Human Leukocyte Antigens Assosiation with Systemic Lupus Arythematosus In Iraqi Patients

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Abstract

Background: The etiology of Systemic lupus erythematosus seems to be multifactorial including environmental as well as genetic factors. The genetic predisposition was supported by the occurrence of Systemic lupus erythematosus in more than one member of a family as well as in identical twins.

Aim of the study: To determine the human leukocyte antigen typing class I (A and B) in patients with Systemic Lupus Erythematousus disease.

Methods: Patients group consisted of 44 Iraqi Arab Muslims patients with Systemic lupus erythematosus disease who presented to Baghdad Medical City from January 2010 to January 2012 from Baghdad Province. The second control group consisted from 80 Iraqi Arab Muslims volunteers from hospital employees and their relatives. Human leukocyte antigen typing done for them using serological method by microlymphocytotoxicity test.

Results: A total of 44 patients with Systemic lupus erythematosus were studied. Patients' age ranged from 6 to 65 years with a mean of 29.61 ± 12.78. The other control group, their ages ranged from 16 to 55 years with a mean of 31.35 ± 10.02 . Females were more than males in both groups. Human leukocyte antigen typing of Systemic lupus erythematosus patients showed A2(16, 36.36, 0.20), A3(14, 31.82, 0.17), B4(10, 22.73, 0.12) , B12 (10, 22.73, 0.12) and B21(10, 22.73, 0.12) were the highest absolute numbers, phenotype frequencies and genotype frequencies respectively. There was a significant difference in between SLE patients and control group in the following alleles (A1, A28, A36, A43,B 6, B12, B14, B15, B16, B35, B42, B53).

Conclusions: Genetic factors do have a role in the development and expression of Systemic lupus erythematosus . human leukocyte antigen -A28 , A36, B12 and B21 had an association with Systemic lupus erythematosus Iraqi patients.

Key words: Human Leukocyte Antigens, Systemic Lupus Erythematosus , Tissue typing

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Introduction

Despite the extensive studies, the cause of systemic lupus erythematosus (SLE) is unknown, but its development is believed to be multifactorial, involving environmental and genetic components [(1)]. Major histocompatibility complex (MHC) genes especially HLA-DRB1 and HLA-DQB1 are strongly implicated in susceptibility to SLE [(2).] Systemic lupus erythematosus HLA associations vary with race and ethnicity and appear to be more easily established in homogenous populations [(3)]. Systemic lupus erythematosus is associated with HLA-DR3 in whites, while the predominant class II alleles in Asians are DR1 and DR2 [(4).] The genetic predisposition was supported by the occurrence of SLE in more than one member of a family as well as in identical twins. Approximately 10% of lupus patients have a first or second degree relative with SLE or closely related disease [(5).]

SLE is an autoimmune disease characterized by immune dysregulation, leading to high levels of autoantibody production specifically against double stranded DNA and Sm autoantibody, immune complex deposition in different organs and tissue injury. HLA genes have received important attention in SLE, and there is confirmation supporting a responsibility for specific extended HLA haplotypes as genetic risk factors for disease expression in several populations. HLA-DR2 and DR9 have shown reliable associations with SLE in European Caucasian populations [(6).] In Koreans, DR9 and DRB1*1501 showed positive association with SLE [(7).]

Genetic analysis of SLE diseases will play an important role in recognition of new molecular targets for intervention with drugs. They would be helpful in prediction of the likely efficiency of particular drug according to genotypes of individuals. The HLA associations are clinically used for diagnosis, prognosis and prophylaxis of a diseases [(8).]

The aim of this study to determine the HLA typing of patients infected with SLE disease.

Methods

Patients group consisted of 44 Iraqi Arab Muslims patients with SLE disease who presented to Baghdad Medical City from January 2010 to January 2012 from Baghdad Province. The inclusion criteria were only patients diagnosed previously as SLE and treated with SLE medications and came to fallow –up. The exclusion criteria were all other autoimmune diseases.

The second control group consisted from 80 Iraqi Arab Muslims volunteers from hospital employees and their relatives.

The permission of medical ethics committee was obtained for them. The Ethical Committee of the Al-Kindi College of Medicine, Baghdad University and Baghdad Medical City Teaching Hospital approved the study, and all samples were obtained with informed consent in accordance with the Al-Kindi Teaching Hospital Declaration.

HLA typing done for them using serological method by microlymphocytotoxicity test, which was developed by Terasaki and McClelland (1964) [(9)]. This test is a complement dependent reaction, in which antibodies recognize antigens on the surface of lymphocytes and form antigen-antibody complexes. The formed antigen-antibody complexes thus are able to activate the added rabbit complement which results in death of reacted cells. Then by a dye exclusion technique, it is possible to score the reaction and to determine the HLA-phenotype.

Statistical analysis was done using MiniTab statistical software program 13.20. A P-value ≤ 0.05 was considered significant.

Results

A total of 44 patients with SLE were studied. Patients' age ranged from 6 to 65 years with a mean of 29.61 ± 12.78. Thirty nine of them were female and the rest were males. The age and sex distribution of patients are described in table-1-. The other control group, their ages ranged from 16 to 55 years with a mean of 31.35 ± 10.02 . Fifty of them were female and the rest were males.

HLA typing of SLE patients showed A2(16, 36.36, 0.20), A3(14, 31.82, 0.17), B4(10, 22.73, 0.12) , B12 (10, 22.73, 0.12) and B21(10, 22.73, 0.12) were the highest absolute numbers, phenotype frequencies and genotype frequencies respectively (Table-2)while the control group demonstrated A1(24, 30, 0.16), A2(28, 35, 0.19), B6(33, 41.25.0.23), B35(21, 26.25, 0.14) were the dominant ones (Figure -1-2) . There was a significant difference in between SLE patients and control group in the following alleles (A1, A28, A36, A43,B 6, B12, B14, B15, B16, B35, B42, B53) as revealed in table-2-. Odd ratio was highest in A28 and B12 as shown in table -1-.

Table-1- Age and sex distribution of SLE patients and control group.

	SLE patients n=44	**Healthy control No.=80**	***P- value**
	No. %	**No. %**	
Sex			
Female	**39 88.6**	**50 62.5**	**0.002***
Male	**5 11.3**	**30 37.5**	
Age at sampling Mean± SD	**29.61 ± 12.78**	**31.35 ± 10.02**	**0.438****
Age range	**6-65**	**16 - 55**	

* Chi-square and** Student's t –test.

Table- 2- HLA typing of SLE patients and control group.

HLA type	Control			Patients			Chi-square	O.R.	P value	95th C.I.
	Absolute	Pheno Freq	Gene freq	Absolute	Pheno freq	Gene freq				
A1	24	30	.16	6	13.64	.07	4.14	0.37	0.042	0.14-0. 99
A2	28	35	.19	16	36.36	.20	0.02	1.06	0.879	0.49-2.29
A3	18	22.5	.12	14	31.82	.17	1.29	1.61	0.256	0.71-3.36
A9	16	20	.11	8	18.18	.10	1.06	0.89	0.806	0.35-2.28
A10	7	8.75	.04	4	9.09	.05	0.01	1.04	0.949	0.29-3.78
A11	7	8.75	.04	8	18.18	.10	2.37	2.32	0.123	0.78-6.89
A19	16	20	.11	4	9.19	.05	2.50	0.4	0.114	0.12-1.28
A28	2	2.5	.01	12	27.27	.15	17.39	14.63	0.005	3.1-69.1
A36	0	0	0	4	9.09	.05	7.52	-	0.006	-
A43	0	0	0	2	4.55	.02	3.7	-	0.054	-
B4	15	18.75	.1	10	22.73	.12	0.28	1.27	0.597	0.52-3.14
B5	13	16.25	.08	4	9.09	.05	1.23	0.52	0.267	0.16-1.69
B6	33	41.25	.23	2	4.55	.02	16.88	0.07	0.005	0.02-0.30
B7	8	10	.05	2	.55	0	1.14	0.43	0.286	0.09-2.11
B8	6	7.5	.04	6	13.64	.07	1.22	1.95	0.268	0.59-6.45
B12	2	2.5	.01	10	22.73	.12	13.29	11.47	0.005	2.38-55.18
B13	5	6.25	.03	4	9.09	.05	0.34	1.5	0.559	0.38-5.9
B14	7	8.75	.04	0	0	0	4.08	0	0.043	0-
B15	4	5	.03	6	13.64	.07	2.86	3.0	0.09	0.8-11.27
B16	8	10	.05	0	0	0	4.7	0	0.03	0-
B17	6	7.5	.04	4	9.09	.05	0.1	1.23	0.75	0.33-4.63
B18	6	7.5	.04	2	4.55	.02	0.41	0.59	0.52	0.11-3.04
B21	12	15	.08	10	22.73	.12	1.16	1.67	0.28	0.65-4.24
B22	2	2.5	.01	2	4.55	.02	0.38	1.86	0.54	0.25-13.66
B27	1	1.25	.01	2	4.55	.02	1.4	3.76	0.25	0.33-42.71
B35	21	26.25	.14	4	9.09	.05	5.19	0.28	0.02	0.09-0.88
B37	2	2.5	.01	0	0	0	1.12	0	0.29	0-
B40	6	7.5	.04	4	9.09	.05	0.1	1.23	0.75	0.33-4.63
B41	1	1.25	.01	2	4.55	.02	1.31	3.76	0.25	0.33-42.71
B42	1	1.25	.01	4	9.09	.05	4.57	7.9	0.03	0.85-73.04
B53	0	0	0	4	9.09	.05	7.52	-	0.006	-
B73	1	1.25	.01	2	4.55	.02	1.4	3.76	0.25	.033-42.71

Discussion

The genetic factors that are important in the pathogenesis of Systemic lupus erythematosus (SLE) were those of the major histocompatibility complex (MHC) on chromosome 6. It is now widely accepted that MHC genes constitute a part of the genetic susceptibility to SLE. In thisstudy we found that SLE is more predominant in females than malesthat is in agreement with other study [10]. Concerning HLA- typing, there is a significant increase in HLA-A 28, HLA- A36 and HLA-B12 in SLE patients than control group. Our results were difference from other studies done in different countries for example Pakistan that they found a significant increase was observed in the frequency of HLA-A*01, A*03, A*11, A*23, A*26 A*69, HLA-B*27, B*40, B*49, B*51, B*52, B*53, B*54, B*95, HLA-DRBI*01, DRBI*03, DRBI*11, DRBI*14 among SLE patients indicating a positive association of these alleles with SLE (10). Others reported that HLA-DR2 and DR9 have shown consistent associations with SLE in European Caucasian populations [11]. In Koreans, DR9 and DRB1*1501 showed positive association with SLE [12, 13]. Thus, Genetic factors have a role in the development and expression of SLE and environmental factors may trigger the disease in genetically susceptible hosts [14]. Further evidence is derived from the association between SLE and the HLA system. Firstly, in 1972, McDevitt and Bodmer reported an association between

SLE and HLA-B8 [15]. This was followed by other studies stating an association between SLE and HLA-A1, B8, B13, and B17 [16]. There were also reports of associations between SLE and HLA-DR2 and DR3 [17]. There was, however, significant association between HLA-DR2 and SLE in white patients, but not in African American and Mexican American patients [18]. Some studies have identified a higher frequency of HLA-DR3 in African Americans [19]. consequently, the association of certain HLA haplotypes with disease in multiple affected members of a family may provide more inclusive genetic information than the single alleles. In one of our families, both the mother and son had SLE and were HLA identical. This is a rather rare situation and, presumably, would be due to shared HLA antigens between the parents. Some studies suggested that haplotype HLA-A9B40DRB1 * 15 and genotypes HLA-DRB1 * 09/DRB1 * 15, HLA-DRB1 * 03/DRB1 * 15 were correlated with SLE. The predisposition of multiple loci seems to have an additive effect. The children with their gene HLA-DRB1 * 15 derived from their fathers might more easily suffer from SLE [20]. Others found that HLA-D complex is dominant in SLE patients and hypothesis states that SLE-autoantibodies are initiated by environmental T cell epitope mimics of the SLE-related autoantigens in hosts with susceptible HLA-D alleles. These autoantibodies diversify over a period of years due the accumulation of cross-reactive T cells. This process ultimately leads to the generation of organ specific autoantibodies and autoreactive effector T cells due to the polyreactive nature of T and B cell receptors from hosts with susceptibility genes to end organ damage, resulting in protean clinical presentations [21]. Other study in Egypt demonstrated that HLA-DRB1*15 allele may be a susceptibility allele in Egyptian children with SLE but is not related to clinical presentation of SLE [22].

The difference in HLA association with SLE in our study and studies in different countries may be due to race, ethnicity, religion and family study that differ from one country to other. Moreover, ethnicity has been found to have a significant role in both disease susceptibility and disease expression. In summary, our studies emphasize previous studies indicating that genetic factors do have a role in the development and expression of SLE. Environmental factors may, perhaps, trigger the disease in genetically susceptible subjects

Conclusions

Genetic factors do have a role in the development and expression of SLE. HLA-A28 , A36, B12 and B21 had an association with SLE Iraqi patients.

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