HLA TYPING OF ULCERATIVE COLITIS IN IRAN

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Abstract — Ulcerative colitis is an acute or chronic inflammatory bowel disease that diffusely involves the colonic mucosa. The etiology of ulcerative colitis is unknown. The involvement of genetic factors in ulcerative colitis is suggested by some reports of familial occurence and the immune abnormalities found in patients and their unaffected female relatives. A number of disease with unknown etiology, familial prevalence, and immune abnormalities have been shown to be associated with HLA antigens. Aiming to clarify whether or not development of ulcerative colitis is associated with HLA antigens in our patient population, we studied the distribution of HLA A, B and C antigens in 30 Iranian patients suffering from ulcerative colitis using the standard microlymphotoxicity technique and compared it with normal Iranian population. There was no significant difference in the distribution of class I HLA antigens in the patients with ulcerative colitis compared to controls. Lower frequencies of A10, B14, B15, BW63 and CW3 were found in the patients group, compared to controls ($p<0.05$, $p<0.03$, $p<0.02$, $p<0.03$ and $p<0.0077$ respectively). These decreases, however were not significant after correction for the number of antigens tested. These differences may explain a different genetic background.

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INTRODUCTION

Ulcerative colitis (UC) is an acute and chornic inflammatory bowel disease that diffusely invovles the colonic mucosa. Many patients follow a chronic course with frequent exacerbations. To explain the etiology of ulcerative colitis, infectous agents, endotoxins, destructive enzymes (lysozome), vascular disturbance, an autonomic nerve imbalance, psychogenic mechanisms, allergic reactions, and immunologic disturbance have all been hypothesized as causes (1). The familial incidence of ulcerative colitis has been recognized for many years, but it has proved difficult to quantity (2). Figures vary widely between series, probably reflecting referal bias among, other factors, but about 10 to 20 per cent of patients will have at least one of the family member affected. Antineutorphil cytoplasmic antibodies have been reported to occur more frequently in healthy first-degree relatives of patients with UC than in healthy individuals (3). Human lymphocyte antigen (HLA) association have been found in many human autoimmune diseases (4). This study was carried out to clarify the frequency of HLA A,B, and C antigens in patients with ulcerative colitis compared to to normal controls.

MATERIALS AND METHODS

Patients

The studies consisted of 30 (18 males and 12 females) patients with UC who were outpatients and inpatients of Emam Khomeini Hospital. The age's range was 18-70 years. On the basis of past and present history, physical examination, intestinal x-ray studies, colonoscopy and histologic diagnosis of UC was established.

HLA Antigens

Well difined antisera from different sources (Behring and Biotest) as well as some local antisera were used for detection of 49 HLA antigens of class I (A, B and C), using the standard microlymphocytotoxicity tests.

Statistical Analysis

For evaluation of HLA association, the X^2-test, or in the case of small numbers Fisher's exact test were employed. P-values were corrected for the number of antigens studied and then termed PC. Relative risk was calculated by the formula (PC/PC) where P or P denote the number of patients positive or negative for a specific antigen and C or C denote the number of controls positive or negative for the antigen, respectively.

RESULTS

Results obtained from HLA typing in patients suffering from ulcerative colitis, together with results seen in the control group are shown in Tables 1,2 and 3 according to regions A,B and C class I HLA system. The latter results were taken from our previous report (5). In order to examine the association between class I HLA antigens and UC, the 2 X^2 table was agreed for each of specified antigens. If the expected frequency for each of the antigens was lower than 5, we used the Fisher test. However, if all the expected frequencies were more than 5, the Chi-square (X^2) was calculated. Meanwhile, in the calculation of X^2, the Yates correction or the linkage correction was considered into account (6). In case of antigens A10, B14, B15, BW63 and CW3 the numbers of P value are less than 0.05. However, if such number

of P value is corrected in order to determine the numbers of antigens (x=4.7) tested we will find out that the corrected P value for each of the antigens are more than 0.05 (7,8,9). Thus, none of the differences observed in the frequencies of class I antigens in patients with ulcerative colitis and in those of control group are statistically significant.

Table 1. Human lymphocyte antigen phenotype frequency in patients with ulcerative colitis and controls.

HLA Antigen Locus A	Ulcerative colitis Frequencies %	Controls Frequencies %
A1	13.3	30
A2	33.3	35
A3	23.3	21
A11	23.3	32
A9	26.7	35
A23	3.3	3
A24	20.0	18
A10	10.0	30
A25	0.0	1
A26	10.0	24
A34	0.0	11
A28	10.0	17
A29	3.3	3
A30	3.3	1
A31	6.7	1
A32	0.0	1

Table 2. Human lymphocyte antigen phenotype frequency in patients with ulcerative colitis and controls.

HLA Antigen Locus B	Ulcerative colitis Frequencies %	Controls Frequencies %
B5	43.3	41
B51	40.0	29
B7	3.3	6
B8	3.3	10
B12	10.0	11
B44	10.0	11
B13	3.3	6
B14	0.0	15
B15	3.3	25
BW62	0.0	5
BW63	0.0	15
B16	6.7	15
B38	3.3	3
B39	0.0	6
B17	6.7	10
B57	0.0	4
B18	3.3	6
B21	20.0	16
B42	0.0	5
BW54	0.0	5
BW55	3.3	7
BW56	0.0	4
B27	6.7	6
B35	30.0	35
B40	10.0	18
BW60	0.0	6
BW42	0.0	11
BW4	86.7	76
BW6	70.0	91

Table 3. Human lymphocyte antigen phenotype frequency in patients with ulcerative colitis and controls.

HLA Antigen Locus C	Ulcerative colitis Frequencies %	Controls Frequencies %
CW2	3	16
CW4	26	40
CW1	13	4
CW3	10	4

DISCUSSION

This study shows no significant differences in frequencies of each 47 HLA A, B and C antigens tested among patients with ulcerative colitis and control group. In the case of antigens A10, B14, B15, BW63 and CW3, the P values were less than 0.05. However, this decrease was not significant after correction for the numbers of antigens tested. Similar studies in different parts of the world have provided different or even in some cases, contradictory results. It has been reported from Japan, patients suffered from ulcerative colitis indicate a significant increase in HLA B5 ($P<0.001$) as well as a significant decrease in HLA B35 ($0.02<P<0.05$) (10). Another study carried out in Tokyo revealed that positive association of HLA ($X^2 = 13.3$, $P<0.01$) with ulcerative colitis (11). It has been shown that the results obtained from Askkenazi jews have been different from Japanese. A research carried out in Tel Aviv indicates a significant increase of HLA B35 ($X^2 = 13.3$, $P<0.005$) in all patients and HLA A24 ($X^2 = 13.78$, $P<0.0005$) in the group with early appearance of the disease (12). A difference, however, is noted in the results of the study about Jews. The study of HLA antigens in 30 other Askkenazi Jews in Haifa has indicated positive association with HLA A2 ($P<0.05$), HLA B40 ($P<0.05$) and a negative association with HLA A10 ($P<0.04$) (13). In Caucasians, such variety of results are also seen. Other studies from Italy, Manchester, Birmingham and Oxford and Vienna have revealed no association between HLA antigens and ulcerative colitis (14,15,16,17). According to another study in

Birmingham, there was a significant increase of HLA A11 (X^2=6.82, P<0.01) and a significant decreass of HLA A3 (X^2=5.26, P<0.05) in patients with ulcerative colitis (18). Woodrow and coworkers showed that there is a significant increase of HLA B27 (X^2=9.47, P<0.046) in the patients (19).

Such contradictory results are often due to the failure in correction of P value. However, when corrections have taken place, the observed differences could be explained by different genetic backgrounds in different races, though the significant difference detected are small. Most of the studies carried out so far association between ulcerative colitis and HLA antigens have cocentrated on class I antigens. On the other hand, an association between some of the class II antigens with many of diseases for which genetic and immunologic factors are involved, has been noted. It seems that appearance of the ulcerative colitis, is influenced by genetic and immunologic factors. Furthur investigations should take into account the analysis of HLA class II antigens in order to reveal or exclude the possible influence of gens coding for HLA antigens upon etiology and pathogenesis of ulcerative colitis.

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