exact probability test [9] were used for comparison and to calculate significance. The definition of statistical significancies was modified [14]. The relative risk calculation and correction was undertaken

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Table 1. HLA-DR antigens in Turkish children with RF

HLA	Patients (n = 93)		Controls (n = 80)		RR	EF
	n	%	n	%		
DR1	20	21.5	20	25	0.82	1.38 (−)
DR2	12	12.9	12	16.2	0.84	2.08 (−)
DR3	20	21.5	19	23.7	0.88	1.78 (−)
DR4	35	37.6	6	7.5	7.4	0.97 (+)
DR5	9	9.7	12	15	0.6	1.26 (−)
DR7	30	32.2	15	18.7	2.06	0.94 (+)
DRw52	31	33.3	17	21.2	1.85	0.93 (+)
DRw53	4	4.3	9	11.2	0.35	0.08 (−)

RR, Relative risk, EF, etiologic fraction; (−), negative association; (+), positive association.

Table 2. Major manifestations and significance of the incidence of HLA-DR antigens in Turkish children with RF

Clinical manifestation	DR1	DR2	DR3	DR4	DR5	DR7	DRw52	DRw53
All RF								
n	20	12	20	35	9	30	31	4
χ^2	0.29	0.38	0.01	19.96	3.65	4.07	3.13	2.07
p	NS	NS	NS	0.001	NS	NS	NS	NS
RR	0.82	0.84	0.88	7.4	0.6	2.06	1.85	0.35
Arthritis								
n	5	4	5	4	3	8	5	—
χ^2	0.03	0.07	0.08	2.05	0.01	4.06	0.08	
p	NS	NS	NS	NS	NS	NS	NS	
RR	1.15	1.47	1.23	3.52	0.74	0.80	3.03	
Chorea[a]								
n	1	4	1	4	2	3	2	—
χ^2	0.27	2.54	a	a	a	a	a	
p	NS	NS	NS	NS	NS	NS	NS	
RR	0.38	4.12	0.40	9.87	1.06	2.17	1.06	
Carditis								
n	15	8	15	31	6	22	26	4
χ^2	0.27	0.38	0.01	25.24	3.56	3.23	4.61	0.83
p	NS	NS	NS	0.0001	NS	NS	NS	NS
RR	0.82	0.93	1.66	9.80	0.35	1.99	2.29	0.48
Chronic isolated mitral insufficiency								
n	10	4	8	17	3	8	13	3
χ^2	0.24	0.11	0.05	24.18	1.76	0.11	3.55	0.03
p	NS	NS	NS	0.0001	NS	NS	NS	NS
RR	1.25	0.68	1.66	12.33	0.36	1.33	2.29	0.76

χ^2, chi square; *p*, probability level; RR, relative risk; NS, not significant; a, Fisher's exact probability test was used for comparisons.
[a] Five of nine cases as isolated chorea.

as described elsewhere [18] and etiologic fraction (EF) calculated as

$$EF = \frac{P\,(RR - 1)}{P\,(RR - 1) + 1}$$

where P is the frequency among the normal population and RR is the relative risk.

Results

The results are presented in Tables 1 and 2. Among class I antigens the frequency of HLA-A2 was decreased, while the frequency of HLA-B5 and of class II HLA-DR7 was increased. However, none was statistically significant. The correlation between RF and HLA-DR4 ($p < 0.001$) was significant. There was no statistically significant association between arthritis, either with class I or class II antigens. The patients with carditis showed a modest ($p < 0.05$) positive association with HLA-DRw52. The frequency of HLA-DR4 among 34 patients with isolated chronic mitral regurgitation was particularly high at 50% ($p < 0.0001$).

Discussion

Many attempts have been made to explain the pathogenesis of RF genetically by searching for an association with HLA antigens. Particular attention has been paid to HLA-DR antigens, which are related to the immune-response genes encoded on the short arm of the sixth chromosome. The corresponding results of our study are summarized in Table 3. Despite the lacking relationship between class I HLA antigens and RF, there is a general acceptance of the positive relationship between class II HLA antigens and increased genetically linked susceptibility for RF and rheumatic heart disease.

It is known that the preceding infection with group A streptococci is required as an inciting factor to trigger the rheumatic process. Previous studies [12, 26] have shown that the immune response to group A streptococcal carbohydrate is genetically controlled. Also, Ayoub et al. [5] have described a significant association between persistence of antibody to the group A streptococcal carbohydrate and HLA-DR2 in a black population and HLA-DR4 in