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Relations between human leukocyte antigens and autoimmune hepatitis in Turkish children

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Background/aims: *We aimed to identify the genetic factors associated with increased tendency toward autoimmune hepatitis, a chronic and progressive inflammatory condition.* ***Methods:*** *A total of 32 children diagnosed with autoimmune hepatitis were included in the present study, and 160 healthy adult blood donors served as controls. In both groups, HLA phenotypes were examined (HLA-A, B, C, DR, DQ) and compared. In addition, the association between the type of autoimmune hepatitis and HLA status was explored.* ***Results:*** *Compared to controls, patients with autoimmune hepatitis had increased frequencies of the following class 1 HLA antigens: A24.9 (28% vs. 9%, p=0.007), A26 (25% vs. 3%, p<0.001), A32 (34% vs. 4%, p<0.001), B38 (9% vs. 0.6%, p=0.015), and B51 (16% vs. 0%, p<0.001). Among class II HLA antigens, DRB1*04 (22% vs. 0%, p<0.001), DRB1*07 (9% vs. 0%, p=0.004), DRB1*11 (12% vs. 0%, p=0.001), DRB1*15 (25% vs. 0%, p<0.001), DRB1*14 (31% vs. 0%, p<0.001), and DR11.5 (9% vs. 0%, p=0.004) were more frequent in patients compared to controls. Type 1 autoimmune hepatitis was associated with high frequencies of A24.9, A26, A32, and DRB1*15, whereas type 2 autoimmune hepatitis was associated with high frequencies of A26, B51, B38, and DRB1*11. On the other hand, frequencies of A32 and DRB1*04 were high among patients with unclassified autoimmune hepatitis.* ***Conclusions:*** *There seem to be associations between certain HLA antigens and susceptibility to autoimmune hepatitis, but variations among different geographical locations suggest a role for environmental factors.*

Key words: HLA antigens, autoimmune hepatitis, genetic predisposition to disease

Türk çocuklarında insan lökosit antijenleri ile otoimmun hepatitin ilişkisi

Amaç: *Kronik ve ilerleyici inflamatuar bir durum olan otoimmun hepatite yatkınlığı arttıran genetik faktörlerin belirlenmesi.* ***Yöntem:*** *Otoimmun hepatit tanılı toplam 32 hasta ile sağlıklı, adült 160 kan vericisi kontrol grubu olarak çalışmaya alınmıştır. Her iki grupta HLA fenotipleri (HLA-A, B, C, DR, DQ) incelenmiş ve karşılaştırılmıştır. Otoimmun hepatit tipleri ile HLA durumu arasındaki ilişki araştırılmıştır.* ***Bulgular:*** *Otoimmun hepatitli hastalarla kontrol grubu karşılaştırıldığında Class-1 HLA antijenleri artmış sıklıkta bulunmuştur: A24.9 (28% vs. 9%, p=0.007), A26 (37% vs. 3%, p=0.004), A32 (34% vs. 4%, p<0.001), B38 (9% vs. 0.6%, p=0.015) ve B51 (15% vs. 0%, p=0.026). Class-2 HLA antijenlerinden: DRB1*04 (21% vs. 0%, p<0.001), DRB1*07 (9% vs. 0%, p=0.004), DRB1*11 (12% vs. 0%, p=0.001), DRB1*15 (21% vs. 0%, p<0.001), DRB1*14 (31% vs. 0%, p<0.001) ve DR11.5 (9% vs. 0%, p=0.004) hastalarda kontrol grubuna göre daha sıktır. Tip 1 otoimmun hepatit artmış A24.9, A26, A32 ve DRB1*15; Tip 2 AIH A26, B51 ve DRB1*11 HLA sıklığı ile ilişkili bulunmuştur. A32 ve DRB1*04 sıklığı tanımlanmamış otoimmun hepatit hastalarında yüksek bulunmuştur.* ***Sonuç:*** *Belirli HLA antijenleri ile otoimmun hepatite yatkınlık arasında bir ilişki olduğu görülmektedir ancak coğrafik lokasyonlar gibi çevresel faktörler de etkili olmaktadır.*

Anahtar kelimeler: İnsan lökosit antijenleri, otoimmun hepatit, genetik yatkınlık

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic, progressive, inflammatory liver disease of unknown etiology, and it is infrequent among children (1). This condition is characterized by morphological changes on liver biopsy in the form of interface hepatitis, hypergammaglobulinemia, high serum transa-

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minase activity, and presence of antibodies against certain tissue antigens (2). Presently, three types of AIH are distinguished: type 1 AIH is characterized by antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA) in the serum in association with hypergammaglobulinemia; type 2 AIH patients have anti-LKM 1 (type 1 liver/kidney microsome) antibodies in serum, and the majority of the cases are children; and type 3 AIH is characterized by the presence of antibodies against soluble liver antigen/liver-pancreas antigen (SLA/LP) (1,3). Some patients share the clinical and histological features of AIH without the presence of immunological markers (autoantibodies) required for sub-classification. These are referred to as unclassified AIH (4).

Although the etiology of AIH is unknown at present, a genetic predisposition, combined with environmental factors, is thought to play a role in the development of the autoreactivity against hepatocytes (2,3). AIH has a complex genetic transmission pattern that is not clearly established. One or more genes increase or decrease the possibility of genetic transmission alone or in combination (1,2,5). In several studies, some alleles were found to display differences in amino acid sequences (6-8), and an increased frequency of human leukocyte antigen (HLA) A1, B8 and DR3/DR4 has been reported in patients with type 1 AIH[9]. Studies in Europe and North America found an association between type 1 AIH and HLA DR3 and DR4, while an association between HLA DR4 and AIH was observed in Japan (6,7,9,10).

Although an immunogenetic basis has been proposed for the pathogenesis of AIH, a difference in the association with HLA subtypes has been noted among geographical areas and ethnic groups.

This study examined the associations of certain HLA alleles with AIH and its subtypes through a comparison of HLA status in affected individuals with healthy controls, in an attempt to identify the genetic factors conferring susceptibility to the disease.

MATERIALS AND METHODS

A total of 32 patients (Group 1) diagnosed with AIH between January 1999 and December 2008 in the Pediatric Gastroenterology Unit of Sisli Etfal Research and Training Hospital were included in the present study, and 160 healthy adult blood donors served as controls (Group 2). Demographic and HLA data were collected and the association between the type of AIH and HLA status was explored. The diagnosis of AIH was based on the criteria defined by the International Autoimmune Hepatitis Group (IAIHG) (11-12). ANA, SMA and anti LKM-1 antibodies were assayed by immunofluorescent antibody assay (IFA). Serological tests for hepatitis B and C were negative for all patients in Group 1, as were the history of blood transfusions and chronic medication use. Serum aminotransferase and IgG levels were elevated in all patients. Other hepatic diseases such as alpha-1 antitrypsin deficiency, Wilson's disease, sclerosing cholangitis, and primary biliary cirrhosis were excluded, and all patients underwent a liver biopsy. Liver biopsies were performed percutaneously by the Menghini technique assessed by an experienced histopathologist for the degree of necroinflammatory activity and fibrosis score using Knodell Histological Activity Index (13,14).

Since age and gender have no effect on HLA status, 160 healthy adult blood donors were included as the control group (Group 2). Controls were serologically negative for hepatitis B and C, and their serum aminotransferase levels were within normal range. In both groups, HLA phenotypes were examined (HLA-A, B, C, DR, DQ).

HLA assessment

Typing for HLA class I and II antigens was performed with the standard complement-dependent lymphomicrotoxicity test at Cerrahpasa Medical Faculty Blood Center-Immunology Laboratory. Lymphocytes were tested with a panel of sera containing well- characterized HLA-specific alloantibodies. Each serum was placed in a microtiter well of a Terasaki plate (60-72 wells/plate). After a short incubation period, rabbit serum was added as a source of complement, and the cells that had bound the alloantibody were lysed, making them permeable to the fluorochrome ethidium bromide. The wells containing the lysed cells were easily discriminated by microscopy (15).

Statistical analyses

SPSS 11.0 software was used for statistical analyses. Data were summarized as mean ± standard deviation and percentages. Chi-square test was used for the comparisons of frequencies. A p value less than 0.05 was considered significant.

RESULTS

In Group 1, of the 32 patients, 46.8% (n=15) were male and 53.2% (n=17) were female, with an ave-

rage age of 8.29±2.77 years (range: 3-13 y) at the time of diagnosis. Of the 32 cases, 15 (46.8%) and 8 (25%) had type 1 and type 2 AIH, respectively, with 9 patients (28.2%) being unclassified. All patients with type 1 AIH were positive for ANA and/or SMA. Type 2 AIH patients were all positive for antibody against LKM 1. All patients in Group 1 had elevated levels of alanine aminotransferase (ALT) (465.41±479.16 IU/L), aspartate aminotransferase (AST) (623.09±707.15 IU/L) and IgG (2623.06± 1202.57 mg/dl).

In Group 2, which consisted of a total of 160 healthy blood donors, the mean age was 42±5.2 years and female to male ratio was 108: 52.

HLA antigen frequencies of the two groups were compared, and when a significant difference was noted in HLA frequency, its relationship with the type of AIH was examined (Table 1). Compared to controls, patients in Group 1 had increased frequencies of the following class I HLA antigens: A24.9 (28% vs. 9%, p=0.007), A26 (37% vs. 3%, p=0.004), A32 (34% vs. 4%, p<0.001), B38 (9% vs. 0.6%, p=0.015), and B51 (15% vs. 0%, p=0.026). Among class II HLA antigens, DRB1*04 (21% vs. 0%, p<0.001), DRB1*07 (9% vs. 0%, p=0.004), DRB1*11 (12% vs. 0%, p=0.001), DRB1*15 (21% vs. 0%, p<0.001), DRB1*14 (31% vs. 0%, p<0.001), and DR11.5 (9% vs. 0%, p=0.004) were more frequent in Group 1 compared to controls. Type 1 AIH was associated with high frequencies of A24.9, A26, A32, and DRB1*15, whereas type 2 AIH was associated with high frequencies of A26, B51 and DRB1*11 (Table 1). On the other hand, frequencies of A32 and DRB1*04 were high among patients with unclassified AIH (Table 1).

DISCUSSION

Many studies have examined the role of class I and II HLA in susceptibility to AIH in different geographical locations and ethnic groups, with varying results (1,2,5,16,17). In the present study, patients with AIH had significantly increased frequencies of several class I (A24.9, A26, A32, B38, B51) and class II (DRB1*04, DRB1*07, DRB1*11, DRB1*15, DRB1*14, DR11.5) HLA antigens, compared to controls. When compared to the results of previous studies, the number of alleles found to be associated with AIH was greater in the present study, which may be attributed to the geographic localization of our country, resembling a bridge for a number of immigrations between the East and West. In addition, among these HLA alleles, A24.9, A26, A32, and DRB1*15 were associated with type 1 AIH, A26, B51 and DRB1*11 were associated with type 2 AIH, and finally A32 and DRB1*04 were associated with the unidentified type.

Various associations have been found in the previous studies examining the relation between HLA antigen status and AIH. The meta-analysis on studies conducted in several Latin American countries (Brazil, Argentina, Mexico, and Venezuela) found a protective effect for DRB1*1302, DQB1*0301 and DR5, while DR52, DQB1*02, DQB1*0603, DRB1*0405, and DRB1*1301 were identified as a risk factor (18). In Taiwanese patients with AIH, a significantly higher frequency of DQ5 was observed in AIH patients compared to controls. In that study, compared to the findings from Western countries, the frequency of A1, B8 and DR3 was lower in AIH patients, and A2, DQ5

Table 1. The association between AIH subtypes and HLA class I/II antigens

HLA	Type 1 (n=15)	Type 2 (n=8)	Unclassified (n=9)	Controls (n=160)	RR (1)	P1	RR (2)	P2	RR (3)	P3
A24.9	7 (46)	1 (12)	1 (11)	15 (9)	4.98	0.001	1.33	NS	1.18	NS
A26	5 (33)	3 (37)	0	5 (3)	10.66	0.001	12	0.004	?	NS
A32	6 (40)	1 (12)	4 (44)	7 (4)	9.14	<0.001	2.85	NS	10.15	0.001
B51	1 (6)	3 (37)	1 (11)	0	?	NS	?	<0.001	?	NS
DRB1*04	1 (6)	1 (12)	5 (55)	0	?	NS	?	NS	?	<0.001
DRB1*07	1 (6)	1 (12)	1 (11)	0	?	NS	?	NS	?	NS
DRB1*11	1 (6)	2 (25)	1 (11)	0	?	NS	?	0.002	?	NS
DR11*15	6 (40)	1 (12)	1 (11)	0	?	<0.001	?	NS	?	NS
DR11*5	1 (6)	1 (12)	1 (11)	0	?	NS	?	NS	?	NS

AIH: Autoimmune hepatitis. Type-1: Type-1 AIH patients. Type-2: Type-2 AIH patients. Controls: Healthy blood donors. RR (1): relative risk of Type-1 versus controls. P1: Type-1 patients compared with controls using Fisher's exact test. RR (2): Relative risk of type-2 versus controls. P2: Type-2 patients compared with controls using Fisher's exact test. RR (3): Relative risk of unclassified patients versus controls. P3: Unclassified patients compared with controls using Fisher's exact test. NS: Not significant. Data are expressed as n (%), unless otherwise stated.

and DR4 were more frequent in AIH compared to controls, but the difference did not reach statistical significance (19). In another study from Taiwan, A1, B8 and DR3 were not observed. However, in the reports from Western countries, these were significantly elevated, either alone or in combination. B35 was significantly higher in AIH patients compared to controls (20). Also, Chinese patients with AIH had significantly increased frequency of DR4 compared to a control group (21-23). In a German study examining a Caucasian pediatric population, HLA B8 occurred at a higher frequency in type 1 and 2 AIH than in controls; however, the difference was significant for type 1, but not for type 2 (24). Another study from Germany reported C7, A2, B8, DR3, and DQ2 to be the most frequent HLA types in type 1 AIH (25). The authors compared their data with those obtained in Italy and North America (26). In the Italian study, B8, C7, DQ2 and DR3 showed a higher frequency in types 1 and 2 AIH compared to controls, and B8-DR3-DQ2 in type 1 compared to controls. In Italian patients, DR4 was more frequent in the patient group, but without being significantly different compared to controls. In patients from North America, B8, DR3, DR4, and B8-DR3-DQ2 were significantly more frequent compared to Italian patients (26). In the studies reporting from Japan, DRB1*0405, DRB4 and DQB1*0401 were significantly more frequent in type 1 AIH (27-29). DRB1*0301 was found to have an association with AIH in North America, West Asia and North Europe (30-32). DRB1*13 had an association with AIH in an Indian population (33). The previous Turkish study did not detect a significant increase in the classical triad of A1-B8-DR3, and the frequency of B8 was 10.9% and 0% in controls and AIH patients, respectively (17).

With regard to certain alleles, some similarities have been noted between our findings and various geographical locations. For instance, DRB1*04 was elevated in studies from North America, Western Asia, North Europe, Japan, Germany, Latin America, China, and Turkey. Similarly, we found a significantly higher frequency of DR4 (DRB1*04) among patients compared to controls (21% vs 0%, p<0.001). However, in contrast to previous studies, this difference was due to the unidentified type, rather than type 1 or type 2 disease. Similar to the findings in North Europe and America, we also observed an increased frequency of DRB1*15 in our AIH patients compared to controls (21% vs. 0%, p<0.001) (30,31). No significant increase was observed in DRB1*03 in the present study despite a higher frequency reported in studies from North America, West Asia and North Europe. In Italy, DR11 was significantly lower in type 1 AIH patients compared to controls, which is in contrast with our findings showing a significant increase in DRB1*11 (DR11) compared to controls (12% vs. 0%, p=0.001) (26).

There is a paucity of studies on type 2 AIH. In a study by Bittencourt et al. (34), patients with type 2 AIH had significantly higher frequency of DRB1*07, DRB4 and DQB1*02 compared to controls. In a Canadian study, DQB1*0201 was found to be primarily responsible for the increase in the susceptibility to type 2 AIH (35). In another study, American and German patients with type 2 AIH had significantly higher frequency of DRB1*07, DRB1*15 and DQB1*06 compared to controls (36). In our study, patients with type 2 AIH had a significantly higher frequency of A26 (37% vs 3%, p=0.004), B51 (37% vs 0%, p<0.001) and DRB1*11 (25% vs 0%, p=0.002) compared to controls (Table 1), with no significant increase in DRB1*07.

HLA DR3 and HLA DR7 confer susceptibility to type 2 AIH, and DR7 positivity is associated with a more aggressive disease course (2). We also found a higher DR7 frequency, but the difference was not significant. We were unable to identify similar results from previous studies with regard to the associations of type 2 AIH found in the present study.

Although studies indicate an association between the absence or presence of certain alleles and the development of AIH, the significant variation observed in different geographical locations suggests a significant role for environmental factors in the context of genetic susceptibility. On the other hand, alleles consistently associated with AIH across different populations, particularly DRB1*04 and DRB1*15, may aid in the diagnosis and deserve further investigation to elucidate genetic mechanisms underlying the condition.

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