Characteristics of Rheumatoid Arthritis relative to HLA-DR in Saudi Arabia

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ABSTRACT

Objective: To determine the clinical characteristics of rheumatoid arthritis in Saudi Arabia in relation to human leukocyte antigen type.

Methods: A group of 91 rheumatoid arthritis patients, 72 females and 19 males were studied for the various clinical, laboratory and radiological parameters along with human leukocyte antigen-DR phenotypes. Since human leukocyte antigen-DR10 was most commonly associated with rheumatoid arthritis in our population, we compared those patients with human leukocyte antigen-DR10 to those without.

Results: The comparison yielded differences in the presence of rheumatoid nodules, erosions, corticosteroid treatment, joint involvement at presentation, hemoglobin levels, and white cell count. Only the last 3 parameters showed a statistical significance.

Conclusion: Human leukocyte antigen type of Saudi patients with rheumatoid arthritis influenced the course of the disease but only to a limited extent.

Keywords: Rheumatoid arthritis, HLA-DR.

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Studies on the genetic basis of rheumatoid arthritis (RA) have focused primarily on the major histocompatibility complex (MHC) genes, specifically human leukocyte antigen (HLA)-DR, which was documented to confer disease susceptibility.[1] The conclusions of many of these studies were the association of HLA-DR4 with RA in caucasian and other ethnic groups.[2-4] HLA-DR1 and DR10 have also been reported to be associated with RA in other population studies.[5-8] However, studies of HLA-DR in relation to disease severity have yielded conflicting results, with some showing an association of severity of RA with HLA-DR4, while others did not.[9-13] We recently have shown the association of HLA-DR10 with RA in Saudi Arabian patients.[14] We now seek to determine, if the presence of disease associated HLA-DR10 is a risk factor for disease severity in our RA patients.

Methods. We studied 91 unrelated adult Saudi patients with RA diagnosed according to the 1987 American Rheumatism Association (ARA) criteria.[15] Records of all 91 patients were reviewed and the following variables were studied: Sex-ratio, age at onset, duration of disease, presence of rheumatoid nodules, weight loss, extraarticular manifestation, mode of onset, joints involved at presentation, disease course, lymphadenopathy, eye involvement, vasculitis, fever and early morning stiffness (EMS). The laboratory parameters, hemoglobin, white blood cell (WBC) count, platelets, erythrocyte sedimentation rate (ESR), rheumatoid factor, urinalysis and anti-nuclear antibodies (ANA) were studied. Radiographs of hands, feet and cervical spine were evaluated. Drugs used by patients were also recorded. The HLA-typing was carried out serologically as previously described.[14] The mean age, duration of disease and means of other quantitative parameters of the immunogenetically defined subsets of patients with RA were compared by t-test. The significance of the association of sex ratio, particular clinical presentation of the

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immunogenetically defined subsets of RA was assessed using either Chi-square test or Fisher's exact test, where appropriate.

Results. The male to female ratio of DR10 and non-DR10 groups was 3/19 (1:6.33) and 16/53 (1:3.31). The age of onset of the 2 groups showed no statistically significant difference, although the non-DR10 group showed an early onset. Clinical parameters such as weight loss, extraarticular manifestations, mode of onset, disease course, fever, lymphadenopathy, eye involvement, EMS and vasculitis showed no statistically significant difference among the 2 immunogenetic subsets. Rheumatoid nodules were recorded in 23% of the HLA-DR10 positive patients compared to 7% of HLA-DR10 negative patients. However, this difference did not reach the level of significance despite approaching it ($p = 0.0575$). The presence of bony erosion also showed disparity between the 2 groups (59% for HLA-DR10 positive patients versus 46% for HLA-DR10 negative patients). This again was not statistically significant. When we considered the difference between the 2 groups with regard to the use of corticosteroids, the HLA-DR10 positive patients exhibited a higher figure compared to the HLA-DR10 negative patients (55% vs. 39%). Again, this difference did not reach significance level. The only significant differences ascertained between the 2 groups in the study were in the categories of joint involvement at presentation in HLA-DR10 positive and negative patients (100% vs. 82%) ($p= 0.04105$), level of hemoglobin and total white blood cell count (Table 1).

Table 1 - Mean +/- standard deviation and percentages of HLA-DR10 positive and negative rheumatoid arthritis patients.

Variable	HLA-DR10 Positive	HLA-DR10 Negative	Significance
Sex Ratio	1:6.33 (M/F = 3/19)	1:3.31 (M/F = 16/53)	Not significant
Age of Onset	46 +/- 13.33 years	39.29 +/- 12.59 years	Not significant
Duration of Disease	8.32 +/- 4.46 years	6.39 +/- 5.06 years	Not significant
Hemoglobin	116.32 +/- 16.24 G/L (22)	126.3 +/- 17.67 G/L (69)	P < 0.05
White blood cell count	7.48 +/- 2.21 x 10^9/L (22)	8.11 +/- 2.51 x 10^9/L (69)	P < 0.05
Platelets	316.47 +/- 76.69 x 10^9/L (19)	336.75 +/- 124.38 x 10^9/L (68)	Not significant
Erythrocyte sedimentation rate	54.5 mm (22)	48.56 mm (68)	Not significant
Early morning stiffness	65.88 min (17)	66.04 min (53)	Not significant
Rheumatoid Nodules	23% (5)	7% (5)	P = 0.0575
Weight loss	5% (1)	4% (3)	Not significant
Extraarticular manifestation	5% (1)	17% (12)	Not significant
Joints involved at presentation:			
Polyarticular	100% (19)	82% (56)	P = 0.04105
Others	0% (0)	18% (12)	
Mode of Onset:			
Acute	0% (0)	2% (1)	
Subacute	100% (19)	95% (59)	Not significant
Palindromic	0% (0)	3% (2)	Not significant
Disease Course:			
Progressive	100% (16)	81% (48)	P = 0.05713
Intermittent	0% (0)	19% (11)	
Fever:			
Yes	0% (0)	3% (2)	
No	100% (19)	97% (67)	Not significant
Lymphadenopathy:			
Yes	0% (0)	1% (1)	
No	100% (19)	99% (68)	Not significant
Rheumatoid Factor:			
Positive	68% (15)	72% (50)	Not significant
Negative	32% (7)	28% (19)	
Eye Involvement:			
Yes	0% (0)	6% (4)	
No	100% (19)	94% (63)	Not significant
Vasculities: No	100% (15)	100% (64)	Not significant
Urinanalysis:			
Normal	90% (20)	80% (50)	
Abnormal	9% (2)	20% (13)	Not significant
Anti-nuclear antibiotics			
Positive	47% (8)	54% (30)	Not significant
Negative	53% (9)	46% (26)	
Radiology:			
Normal	5% (1)	6% (4)	
Osteopenia	95% (21)	93% (64)	Not significant
Erosion	59% (13)	46% (31)	Not significant
Cervical x-ray			
Normal	50% (8)	57% (27)	
Abnormal	50% (8)	43% (20)	Not significant
DMARDS	100% (20)	100% (67)	Not significant
Steroid Treatment	55% (11)	39% (26)	Not significant

HLA: Human leukocyte antigen M/F=male/female

Discussion. In the present study, we have evaluated the role of the associated HLA-DR10 marker with RA in our Saudi Arabian patients, and compared the clinical, laboratory and radiological data between the HLA-DR10 positive and negative RA patients. Although there was a difference between the 2 groups in the presence of rheumatoid nodules, erosion and steroid treatment, this difference was statistically insignificant. Those differences, which showed statistical significance, were in the parameters of hemoglobin level, WBC count and joint involvement at presentation.

Most studies showed that HLA-DR4 in RA is associated with more severe disease.[16-18] Riott et al, and Van Zeben et al, suggested that homozygosity of HLA-DR4 was associated with more severe disease.[19,20] Perdriger et al reported that the presence and dosage of HLA-DRB1 encoding the rheumatoid epitope, most specifically, HLA-DR4 alleles, is associated with more severe disease.[21] Similar results were also reported for the ethnic Chinese and Japanese RA patients.[22-24] Studies on French RA patients reported the association of more severe articular damage with the presence and the gene dosage of the shared epitope.[25] However, Benazet et al, showed no association of extraarticular features with HLA-DRB1 alleles, which he attributed to the low frequency of HLA-DRB1*0401 in his patients' group.[26] Teller et al, in a study on Hispanic American RA patients reported that there was no association of shared epitope alleles and severity of RA.[27] This also agrees with the reported study on African Americans.[28] A Pakistani study, which reports HLA-DR10 association with RA, compared RA patients with and without shared epitope, and did not show any difference in the disease activity or severity.[29] A similar study originating from Kuwait, which is in the same region as Saudi Arabia, showed no association of susceptibility of RA with HLA-DR4 or DR1, instead their association was with DR3. The severity of disease in that study was not related to the presence or absence of the associated HLA-DR allele.[30] Yelamos et al, who found an association of DR10 with RA along with the DR4 in a Spanish population, commented on whether differences in susceptibility alleles in different populations may reflect a difference in patient selection, related to disease severity, or are due to other genetic or environmental factors.[7]

In conclusion, the results obtained in the present study on the lack of association of HLA-DR10 and severity are not dissimilar to some of the reported studies above.

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