Human T-Cell Lymphotropic Virus Type 1 Infection and Ocular Manifestations in São Paulo, Brazil

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Objectives: Although human T-cell lymphotropic virus type 1 (HTLV-1)–associated uveitis has been well recognized in Japan, related studies in Brazil are scarce. We performed a serologic survey for HTLV-1 infection among patients with uveitis and investigated the ocular findings in HTLV-1–asymptomatic carriers.

Methods: One hundred ninety serum samples from patients with uveitis of determined (n = 137) and undetermined origins (n = 53) being examined at the Uveitis Service, University of São Paulo, São Paulo, Brazil, underwent testing using HTLV enzyme-linked immunosorbent assay and discriminatory Western blots. One hundred five asymptomatic blood donors and/or their relatives who were seropositive for HTLV-1 (carrier group) and 105 age- and sex-paired blood donors who were seronegative for HTLV-1 (control group) underwent ocular evaluation. For the statistical analysis, χ² test was used.

Results: Only 1 patient with uveitis was seropositive for HTLV-1, and she belonged to the group with uveitis of undetermined origin. Results of tear films were evaluated in 52 carriers. The prevalence of a decreased tear break-up time was significantly higher in the carrier compared with the control group (P = .02). Two carriers had keratoconjunctivitis sicca. Three of the 105 carriers exhibited mild uveitis (cells in the vitreous, retinal and choroidal infiltrates, retinal vasculitis, and bilateral pars planitis). Retinal pigmentary changes were found in both groups (no statistical difference).

Conclusions: Early tear abnormalities may be present in asymptomatic carriers, and mild uveitis may be found among them. The relatively low seroprevalence of HTLV-1 in the Brazilian population made it difficult to establish the real importance of HTLV-1–associated uveitis among our patients with uveitis.


The human T-cell lymphotropic virus type 1 (HTLV-1) is a retrovirus of the Oncovirinae subfamily and is the first retrovirus to be specifically linked to malignant neoplasms in humans.1,2 It has a worldwide distribution, with clustering in specific geographic areas that include southwestern Japan, the Caribbean islands, and parts of Central Africa.3 The virus is transmitted vertically from infected mother to child or horizontally through sexual intercourse and blood and its cellular components. It is known to cause adult T-cell leukemia/lymphoma (ATLL)4 and HTLV-1–associated myelopathy or tropical spastic paraparesis (HAM-TSP).5 Ocular manifestations that have been described in HTLV-1–infected individuals include opportunistic infection and tumor infiltration of the eye and orbit in patients with ATLL6-9; retinal microvascular changes, intraocular inflammatory disturbances, retinochoroidal degeneration, and keratoconjunctivitis sicca (KCS) in patients with HAM-TSP7,9-12; and HTLV-1–associated uveitis (HU) in asymptomatic carriers.7,9,13-16

Seroepidemiological surveys of high-risk groups17,18 and blood donors from different parts of Brazil19,20 show relatively high HTLV-1 seroprevalence rates compared with nonendemic areas such as the United States. The highest prevalence rate of HTLV-1 infection among healthy subjects has been found in Northeastern Brazil (1.8%).21 Moreover, several cases of ATLL22 and HAM-TSP23,24 have been reported in Brazil. To better characterize the occurrence of HU and other related ocular manifestations in the city of São Paulo, Brazil, we performed a serologic survey for HTLV-1 infection in 190 patients with uveitis and investigated the ocular findings in HTLV-1–asymptomatic carriers compared with a control group seronegative for HTLV-1.
PATIENTS, MATERIALS, AND METHODS

SEROPREVALENCE OF HTLV-1 AMONG PATIENTS WITH UVEITIS

Our study included 190 patients with uveitis examined at the Department of Ophthalmology, University of São Paulo, São Paulo, Brazil, from August 1, 1993, to December 31, 1995. Their clinical characteristics are described in Table 1. They were 63.1% white, 12.1% black, 21.1% mixed white and black (hereafter referred to as mixed race), and 3.7% Asian. Uveitis was anterior in 31 patients (16.3%), intermediate in 17 (8.9%), posterior in 62 (32.6%), diffuse in 68 (35.9%), sclerouveitis in 7 (3.7%), and retinal vasculitis in 5 (2.6%). Fifty-three patients (27.9%) had uveitis of unknown origin after extensive ophthalmic and systemic examinations, and 137 patients (72.1%) had uveitis associated with a presumed cause (juvenile rheumatoid arthritis, toxoplasmosis, Behçet disease, and others). Investigation of HTLV-1 and -2 serologic status was performed using enzyme-linked immunosorbent assay (Hemobio HTLV I/II HBK 424; Embrabio, São Paulo, Brazil). Seropositive results were further confirmed using discriminatory Western blot tests (HTLV Blot 2.4; Genelabs Diagnostics, Singapore). Seropositivity for HTLV-1 was defined as reactivity to gag (p24), env (rgp21-2 or gp46), and an HTLV-1–specific recombinant peptide (rgp46-I) on Western blot strips.

OCULAR FINDINGS IN HTLV-1–ASYMPTOMATIC CARRIERS

The carrier group consisted of 105 asymptomatic blood donors and their relatives who were seropositive for HTLV-1 (43 female and 62 male carriers). They were referred for ophthalmologic examination from January 1, 1994, to May 31, 1996, after oral informed consent. Their characteristics are described in Table 1. Mean age was 39.9 years (range, 11-67 years). There were white, black, mixed race, and Asian individuals. The most frequent risk factors for retroviral infection were breast feeding (70.5%), sexual promiscuity (43.8%), intravenous drug use (7.6%), and blood transfusion (6.7%).

Asymptomatic carriers of HTLV-2 were excluded from the study. In 55 carriers (52.4%), amplification of proviral genomic sequences using polymerase chain reaction was performed, and in all cases infection could be molecularly confirmed. Three carriers were coinfected with human immunodeficiency virus.

Ocular examination included measurement of visual acuity, motility examination, biomicroscopy, applanation tonometry, and binocular indirect ophthalmoscopy. Fifty-two carriers, randomly selected, underwent tear film evaluation using the following tests: tear breakup time (BUT), Schirmer I test, and rose bengal staining. Fifty-six carriers (53.6%) had KCS diagnosed in 2 carriers, and ocular hypertension in 2 carriers. Fifty-two sex- and age-paired controls were randomly selected for tear film analysis.

The statistical analysis of the seroepidemiological and clinical data was performed using Χ² test.

RESULTS

SEROPREVALENCE OF HTLV-1

The seroprevalence of HTLV-1 among patients with uveitis was 1 (0.5%) of 190 patients. In patients with uveitis of determined and undetermined origins, prevalence was 0 of 137 and 1 (1.9%) of 53 patients, respectively. The single patient in the latter group was a 48-year-old woman who had had a severe bilateral sclerouveitis for 5 years. Results of all systemic evaluation were negative. She had no known risk factor for retroviral infection and had once been treated with systemic corticosteroids and immunosuppressants.

OCULAR FINDINGS IN HTLV-1–ASYMPTOMATIC CARRIERS

Visual acuity in the carrier and control groups at initial examination was at least 0.8 on the Snellen chart in 89.5%. The diverse causes of visual acuity lower than 0.8 included amblyopia, high myopia, inactive herpetic iridocyclitis, traumatic retinochoroiditis, and optic nerve dysplasia.
lence of a decreased BUT was significantly higher in the carrier compared with the control group ($P = .02$). Two carriers received diagnoses of KCS, whereas none was found in the control group. Twenty-one (40.4%) of the 52 carriers had abnormal results in at least 1 of the tear film evaluation tests, compared with 12 (23.1%) of the 52 controls ($P = .06$).

Intraocular inflammatory signs were found in 3 patients in the carrier group only. Signs included mild anterior vitreous cells, mild vitreous opacities, localized retinal and choroidal infiltrates, localized retinal vasculitis, and bilateral pars planitis. Carrier 1, an asymptomatic 23-year-old man of mixed race, was first seen with bilateral pars planitis associated with peripheral ischemic retinopathy. He had a systemic diagnosis of linear scleroderma; nevertheless, sickle cell disease, diabetes mellitus, and other possible origins of peripheral retinopathy were excluded. Familial exudative vitreoretinopathy could not be completely excluded, because family evaluation was not possible. His wife was also an asymptomatic HTLV-1 carrier. The only risk factor for retroviral infection was breast-feeding. He also had abnormal BUTs and results of Schirmer I test. All individuals were asymptomatic, and the changes were unilateral except for those in carrier 1. Since they were all asymptomatic, no therapy was prescribed. None of them were coinfected with human immunodeficiency virus.

Table 1. Demographic Characteristics of Patients With Uveitis, HTLV-1–Asymptomatic Carriers, and Controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n = 190)</th>
<th>Carriers (n = 105)</th>
<th>Controls (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>23 (12.1)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>20-39</td>
<td>89 (46.8)</td>
<td>51 (48.6)</td>
<td>51 (48.6)</td>
</tr>
<tr>
<td>≥40</td>
<td>78 (41.0)</td>
<td>53 (50.5)</td>
<td>53 (50.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73 (38.4)</td>
<td>62 (59.0)</td>
<td>62 (59.0)</td>
</tr>
<tr>
<td>Female</td>
<td>117 (61.6)</td>
<td>43 (41.0)</td>
<td>43 (41.0)</td>
</tr>
</tbody>
</table>

*HTLV-1 indicates human T-cell lymphotropic virus type I. Carriers were seropositive for HTLV-1; controls, seronegative. Percentages have been rounded and may not sum 100.

Table 2. Results of Tear Film Evaluations in Carriers and Controls

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Carriers (n = 52)</th>
<th>Controls (n = 52)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tear break-up time, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10, both eyes</td>
<td>16 (30.8)</td>
<td>6 (11.5)</td>
<td></td>
</tr>
<tr>
<td>≤10, 1 eye</td>
<td>8 (15.4)</td>
<td>5 (9.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Normal</td>
<td>28 (53.8)</td>
<td>41 (78.8)</td>
<td></td>
</tr>
<tr>
<td>Schirmer I test, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10, both eyes</td>
<td>12 (23.1)</td>
<td>6 (11.5)</td>
<td></td>
</tr>
<tr>
<td>≤10, 1 eye</td>
<td>1 (1.9)</td>
<td>5 (9.6)</td>
<td>.12</td>
</tr>
<tr>
<td>Normal</td>
<td>39 (75.0)</td>
<td>41 (78.8)</td>
<td></td>
</tr>
<tr>
<td>Rose bengal staining score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44 (84.6)</td>
<td>45 (86.5)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 (11.5)</td>
<td>7 (13.5)</td>
<td>.78</td>
</tr>
<tr>
<td>2</td>
<td>2 (3.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

*Groups are described in Table 1. Percentages have been rounded and may not sum 100.

Figure 1. Right eye of carrier 2 showing the 2-week resolution of the active retinal choroidal lesion.

Figure 2. Area of superior peripheral retinal vasculitis of the left eye of carrier 3.

2, a 34-year-old woman of mixed race, was first seen with inflammatory cells in the vitreous and a whitish retinochoroidal lesion in 1 eye (Figure 1). After a few weeks, the borders of the lesion became slightly pigmented, and vitreous cell number was reduced. Results of systemic investigation were unremarkable, with negative toxoplasma titers and an isolated positive result of Mantoux test (normal results of lung x-ray and urinalysis). No risk factor for retroviral infection was reported. She had abnormal BUTs and results of Schirmer I test. Carrier 3, a 30-year-old white man, had a sectorial superior peripheral retinal vasculitis in 1 eye (Figure 2). The only risk factor for retroviral infection was breast-feeding. He also had abnormal BUTs and results of Schirmer I test. All individuals were asymptomatic, and the changes were unilateral except for those in carrier 1. Since they were all asymptomatic, no therapy was prescribed. None of them were coinfected with human immunodeficiency virus.
SEROEPIDEMIOLOGICAL SURVEY

Several epidemiological surveys have shown that in endemic areas, such as southwestern Japan, HTLV-1 seroprevalence in the general population is as high as 37%, whereas in blood donors of nonendemic regions, such as the United States, it is as low as 0.02%. Surveys performed among Brazilian blood donors have detected seroprevalences ranging from 0.08% (southern region) to 1.8% (northeastern region). Surveys performed among specific groups, such as Brazilian Indians and groups at high risk for retroviral infection, have detected seroprevalences as high as 38%. In São Paulo, the seroprevalence among blood donors is 0.14%.

Our seroprevalence survey of HTLV-1 infection in patients with uveitis of undetermined origin showed a 1.8% seropositivity prevalence compared with none in patients with uveitis of determined origin. Other studies have found a seroprevalence of 2 (3.6%) of 55 Brazilian patients with uveitis of unknown origin and a local seroprevalence in blood donors of 0.32%. The 2 patients who were seropositive for HTLV-1 in the latter series were 12 and 19 years of age, and both had anterior uveitis. In larger surveys performed in Japan, HTLV-1 seroprevalence in patients with uveitis of undetermined origin was 4 to 8 times higher than in patients with uveitis of determined origin, patients with nonuveitic ocular disease, or the general population. Our results suggest that the HTLV-1 seropositivity in patients with uveitis of undetermined origin is approximately 10 times higher than that of blood donors. However, our population study is still too small for any statistical analysis that could confirm the high prevalence of HU in Brazil.

OCULAR FINDINGS IN HTLV-1–ASYMPTOMATIC CARRIERS

Although several of the ophthalmologic abnormalities among HTLV-1–asymptomatic carriers described herein are also present in the general population, abnormal results of tear film evaluation, mild intraocular inflammation, and some retinal pigmentary disturbances were remarkable in this group of patients.

Tear film clinical evaluation, based on results of the BUT, Schirmer I test, and rose bengal staining, disclosed substantial abnormalities in the HTLV-1–asymptomatic carrier group. The standard measure to evaluate tear quantitative deficiency is the Schirmer I test. Tear BUT tests tear stability, and rose bengal staining demonstrates the integrity of the ocular surface. In our study, KCS was diagnosed in 2 carriers. Systemic and laboratory evaluations were not performed; therefore Sjögren syndrome could not be characterized. However, KCS has also been described in 21 (70%) of 30 patients with HAM-TSP in a French study, and Sjögren syndrome has been described in patients with HAM-TSP. Terada et al confirmed a significantly higher (P < .001 using χ² test) HTLV-1 seroprevalence among patients with Sjögren syndrome (23%) than among blood donors (3%).

In our study, uveitis was found in 3 (2.8%) of 105 HTLV-1–asymptomatic carriers. Carrier 1 was first seen with a systemic diagnosis of linear scleroderma, which is not associated with intermediate uveitis. Carrier 2 had a negative toxoplasma titer and positive results of a Mantoux test, which is a nonspecific reaction because Brazilians usually receive bacille Calmette-Guérin vaccine in childhood and therefore have positive results. Carrier 3 had negative results of all systemic evaluations. Therefore, the 3 carriers may have HTLV-1–related uveitis. The following 3 points should be considered in our study: (1) the 3 uveitis cases described differ in some ways from those described in Japan and might not be cases of HU, despite our above considerations; (2) the fact that carriers were examined regardless of any ocular complaint may have allowed identification of very early or minimal ocular inflammatory changes and thus the assessment of a high frequency of uveitis; and (3) the study design was biased in that blood donors are usually healthy individuals.

In an epidemiological survey performed in North Kyushu in Japan, the prevalence rate of HU was estimated to be 112 per 100,000 carriers (0.1%). In that survey, questionnaires concerning patients with uveitis were sent to all ophthalmologic institutions in the study area, and serum HTLV-1 antibody titer of these patients was measured. Eighteen of 317 patients with uveitis were counted as having HU. Based on these data, together with the age- and sex-matched population of HTLV-1 carriers in the region where the study was performed, the crude prevalence rates of HU per 100,000 HTLV-1 carriers was estimated. Another epidemiological survey performed in South Kyushu revealed a very similar prevalence rate: 90 per 100,000 carriers.

Retinal pigmentary changes characterized by hyperpigmented or hypopigmented lesions and sectorial areas of pigment alterations were found in the carrier and control groups. The comparative study between individuals who were seropositive and seronegative for HTLV-1 demonstrated that these retinal pigmentary changes are not specific to HTLV-1 infection. However, the meaning of these lesions is presently unknown, and, as they might be the result of previous inflammatory lesions, they should be monitored continuously. In 1 carrier, nontraumatic unilateral pigmentary changes similar to retinitis pigmentosa were observed; retinochoroidal degeneration has been described in patients with HAM-TSP.
Besides the lacrimal film abnormalities found in the asymptomatic group, infectious corneal disease developed in 2 (8.0%) of 25 carriers with a 1-year follow-up. Further studies are needed to establish any correlation between HTLV-I and corneal disease.

Our study showed that HTLV-I–asymptomatic carriers have early abnormal results on tear films and may have mild uveitis. Therefore, a periodic eye examination should be suggested to HTLV-I–asymptomatic carriers. Infection with HTLV-I may also be an unusual cause of uveitis in Brazil, and it should be surveyed among patients with uveitis. However, the relatively low HTLV-I seroprevalence in our population made it difficult to establish the real importance of HU. The follow-up of this HTLV-I–asymptomatic carrier group should add further information about the incidence of HU and the time course evolution of other HTLV-I–associated diseases.

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