HL[illegible]file in Patients with AIDS and Tuberculosis

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Studies carried out in var[illegible]ulations have reported an association between some HLA specificities and susceptibility to tuberculosi[illegible]estigated the class I and class II HLA profile in Brazilian patients of various ethnic backgrounds who ha[illegible]nd tuberculosis. Twenty-two adult patients with AIDS and tuberculosis (Group I), 103 patients with AIDS w[illegible]berculosis (Group II) and 423 healthy individuals not infected with HIV (Group III) were evaluated. Diagnosis of HIV infection was made by ELISA, confirmed by a gelatin particle agglutination test. Diagnosis of tuberculosis was made based on clinical/radiological presentation and direct bacilloscopy or clinical specimen cultures. Class I antigens were typed by microlymphotoxicity. Class II alleles were characterized by the polymerase chain reaction (PCR). Differences in frequency of HLA specificities between groups were found in the following antigens/alleles: Group I x Group II: HLA-A31 – p=0.026; HLA-B41 – p= 0.037; HLA-DRB1*10 – p=0.037; HLA-DQB1*5 – p=0.009. Group I x Group III (control): HLA-A31 – p = 0.000008; odds ratio (OR)=31.75; HLA-B41 – p=0.003; HLA-DQB1*5 – p=0.02. HLA-A31 and HLA-B41 antigens and the HLA-DRB1*10 and HLA-DQB1*05 alleles were over-represented in patients with AIDS and tuberculosis (Group I), suggesting that these HLA molecules are associated with susceptibility to tuberculosis in Brazilian patients with AIDS.

Key-Words: AIDS, tuberculosis, host genetic factors, HLA.

Tuberculosis is an important public health problem in Brazil and has been one of the most frequent infection complications in patients with AIDS [1], because the integrity of the immune response of the host is needed for control the course of this disease. In addition, there is a relation between the immunological response and the HLA profile of an individual, which results in greater or lesser genetic susceptibility to certain infections, such as tuberculosis [2-10].

Various HLA subtypes have been indicated individually or as part of haplotypes as indicators of AIDS; almost all of them confer susceptibility to, and some of them confer protection against development of this disease [11-17].

In view of the fact that the Brazilian population consists of different ethnic groups, our objective was to investigate the Class I and Class II HLA profile in patients who had AIDS and tuberculosis from the Ribeirão Preto region, SP. In this region, the Caucasoid population is predominantly of European origin and most black individuals are descendants of the Bantu population [18].

Material and Methods

For analysis purposes, the patients were divided into three groups. Group I consisted of 22 patients with tuberculosis and AIDS, consisting of 15 males and seven females ranging in age from 21 to 44 years (median = 33 years). The CD4+ cell count for these patients ranged from 4 to 339 (median = 110) and the logarithms of the viral load of human immunodeficiency virus (HIV) ranged from 2.7 to 6.11 (median = 4.94). Eighteen of these patients were under treatment with highly active antiretroviral therapy (HAART).

Group II consisted of 103 individuals with AIDS, but without tuberculosis; 66 of them were men, ranging in age from 21 to 59 years (median = 34 years). In this group the CD4+ cell count ranged from 1 to 623 (median = 96) and the logarithms of the HIV viral load ranged from 1.99 to 6.92 (median = 4.81). Seventy-one of these patients were under treatment with HAART.

Group III, the population control, consisted of 423 healthy non-HIV-infected individuals from the same geographic region and of the same ethnic composition as Groups I and II. Among these subjects, 257 served as controls in the study of class I antigens and 166 in the investigation of class II alleles.

HIV infection was diagnosed by the ELISA method (Abbott Recombinant HIV-1/HIV-2 IEA™), confirmed by a gelatin particle agglutination test (Serodia™, Fujerebio Inc., Tokyo, Japan). Tuberculosis was diagnosed on the basis of clinical/radiological presentation and confirmed by direct bacilloscopy and/or culture of biological specimens.

Class I HLA antigens were typed by classical serology, with 66 specificities tested.

Sequence-specific primers (SSP, Opels, Heildeberg, Germany) hybridized with DNA amplified by the polymerase chain reaction were used for class II HLA allele typing (HLA-DRB1* and HLA-DQB1*), using commercial kits (OneLambda, Canoga Park, CA, USA), for a total of 21 specificities. The association between HLA profile and diseases was investigated according to Svejgaard &Ryder (1994) [19].

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Probability values (p) were obtained by the chi-square (χ^2) test with Yates correction or by the two-tailed Fisher exact test, with the level of significance set at $p \leq 0.05$ (95% confidence interval). When the differences between groups were significant ($p \leq 0.05$), the odds ratio (OR) was also calculated.

Results

Table 1 lists the antigen and allele frequencies that were significantly different between groups.

tuberculosis compared to the patients with AIDS but without tuberculosis (p=0.028; OR=3.83; CI=1.20-12.24; and p=0.0039; OR=20.32; CI=3.16-127.95, respectively). Similarly, the HLA-A31 and HLA-B41 antigens were more frequent in the population with AIDS and tuberculosis compared to the population controls (p=0.0001; OR=20.37; CI=4.64-89.35; and p=0.0039; OR=20.32; CI=3.16-127.95, respectively).

A previous study conducted at the same institution demonstrated that the HLA-A31 antigen is strongly associated with AIDS in patients from the northeastern region of the state

Table 1. Class I and II antigens and alleles that differed in frequency between groups with AIDS and tuberculosis (TB).

Antigens/ alleles	AIDS and TB (Group I) N=22		AIDS (Group II) N=103		Controls (Group III) Class I N=257		Controls (Group III) Class II N=166		Group I x Group II	Group I x Group III	Group II x Group III
	N	%	N	%	N	%	N	%			
HLA-A31	6	27.3	9	8.7	3	1.2	-	-	p=0.028 OR=3.83	p=0.0001 OR=20.37	p=0.001 OR=8.11
HLA-B41	3	13.6	2	1.9	2	0.8	-	-	p=0.0039 OR=20.32	p=0.0039 OR=20.32	NS
HLA-DRB1*10	3	13.6	2	1.9	-	-	6	3.6	p=0.0039 OR=20.32	p=0.073	NS
HLA-DQB1*05	14	63.6	32	31.0	-	-	59	35.5	p=0.0001 OR=12.30	p=0.018 OR=3.17	NS

NS=not significant; OR=odds ratio.

Analysis of Table 1 shows that HLA-A31 and HLA-B41 antigens were over-represented in the TB group (Group I x Group II: p=0.028 and 0.0039, respectively; Group I x Group III: p=0.001 and 0.0039, respectively). Allele HLA-BRB1*10 was over-represented in patients with TB and AIDS, compared with AIDS patients without TB (p=0.0039), and allele HLA-DQB1*05 was also over-represented in the TB group, in all comparisons (Group I x Group II: p=0.0001; Group I x Group III: p=0.018).

Discussion

Vijaya Lakshimi et al. (2006) [8], in a study of the association of class I molecules (HLA-B) in patients with pulmonary tuberculosis who also had AIDS, or not, detected an association of HLA-B52(5) with protection against, and of HLA-B51(5) with susceptibility to tuberculosis, regardless of whether the patient was HIV-infected or not.

Also, in an investigation of class I HLA subtypes, Soto et al. (2007) [10], in a study on Mexican patients, demonstrated an association of HLA-B35 with pulmonary tuberculosis and of HLA B39 and HLA B40 with extrapulmonary tuberculosis, and Pospelov et al. (2007) [9], in a study of Russian patients, detected a positive association of HLA-B27 antigen with tuberculosis.

In our study (Table 1), the HLA-A31 and HLA-B41 antigens were more frequent in the group of patients with AIDS and of São Paulo [17]. We also found that the presence of the HLA-A31 antigen was associated with tuberculosis in patients with AIDS in the present study. When the patients with AIDS, but without tuberculosis (Group II), were compared with the population control, the HLA-A31 antigen was also more frequent in the population with AIDS (p=0.001; OR=8.11; CI=1.96-38.65).

Several studies conducted on different populations have also demonstrated an association of some class II alleles with tuberculosis. The haplotypes DRB1*1601, DQB1*0502 alleles and DQB1*1601-DQB1*0502, DRB1*04-DQB1*03, DRB1*14-DQB1*5 have been found to be related to a higher risk of developing tuberculosis, whereas a low frequency of the DQB1*0201 allele and of the DRB1*11-DQB1*03 haplotype was found to be associated with tuberculosis in Polish patients [7,20]. Similarly, Kim et al. (2005) [21] demonstrated that the DRB1*0803 and DQB1*0601 alleles were associated with the progression of tuberculosis in Korean patients, and Pospelov et al. (2007) [9] reported an association of HLA-DRB1 13 (6) and HLA-DRB1 14 (6) with this disease.

In our study, the HLA-DRB1*10 and HLA-DQB1*05 alleles were also more frequent in the group of patients with AIDS and tuberculosis compared to the group of patients with AIDS, but without tuberculosis (p=0.0039; OR=20.32; IC=3.17-127,95; and p=0.0001; OR=12.30; CI=4.78-31.64, respectively).

When patients with AIDS and tuberculosis were compared to the population control, the DQB1*05 allele was also found to be more frequent among patients (p=0.018; OR=3.17; CI=1.25-8.00). We suggest that the HLA-A31 and HLA-B41 antigens and the HLA-DRB1*10 and HLA-DQB1*05 alleles are associated with susceptibility to tuberculosis in patients with AIDS from the northeast region of the state of São Paulo.

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