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Toxoplasmic encephalitis: role of Human Leucocyte Antigens/alleles associated with rapid progression to Acquired Immunodeficiency Syndrome

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ABSTRACT

Background/aims: The frequency of Human Leucocyte Antigens/alleles associated with rapid progression from Human Immunodeficiency Virus infection to Acquired Immunodeficiency Syndrome was evaluated in Brazilian patients with Acquired Immunodeficiency Syndrome with and without Toxoplasmic Encephalitis.

Methods: 114 patients with Acquired Immunodeficiency Syndrome (41 with Toxoplasmic Encephalitis, 43 with anti-*Toxoplasma gondii* antibodies, without Toxoplasmic Eencephalitis, and 30 without anti-*Toxoplasma gondii* antibodies circulating and without Toxoplasmic Encephalitis) were studied.

Results: Human Leucocyte Antigens/alleles associated with rapid progression to Acquired Immunodeficiency Syndrome, particularly HLA-B35, -DR3, and -DR1 allele group, were significantly less represented in patients with Toxoplasmic Encephalitis and Acquired Immunodeficiency Syndrome.

Conclusion: The presence of these Human Leucocyte Antigens/Alleles that predispose to Acquired Immunodeficiency Syndrome progression was associated with resistance to Toxoplasmic Encephalitis among Human Immunodeficiency Virus-1 carriers.

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Introduction

Human leukocyte antigens (HLA) genes have been reported to be associated with increased susceptibility to the development of specific disease or with progression to AIDS outcomes.[1–3] The progression from human immunodeficiency virus (HIV) infection to AIDS has been strongly associated with HLA-A1-Cw7-B8-DR3-DQ2 and HLA-A11-Cw4-B35-DR1-DQ1 haplotypes, conferring a high risk of rapid progression to AIDS.[4–7] It has been assumed that associations between progression to AIDS and particular HLA alleles reflect differential antigen presentation by classes I or II molecules exhibiting particular motifs in the peptide binding groove.[8] For example, the most harmful effects of HLA-B*35 are seen with the molecules encoded by the HLA-B*35:02 and B*35:03 alleles, which have proline at anchor position 2 of their loaded peptide and a non-tyrosine residue at position 9.[9] For instance, the HLA-B*35:01 molecule containing tyrosine at position 9 does not have any substantial effect on disease prognosis. While both HLA-B*35 subtypes can equally induce a cytotoxic T lymphocyte (CTL) response, viral load was cleared less effectively by non-tyrosine-containing HLA-B*35:02 and B*35:03 molecules compared with HLA-B*35:01.[10] It may, therefore, be possible that altered epitope recognition by HLA-B*35:02 and B*35:03 will induce CTL that may not specifically function against HIV-1-infected cells.[11]

Toxoplasma gondii infection is widespread in humans, with estimated infection rates ranging from 50% to 80% of the general population in South America.[12] In some areas of Southern Brazil, the prevalence of antibodies against *T. gondii* may be as high as 98%.[13,14] Toxoplasmosis in the immunocompromised host is most probably due to reactivation of a previous latent infection and can be life-threatening.[15] Encephalitis is the most important manifestation of toxoplasmosis in immunosuppressed patients as it causes severe damage and death.[16] It is estimated that in countries with a high prevalence of *T. gondii*, toxoplasmic encephalitis is the most common cerebral lesion in HIV patients.[17]

Few studies reported an association between HLA markers and toxoplasmic encephalitis in AIDS patients.[18–21] We have previously reported that susceptibility to toxoplasmic retinochoroiditis was associated with HLA alleles related with rapid progression to AIDS,[22] and the availability of genetic markers for other AIDS severe complications may discriminate patients with poor prognosis. To further explore whether HLA markers associated with rapid progression to AIDS could also be associated with the development of toxoplasmic encephalitis, we evaluated these markers in Brazilian AIDS patients with or without toxoplasmic encephalitis.

Material and methods

Patients

The study was conducted on 114 adult HIV-infected patients (81 males) aged 21–59 years (median = 33) presenting AIDS, diagnosed 1–108 months (median = 22) before inclusion in this study. Forty-one patients experienced toxoplasmic encephalitis, diagnosed clinically and by brain computerized tomography and by the presence of antibody against *T. gondii* (Group 1). Two additional AIDS patient groups without toxoplasmic encephalitis were studied; i.e., a group of 43 patients with positive anti-*T gondii* antibodies but without toxoplasmic encephalitis (Group 2), and 30 patients with neither anti-*T. gondii* antibodies nor toxoplasmic encephalitis (Group 3). Patients were selected from the Acquired Immunodeficiency Outpatient Clinic at the University Hospital of the Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil. A total of 161 healthy bone marrow donors from the University Hospital of Faculty of Medicine of Ribeirão Preto with no known infectious, chronic, or autoimmune disorders were also studied.

Ethical aspects

The local Ethics Committee of the University Hospital of Faculty of Medicine of Ribeirão Preto and the National Brazilian Ethics Committee approved the study protocol, and informed consent was obtained from all individuals (HCFMRP-USP # 8992/2001 and CONEP # 203/2002).

Anti-*T. gondii* antibodies

The search for anti-*T. gondii* antibodies in serum was performed by indirect immunofluorescence by the method of Camargo[23] using an anti-human IgG fluorescent conjugate (Bio-Meriéux). Serum samples with >1/16 titers were considered to be positive.

HLA typing

HLA class I antigens expressed on the surface of peripheral blood lymphomononuclear cells were typed using a microlymphocytotoxity assay.[24] DNA was obtained from peripheral blood mononuclear cells using a salting out procedure. HLA class II allele typing was performed using commercial kits (One Lambda, Canoga Park, CA), as previously described.[25]

HLA specificities associated with the rate of progression to AIDS

Since HLA-A1, A11, B8, B35, DR3, DR1, DQ2, DQ1 antigens have been described in the literature in association with rapid progression to AIDS[4,26] in many ethnic groups, these markers were considered for analysis in the present study.

Statistical analysis

HLA antigen and HLA allele group frequencies were calculated by direct counting. The strength of the association between toxoplasmic encephalitis and HLA specificities was evaluated calculating the relative risk (RR) and Odds Ratio (OR). The Fisher's exact test was used for comparisons, and it was considered to be significant at $p < 0.05$.