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RAPID COMMUNICATION

Genetic association of autoimmune hepatitis and human leucocyte antigen in German patients

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Abstract

AIM: To report on our large German collective and updated data of 142 patients with autoimmune hepatitis (AIH) type 1.

METHODS: Key investigations performed were liver biopsy, serum autoantibodies as well as serum markers such as IgG and elevated transaminases. Antinuclear antigen (ANA) and smooth muscle antigen (SMA) autoantibodies characterized type 1 AIH. Type 3 (AIH) was solely characterized by the occurrence of soluble liver antigen/liver-pancreas antigen (SLA/LP) autoantibodies either with or without ANA or SMA autoantibodies.

RESULTS: Most prevalent HLAs were A2 (68 patients, 48%), B8 (63 patients, 44%), C7 (90 patients, 63%), DR3 (49 patients, 38%), DR4 (49 patients, 38%) and DQ2 (42 patients, 30%). Compared to the Italian and North American patients, we found fewer patients with a DQ2 subtype. Furthermore, the B8-DR3-DQ2 human leucocyte antigen (HLA) was also less prominent compared to the North American patients. However, prevalences of B8, DR3, DR4, DR7, DR11 and DR13 were comparable to the Italian and North American patients. Furthermore, we report on an additional subgroup of patients with SLA/LP positive AIH. Generally, in this subgroup of patients the same HLA subtypes were favoured as the AIH type 1.

CONCLUSION: Although HLA subtypes were comparable between these three collectives, the German patients were distinct from the Italian and North American patients with respect to DQ2 and from the North American patients with respect to B8-DR3-DQ2 HLA. A clinical correlation, e.g. difference in severity or treatability of AIH type 1, has yet to be determined.

Key words: Autoimmune hepatitis; Human leucocyte antigen; Immunogenetics

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INTRODUCTION

Autoimmune hepatitis (AIH) is characterized by portal lymphatic infiltrates on liver histology and in most patients with the occurrence of autoantibodies such as antinuclear, smooth muscle antibody-positive (ANA/SMA, type 1), liver-kidney microsomal antibody-positive (LKM-1), and soluble liver antigen/liver-pancreas antigen (SLA/LP) antibodies. Untreated, the disease usually runs an unfavorable course with 5 year survival rates of 50% and 10 year survival rates between 10% and 27%[1,2]. However, in most patients the disease can be controlled with immunosuppressants such as prednisolone and azathioprine, resulting in an almost normal average life expectancy[3].

Although the pathomechanism of the disease is still unknown, an underlying genetic predisposition has been suggested due to the fact that patients are predominantly of female gender (women to men ratio equals to approximately 6:1) and the association of the disease with certain human leucocyte antigens (HLAs). Muratori *et al*[4] recently published an extensive study on two large populations, Italian and North American, and demonstrated a distinct genetic association of HLA with the disease. B8-DR3-DQ2 was reported to be the most frequent genotype in Italian patients with AIH type 1 but significantly less frequent in North American patients. In addition, a clear difference in occurrence of the DR4 genotype was demonstrated with fewer patients in Italy presenting with such a genotype. Furthermore, the C7, DR3, DR11, DR13, and DQ2 loci were investigated but no significant differences between

Table 1 Most prevalent HLA subtypes in German patients with autoimmune hepatitis type 1

HLA	AIH type I German patients
C7	90 (63%)
A2	68 (48%)
B8	63 (44%)
DR3	49 (38%)
DR4	49 (38%)
DQ2	42 (41%)

these two populations could be found.

In order to further elucidate these genetic associations and differences, we now report on the HLA antigens in our large German collective of 142 patients with AIH type 1 and compared it to published data, especially in the Italian and North American populations. In addition, we report on our small subgroup of 29 patients with SLA/LP positive AIH.

MATERIALS AND METHODS

Subjects

One hundred and forty-two consecutive patients with definite, autoantibody positive AIH type 1 and 29 consecutive patients with SLA/LP positive AIH, who had been referred to the Department of Internal Medicine I, Mainz University Hospital, were investigated. All patients lacked serological evidence of chronic viral hepatitis B and C by third-generation enzyme-linked immunoassay. There was no evidence for illicit drug abuse, excessive alcohol intake (> 4 oz/wk) or exposure to hepatotoxic drugs. Diagnosis of AIH was established according to the revised Scoring system described previously[5].

Methods

Key investigations performed were liver biopsy, serum autoantibodies as well as serum markers such as IgG and elevated transaminases. Similar to Muratori's study[4] and according to international standards, ANA and SMA autoantibodies characterized type 1 AIH. Type 3 (AIH) was solely characterized by the occurrence of SLA/LP autoantibodies either with or without ANA or SMA autoantibodies.

Of our 142 patients with AIH type 1, 119 were women (84%) and 23 were men (16%). Of these patients, 108 (76%) were positive for ANA, 101 (71%) for SMA autoantibodies, and 67 (47%) patients had both ANA and SMA autoantibodies. DR and DQ alleles were not examined in all patients. DR alleles were investigated in 129 patients and DQ in 103 patients. Of the 29 patients with AIH type 3, 22 were women (76%) and 7 were men (24%). Since HLA loci are thought to be genetically fixed and to be independent of age, serum markers or immune globulins, patients were not further characterized in that respect.

RESULTS

The most commonly found HLA subtypes in our patients with AIH type 1 were C7 (90 patients, 63%), A2 (68 patients, 48%), B8 (63 patients, 44%), DR3 (49 patients, 38%), DR4 (49 patients, 38%) and DQ2 (42 patients, 30%) (Table 1). As significant differences had been demonstrated in the Italian and North American populations regarding the distribution of the B8-DR3-DQ2 and DR4 HLA subtypes, these subtypes were also analysed along with the additionally reported C7, DR7, DR11, DR13, and DQ2 loci. The B8-DR3-DQ2 subtype was identified in 28 (27%) German patients with AIH type 1. And 49 patients (38%) were tested positive for the DR4 locus. In addition, almost half of all patients with AIH type 1 were positive for the HLA subtype B8 (45%) and 38% for DR3 (Table 2). The C7 HLA subtype which was highly prevalent in Italian patients with AIH type 1 was also common in the German population with 90 patients (63%). Further HLA subtypes reported and compared in Italian and North American patients were less prevalent in the German population. DR11 was positive in 17 (13%) of patients. Also DR13 could be identified in 17 (13%) of patients. Compared to the North American and Italian patients the DQ2 allele was also less prominent with 42 (41%) of patients.

For patients with SLA/LP positive AIH, HLA association had previously not been reported. Thus, we assessed the association of HLA of 29 patients with SLA positive, type 3 AIH (Table 3). Given a significantly smaller collective, there seemed to be a trend for SLA/LP positive AIH to be associated with the same HLA as AIH type 1. The most prevalent HLA in our patients with AIH were A2 in 16 patients (55%), B8 in 15 patients (52%), C7 in 22 patients (76%), DR3 in 12 patients (41%), and DQ2 in 13 patients (45%). Interestingly, only 3 patients did not carry either DR3 or DR4.

DISCUSSION

The etiology of AIH is still unknown. However, an underlying genetic predisposition has been suggested due to the fact that patients are predominantly of female gender and the association of the disease with certain HLA. Muratori *et al*[4] recently published an extensive study on two large populations, Italian and North American, and demonstrated a distinct genetic association of HLA antigens with the disease. Since this study not only investigated the commonly studied HLA antigens type Ⅱ but also extensively investigated the HLA antigens type Ⅰ, this study was of significant value. In order to further elucidate HLA association with AIH and to compare our collective of patients with AIH, which is among the largest reported, to published populations in different regions of the world, we here present our data on HLA association in German patients.

Within the Italian population significant association of AIH was demonstrated for HLA antigens B8 (32%), C7 (51%), DQ2 (53%) and for the combined HLA type B8-DR3-DQ2 (30%). The frequencies of B8 and C7 were confirmed by our study (45% and 63%). In addition, an earlier British study had also reported on an association of increased frequency of C7 with AIH type 1[6]. In contrast, DQ2 was found less prominent in German patients compared to Italian (41% *vs* 53%) and North American

Table 2 Prevalence of HLA subtypes in German patients with autoimmune hepatitis type 1 and comparison to worldwide populations

HLA	Germany *n* = 142	Italy[5] *n* = 57	N. America[5] *n* = 149	N. America II[8] *n* = 161	UK[6] *n* = 87	West India[10] *n* = 20	Japan[7] *n* = 77	China[9] *n* = 32	Brazil[8] *n* = 115	Turkey[11] *n* = 17
A2	48%					16%				
B8	45%	32%	49%			3%				
C7	63%	51%			70%	29%				
DR3	38%	30%	52%	47%		11%	31%	16%	32%	17%
DR4	38%	23%	43%	45%		3%	83%	50%	16%	59%
DR7	16%	16%	15%							
DR11	13%	18%	7%							
DR13	13%	26%	16%							
DQ2	41%	53%	57%							
B8-DR3-DQ2	27%	30%	48%							

(41% *vs* 57%) patients, but still at a higher frequency compared to the Italian control population (30%). Finally, the combined HLA subtype B8-DR3-DQ2 was less frequent in German patients, especially compared to North American patients (27% *vs* 48%). This may mostly be due to the significant lower frequency of the DQ2 HLA in German patients.

On the contrary, our patients displayed DR4 HLA frequency that was highly similar to the North American patients and significantly higher than the reported Italian HLA associations. An association of DR4 with AIH type 1 had been reported and in other populations, especially in Japan (83%) and Brazil (50%) it had an even higher frequency[7,8].

Frequency of HLA DR3 was highly similar between German and North American patients (45% and 52%), which were clearly higher than in all other populations reported thus far. Comparable to Italian patients DR3 was found at 31% in Japanese and 32% in Brazilian patients. In smaller populations from Western India, China and Turkey, this HLA antigen was even found at 11% to 17%[9-11]. Moreover, 49 of all patients carried neither DR3 nor DR4. However, a search for highly prevalent HLA in these patients did not reveal any additional, obvious new association, independent of DR3 or DR4.

All other HLA frequencies, specifically reported and compared by Muratori were comparable between our collective and the Italian and the North American study groups. The results of all three study groups are summarized in Table 2.

To date, most studies on HLA association with AIH mainly focused on AIH type 1 patients and reported only a few AIH type 2 patients. Thus far, HLA association of SLA/LP positive AIH has not been reported in a significant number of patients. Therefore, we extended our analysis of HLA antigen association to SLA/LP positive AIH. Given a smaller group of only 29 patients, HLA frequencies seemed to be similar to patients with AIH type 1. Comparable to AIH type 1, a high frequency of C7 (77%) was found. Frequencies for A2, B8, and DR3 were comparable to those of our German patients with AIH type 1 but also to AIH type 1 patients of the Italian and North American groups, who had not reported data on their AIH type 3 patients. Clearly a higher frequency of HLA DQ2 was observed in patients with SLA/LP positive AIH compared to our patients with AIH type 1. However, these higher HLA DQ2 frequencies are comparable to the DQ2 frequencies of the Italian and North American groups. Together, these data suggest a common genetic association and background for AIH types 1 and 3. This is in accordance with the observation that type 1 and SLA/LP positive AIH are also comparable with respect to their clinical course[2].

Table 3 Most prevalent HLA subtypes in German patients with SLA/LP positive autoimmune hepatitis

HLA	AIH SLA/LP positive German patients *n* = 29
A2	16 (55%)
B8	15 (52%)
C7	22 (76%)
DR3	12 (41%)
DQ2	13 (45%)

In conclusion, German AIH type 1 patients were demonstrated to be genetically distinct from Italian or North American patients and other populations, especially with respect to a significantly lower frequency of HLA DQ2 and a lower occurrence of HLA B8-DR3-DQ2. Other HLAs were found at similar frequencies, suggesting an underlying genetic background of AIH type 1. Analysis of a smaller group of 29 patients with SLA/LP positive AIH pointed towards comparable HLA frequencies in patients with AIH type 1 and SLA/LP positive AIH, which is in accordance with a similar clinical course. The challenge is yet to investigate whether these findings may help to better understand the etiology of AIH, to predict prognosis of the disease, or to further improve therapeutic concepts.

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