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Is There Any Relationship Between Human Leucocyte Antigen Class II and Chronic Urticaria? (Chronic Urticaria and HLA Class II)

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The Human Leukocyte Antigen (HLA) typing of large groups of patients with various autoimmune diseases has demonstrated that some HLA alleles occur at higher frequencies in specific diseases than in the general population. Chronic urticaria has been shown to have an autoimmune basis by a previous study which found an association between chronic urticaria and specific HLA groups. We investigated the HLA subtypes of Turkish chronic urticaria patients. For this purpose 42 Turkish patients with chronic urticaria and 115 healthy controls were typed for HLA-DR and DQ by PCR-SSP (Polymerase Chain Reaction Sequence Specific Primers) low resolution DNA technique. We found an increased frequency of DR4 (42.9%, p=0.01) in chronic urticaria patients in comparison with that in healthy controls. This study supports the hypothesis that HLA alleles may be involved in the pathogenesis of chronic urticaria and that they appear to be directly involved in the initiation of the immune response.

Key Words: Chronic urticaria, HLA subtypes, skin

INTRODUCTION

Urticaria is a common condition composed of transient, edematous, itchy, cutaneous swellings with individual lesions lasting less than 24 hours. Chronic urticaria has been shown to have an autoimmune basis.[1] In some patients, histamine releasing autoantibodies are directed against epitopes on the alpha chain of the Ig E high affinity receptor, FcεRI α, whereas histamine release is mediated through anti Ig E autoantibodies in others.[2] It is well known that patients with one autoimmune disease are at higher risk for having a second autoimmune disease. Previous studies reported an increased frequency of autoimmune thyroiditis in patients with chronic urticaria.[3,4] More autoimmune diseases have been shown to be associated with alleles of the Human Leukocyte Antigen (HLA) region. HLA molecules are polymorphic membrane glycoproteins which play a major role in the initiation and maintenance of immune responses. In this study we investigated the major histocompatibility complex (MHC) Class II type alleles in blood from Turkish chronic urticaria patients. The results were compared with a healthy control population of the same age group in order to determine if there is a relation between HLA groups and chronic urticaria.

Our patient group consisted of 42 patients, who had had urticarial lesions of unknown etiology for more than six weeks. Ten of the patients were male and 32 female. The ages ranged from 18 to 70 years with a mean age of 40.40 ± 12.09. None of the patients had features for vasculitic urticaria like abdominal or joint pain, persistent lesions for more than 24 hours, increase in erythrocyte sedimentation rate or decrease in complement levels. As a control group we chose 115 healthy people matched for age and ethnic composition, with no personal or family history of chronic urticaria.

DNA was prepared from ethylenediamine tetraacetic acid - anticoagulated blood taken from the 42 urticaria patients. A salting-out method

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was used to extract genomic DNA, which was then precipitated, washed with ethanol and resuspended in water. For each sample, polymerase chain reaction (PCR) using sequence-specific polymers (Olerup SSP DQ-DR Combi tray, Genovision, Vienna, Austria) was used to determine the MHC Class II type, designed to detect all known alleles present in DRB1 and DQB1 loci. The total volume of 373 μL, consisting of 114 μL PCR master mix, 3 μL Taq polymerase (5 units/μL), 74 μL genomic DNA (30 ng/μL) and 182 μL distilled water was distributed among 32 plates resulting in 10 μL final volume each. Cycling parameters employed in a GeneAmp PCR 9600 (Perkin Elmer Cooperation, Warrington, U.K.) were as follows: 94C for two minutes followed by ten cycles of 10 s at 94C, 60 s at 65C, then 20 cycles of 10 s at 94C, 50 s at 61C and 30 s at 72C. After PCR amplification, the contents of each reaction were electrophoresed in 2% agarose gels containing 0.5 μg /mL ethidium bromide and visualized using ultraviolet irradiation.[5,6] Data was statistically analyzed by chi-square test using SPSS 11.0. Statistical significance was set at p values smaller than 0.05.

The results are listed in Table 1. HLA DRB1*04 (HLA DR4) showed a statistically significant increase in patients with chronic urticaria compared to the control group ($p < 0.05$). No other significant differences were detected.

Many studies have investigated the etiology of chronic urticaria. Recent researches has focused primarily on an autoimmune basis. Hide, et al. showed that, demonstration of the functionally important Ig G antibodies directed to the α subunit of the high affinity Ig E receptor (FcεRIα) on basophils is one of the most direct evidence of autoimmune process, like found in chronic urti-

Table 1. Distribution of HLA Groups in Chronic Urticaria Patients and Controls

HLA Antigens	Chronic Urticaria Group (n=42)		Control Group (n=115)		p
	N	%	n	%	
DRB1*01 (DR1)	7	16.7	12	10.4	0.28
DRB1*03(DR3)	3	7.1	20	17.4	0.11
DRB1*04(DR4)	18	42.9	26	22.6	0.01
DRB1*07(DR7)	10	23.8	15	13.0	0.10
DRB1*08(DR8)	3	7.1	4	3.5	0.32
DRB1*09(DR9)	0	0	7	6.1	0.10
DRB1*10 (DR10)	0	0	6	5.2	0.13
DRB1*11(DR11)	10	23.8	27	23.5	0.97
DRB1*12 (DR12)	1	2.3	5	4.3	0.57
DRB1*13 (DR13)	10	23.8	44	38.3	0.09
DRB1*14 (DR14)	3	7.1	12	10.4	0.53
DRB1*15(DR15)	10	23.8	24	20.8	0.69
DRB1*16 (DR16)	3	7.1	4	3.5	0.32
DQB*02 (DQ2)	11	26.2	36	31.3	0.54
DQB*04 (DQ4)	4	9.5	3	2.6	0.06
DQB*05 (DQ5)	13	31	33	28.7	0.78
DQB*06 (DQ6)	16	38.1	34	29.6	0.31
DQB*07 (DQ7)	16	38.1	56	48.7	0.24
DQB*08 (DQ8)	13	31	31	27.0	0.62
DQB*09 (DQ9)	1	2.3	6	5.2	0.24

caria[7-9] In addition, the increasing frequency of specific HLA subtypes further supports the immunologic basis of chronic urticaria.[2,8]

An increasing number of studies show HLA associations in several immunologic diseases. Apart from the studies showing the increased incidence of HLAB51 in Behcet's disease, we have previously investigated HLA DR and DQ antigens in patients allergic to nickel and a correlation with DQ A0501 was found in Turkish nickel allergic patients.[10,11] On the other hand, there are also some reports of well known immunologically based diseases such as atopy, in families with house dust mite allergy, without any significant association between HLA-DR, HLA-DQ and DP genotypes.[12]

A considerable number of studies have shown that particular HLA class II alleles are the risk factors for or protective factors against the development of sensitization to specific allergens.[13,14] This is suggested as being due to the following reasons:

1. HLA molecules may act as receptors for viruses and toxins which may lead to disease onset.
2. Some HLA molecules may be selective for the disease agent's peptide and people carrying these HLA molecules are at risk for that disease.
3. HLA molecules and some etiological agents may have similar antigenic determinants.

In our study, a correlation between HLA groups and chronic urticaria was studied and a significant association was found with HLA DR4. We believe that this supports the autoimmune and immunologic basis of chronic urticaria.

In a review of the literature, several HLA studies were found on urticaria related diseases such as hereditary angioedema, mastocytosis, familial exercise-induced anaphylaxis and dermographism.[15-19] However, only two studies have already been performed on the association between chronic urticaria and HLA (Table 2).[2,20] Van Neste et al investigated HLA Class I antigens in 27 patients in 1978 and they did not show any significant correlation.[20] More recently, O'Donnell et al performed a PCR based, MHC Class II study in 1999. They found a strikingly increased frequency of HLA DR4 and DQ8 and a decreased frequency of HLA DR15 and DQ6.[2]

Many questions still remain to be answered in chronic urticaria such as the triggering of the autoimmune process, temporary spontaneous remissions and the genetic heterogeneity of the

Table 2. Urticaria Related Disorders and HLA Association

Author	Year	Number of Patients with Urticaria	HLA Class	Findings
Blumenthal	1978	81 (Hereditary Angioedema)	Class I	No correlation (14)
Eggert	1982	19 (Hereditary Angioedema)	Class I	No correlation (15)
Olafsson	1985	50 (Mastocytosis)	Class I	Increased
				HLA B12 (16)
Longley	1987	5 (Familial exercise-induced anaphylaxis)	Class I	Increased
			Class II	HLA A3, B8, DR3 (17)
Salazar Villa	1992	25 (Dermographism)	Class I	Increased
				HLA A1, A2,B5,B16 (18)
van Neste	1978	27 (Chronic Urticaria)	Class I	No correlation (19)
O'Donnell	1999	100 (Chronic Urticaria)	Class II	Increased HLA DR4 DQ8
				Decreased
				HLA DR15 DQ6 (2)
Present Study	2000	42 (Chronic Urticaria)	Class II	Increased
				HLA DR4

patients. The IgE receptor autoantibodies are found in about one third of patients with chronic idiopathic urticaria.[21] According to O'Donnell et al, the importance of HLA associations in the mechanisms of autoimmunity is not completely clear. Strong positive DR4 allele association suggests a "genetic component" in the pathogenesis of chronic urticaria, whereas, other genetic or environmental factors may also play role in the development of α chain antigenicity.[2] We investigated the correlation of HLA profile of Turkish urticaria patients. The frequency of HLA DR4 was significantly higher in these patients than in controls. Our finding is consistent with the result of O'Donnell et al's study. Actually, although they showed that HLA DQ8 was increased and HLA DR15 and DQ6 were decreased in a British population, we lacked the evidence to determine a significant association between HLA DQ groups genotyping in Turkish urticaria patients. This supports the influence of alternative genetic and environmental factors in the etiopathogenesis of chronic urticaria.

We believe that HLA alleles may be involved in the development of chronic urticaria as a triggering factor in the autoimmune process. These HLA Class II antigens appear to be directly involved in the initiation of the immune response. However, additional, multiple etiological factors may play a role in the etiopathogenesis of chronic urticaria and further studies with larger populations from different parts of the world are still needed.

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