Infectious Uveitis in Thailand: Serologic Analyses and Clinical Features


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Infectious Uveitis in Thailand: Serologic Analyses and Clinical Features

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ABSTRACT

Purpose: To determine the seroprevalence of various infectious agents in Thai patients with uveitis.

Methods: Prospective study of 101 consecutive patients with uveitis, 100 HIV-infected retinitis patients, and 100 nonuveitis controls.

Results: Antibodies against T. gondii were detected in 31/101 non-HIV patients, mostly with posterior uveitis and focal retinitis, and were significantly higher than in other groups examined. Antibodies for T. pallidum and Leptospira were observed more frequently in patients with HIV-infected retinitis. Active tuberculosis in non-HIV patients was not found.

Conclusions: Seroprevalence of T. gondii antibodies in patients with non-HIV posterior uveitis was higher than in nonuveitis controls and HIV patients with retinitis.

Keywords: HIV; infection; serology; Thailand; uveitis

Uveitis is a major cause of severe visual impairment in the world.1, 2 It is crucial to discriminate infectious from noninfectious causes of uveitis since their prognoses and treatment regimens are entirely different. Treatment of infectious uveitis with antibiotics may lead to improvement or even a cure of ocular disease and might even prevent further systemic involvement. The immunosuppressive treatment of infectious uveitis can be harmful, especially in areas where acquired immune deficiency syndrome (AIDS), tuberculosis, and other infectious diseases are endemic.3 Infectious etiology was documented in at least 20–30% of all uveitis cases.4 Therefore, it is essential that the diagnosis of intraocular
infection is made before the immunosuppressive treatment is instituted.

In Thailand, cytomegalovirus (CMV) retinitis is a well-known cause of retinitis in human immunodeficiency virus (HIV)-infected patients. However, other causes of infectious uveitis in Thailand have not yet been systematically studied. Here we determine the seroprevalence of various infections known to cause uveitis in other parts of the world in 101 consecutive Thai patients with non-HIV uveitis and in 100 HIV-infected patients with retinitis and compare the results with 100 nonuveitis controls.

METHODS

We performed a prospective study on sera of 101 new consecutive patients with non-HIV uveitis and 100 consecutive HIV-infected patients with retinitis consulting the ophthalmology department of Chiang Mai University Hospital, which represents a large tertiary teaching center serving the whole of northern Thailand. In addition, 100 nonuveitis control subjects from the same geographical areas as the patients were included. The anonymous serum samples of controls were selected by age and gender using quota sampling from the remainder of the community health services samples at the Faculty of Associated Medical Sciences in Chiang Mai. Clinical data of the patients were registered, including gender, age at onset of uveitis, duration and laterality of uveitis, location and activity of uveitis, and associated systemic complaints and diseases. Whenever possible, fundus photographs of the eyes of the patients with uveitis were taken. The HIV-infected patients all had posterior uveitis with clinical features consistent with the diagnosis of cytomegalovirus retinitis and all were treated by administration of intravitreal ganciclovir injections. Seventy HIV-positive patients were sampled during the active stage of their ocular disease and 30 during the quiet phase following the local treatment with ganciclovir.

The patients who originally enrolled as having uveitis and nonuveitis controls were all tested for HIV by using Vironostika HIV Uni-Form II Ag/Ab (Biomerieux, France). The positive samples were tested by gelatin particle agglutination test (Serodia.HIV, Japan). The samples positive in both tests were excluded from further analysis (1 in the uveitis group and 1 in the control group). The HIV status of patients with retinitis was examined at Maharaj Nakorn Chiang Mai University Hospital. Three methods were used to confirm HIV infection, including two ELISA-based methods, Enzygnost Anti-HIV 1/2 Plus (Dade Behring, Germany) and Elecsys HIV AG (Roche Diagnostics, Germany). The samples that gave positive results in both tests were tested by the immunochromatographic-based method, the Determine HIV -1/2 assay (Abbott, USA). Toxoplasma gondii (T. gondii)-specific IgG antibody in serum was investigated by enzyme-immuno-assay (EIA) with Enzygnost Toxoplasmosis/IgG (Dade Behring) using the manufacturer’s conditions. Optical density generated by any sample that was higher than the negative cutoff but lower than the positive value (equivocal result) was considered negative. All sera were screened for antibody specific to Treponema pallidum (T. pallidum) by using the immunochromatographic test BIOLINE Syphilis 3.0 (Pacific Biotech, Thailand). The borderline and positive samples were retested by using the ELISA-based method ICE+ Syphilis (Abbott-Murex, USA). Only the samples reacting in both methods were considered positive and were tested with the Venereal Disease Research Laboratory test (VDRL: Becton Dickinson, USA), except for one specimen where insufficient volume precluded the VDRL testing. Leptospira antibody was determined in all samples by the fluorescent antibody test or by the SD Bioline Leptospira IgG test (Standard Diagnostics, Korea). The fluorescent antibody test was performed with leptospira-coated slides provided by the Department of Medical Science, Ministry of Public Health, Thailand, reacting with IgG to common leptospiral serotypes found in Thailand. Screening test-positive sera (titer ≥1:50) were confirmed using the microagglutination test (MAT) at the Department of Medical Science, Ministry of Public Health, Thailand. A MAT titer of ≥1: 400 was interpreted as current infection. All commercial tests were performed according to the manufacturers’ instructions. In addition, all non-HIV-infected patients with uveitis were evaluated for the presence of tuberculosis using chest X-ray and sputum cultures.

The approval of the institutional review board was received and the study was completed with an anonymized data set of the controls. The data were computerized and statistically analyzed by Fisher’s exact test; a value of \( p < .05 \) was considered significant.

RESULTS

The mean age of patients with non-HIV uveitis was 39 years (range, 9–85), of patients with HIV 37 years (range, 24–55), and of controls 40 years (range, 20–60). General characteristics of patients and controls are shown in Table 1.

The results of T. gondii, T. pallidum, and Leptospira serology are given in Table 2. Non-HIV uveitis patients had more frequently positive T. gondii serology than the controls (31/101 versus 17/100, \( p = .023 \) and the
Table 1. General characteristics of patients with uveitis and nonuveitis controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-HIV uveitis</th>
<th>HIV-positive uveitis</th>
<th>Nonuveitis controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>101</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Average age in years (range)</td>
<td>39 (9–85)</td>
<td>37 (24–55)</td>
<td>40 (20–60)</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>52:49</td>
<td>46:54</td>
<td>50:50</td>
</tr>
</tbody>
</table>

HIV-positive retinitis patients (31/101 versus 19/100, \( p = .055 \)). The non-HIV patients with posterior uveitis had the highest prevalence of positive \( T. gondii \) serology results compared to other anatomical types of uveitis (15/35, 43\% versus 16/66, 24\%; \( p = .05 \)). Six out of 15 patients (40\%) with posterior uveitis and positive \( T. gondii \) serology had focal retinal lesions compatible with the standard features of ocular toxoplasmosis.

The rate of \( T. pallidum \) infection was significantly higher in HIV-positive patients with retinitis (13/100) compared to HIV-negative uveitis patients (5/101, \( p = .046 \)) and nonuveitis controls (2/100, \( p = .003 \)), however, it was not distinct from that of the non-HIV patients with posterior uveitis (13/100 versus 1/35, \( p = .09 \)). Out of 13 patients with HIV-positive retinitis and positive EIA results, 5 were VDRL positive and considered to have a current infection. Positive \( T. pallidum \) serology was most common in HIV patients with active retinitis (12/70 compared to 1/30 inactive cases, \( p = .06 \)). Antibodies against both \( T. gondii \) and \( T. pallidum \) were found in 5 HIV-positive patients (4 with active and 1 with inactive retinitis), but only 1 case with active retinitis was VDRL-positive. In 101 non-HIV uveitis patients, 5 patients showed the presence of anti-\( T. gondii \) antibodies but only 4 samples were available for VDRL testing, 2 of which were positive. In nonuveitis controls, 2 of 100 samples were positive for both the anti-\( T. gondii \) test and the VDRL.

A higher prevalence of \( Leptospira \) antibody in the HIV-positive retinitis group (9/100, 9\%) was observed compared to the nonuveitis controls (2/100, 2\%, \( p = .03 \)). No differences in \( Leptospira \) serology were found between HIV patients with active and inactive retinitis (7/70 versus 2/30; \( p = .594 \)) and between the non-HIV uveitis group and the controls (3/101 versus 2/100; \( p = .505 \)). The MAT test was positive in only 1 non-HIV patient with panuveitis, in whom a positive current infection with \( Leptospira interrogans \) serovar \( australis \) was confirmed by a MAT titer of 1:400.

None of the patients with non-HIV uveitis had evidence of active tuberculosis.

DISCUSSION

Our results point out the higher prevalence of positive \( T. gondii \) antibodies in patients with non-HIV uveitis

Table 2. Seroprevalence of \( T. gondii, T. pallidum, \) and \( Leptospira \) in HIV-negative uveitis, HIV-positive uveitis, and nonuveitis controls

<table>
<thead>
<tr>
<th></th>
<th>( T. gondii )</th>
<th>( T. pallidum ) (N)</th>
<th>( Leptospira ) ( b ) (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>HIV-negative uveitis</td>
<td>101</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Anterior</td>
<td>27</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Intermediate</td>
<td>14</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Posterior</td>
<td>35</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>25</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>HIV-positive uveitis</td>
<td>100</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Active</td>
<td>70</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Inactive</td>
<td>30</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Non-uveitis controls</td>
<td>100</td>
<td>17</td>
<td>17</td>
</tr>
</tbody>
</table>

\(^{a}\)Insufficient volume precluded VDRL testing in one sample.

\(^{b}\)MAT antibody titer was positive in a titre 1:400 to \( Leptospira australis \).

Note: EIA, enzyme-immuno-assay; VDRL, Venereal Disease Research Laboratory test; IFA, immunofluorescence antibody test; MAT, microagglutination test.
(specifically in those with posterior uveitis) compared to nonuveitic controls or HIV-positive patients with retinitis. Our findings suggest that in Thailand, infection with *T. gondii* may play a role in the pathogenesis of non-HIV posterior uveitis. Although we demonstrated a higher frequency of positive *T. pallidum* and *Leptospira* antibodies in HIV-positive patients with retinitis compared to non-HIV uveitis and controls, the question of whether these microorganisms are really involved in the pathogenesis of their ocular diseases cannot be answered by the present study. The definitive proof of ocular infections would require the examination of intraocular fluids.

Infectious causes of uveitis differ largely around the world. *Mycobacterium tuberculosis* and *T. gondii* were common infective causes of uveitis in India and Indonesia, whereas *Toxoplasma* uveitis was strikingly low in Japan and China. In Thailand, seroprevalence of toxoplasmic antibodies was investigated in pregnant women, blood donors, and kidney recipients, and seropositive rates of these groups varied from 10 to 15%, which is lower than in Western Europe and similar to U.S. seroprevalence. In China, where *Toxoplasma* uveitis is not observed, the seropositivity in the population is between 2 and 9%, with the exception of one study, which reported that *T. gondii* IgG prevalence among pregnant women in Chengdu was 39%. In previous reports, a marked difference in *T. gondii* IgG levels between Thai and Austrian pregnant women was also noted. These differences were attributed either to the different strain of virulences of *T. gondii* around the world or to the possibility that Thai women were infected at a younger age than Austrian women, which would also explain their lower IgG levels. In addition, many other factors may be responsible for these differences, including the eating habits and presence of *T. gondii* in potential sources of human infections, and, not least, different definitions of positive and negative serologic cutoff points. Our study confirms the presence of the *T. gondii* antibody in 17% of the general population in northern Thailand. In Bangkok in 1995, toxoplasmic IgG was detected in 3.2% of healthy persons, in 12.5% of patients with ocular disease, and in 42.5% in HIV-positive patients. However, we found no significant difference between the prevalence of *T. gondii* antibody in HIV-infected retinitis patients (19%) and in the general population (17%), which is similar to a report of a Bangkok survey in HIV-positive and HIV-negative persons. In contrast, 43% (15/35) of HIV-negative patients with posterior uveitis were positive for *T. gondii* IgG, which is higher than in other uveitis locations and indicates a high probability of toxoplasmic uveitis. A previous study from Singapore revealed a similar distribution of *T. gondii* serology in patients with uveitis and controls. In addition, clinical features typical of ocular toxoplasmosis were noted in 40% of seropositive patients with posterior uveitis. The unusual forms of toxoplasmic chorioretinitis are increasingly being reported. In addition, the combination of seropositivity for toxoplasma and uveitis in atypical cases could also be caused by the coincidence as 17% of controls were also positive. In addition, ocular toxoplasmosis in Thailand might have different characteristics and should be further studied.

Syphilis and leptospirosis are considered important causes of uveitis in developing countries. In our study, the evidence of prior infection with *T. pallidum*, *Leptospira*, and *Mycobacterium tuberculosis* was not common in non-HIV uveitis patients, which demonstrates that these microorganisms probably do not frequently cause uveitis in northern Thailand. In northern Thailand, the prevalence of *T. pallidum* antibodies seems to be stable according to a report of 2.7% in men and 2.1% in women in a 1998–2001 survey, which is similar to our result of 2%. However, in our series, the prevalence of *T. pallidum* antibody was higher in HIV-infected retinitis patients (13/100 HIV) and could indicate that these patients might have ocular disease related to their syphilis. Although the design of our study precluded the confirmation or exclusion of syphilitic uveitis, our data show that HIV-infected patients with retinitis were more frequently exposed to *T. pallidum* infection than other groups studied. This finding is supported by a report conducted in the northern Thai population showing that persons having syphilis were 3 times more likely to have HIV. Also in reports from the United States of America and Europe, the prevalence of ocular syphilis among HIV-infected patients in the HAART era is rising. It might be possible that the association between HIV and syphilis arises from the fact that they share common risk factors or that the ocular syphilis might be misdiagnosed in HIV-infected patients. It is our opinion that the possibility of concurrent syphilis should be considered in all HIV-positive patients with intraocular inflammation. Further investigations into syphilitic uveitis in Thai HIV-infected patients are needed.

Data observed in this study showed that *Leptospira* is not a major cause of uveitis in the northern Thai population. Although leptospirosis was reported as an emerging infectious disease in Thailand, our data showed that only 2% of the general population was positive in the screening for *Leptospira* antibody. This low percentage might be explained by geographical difference, since the most cases (90% of all Thai infections) were reported in the northeastern region of Thailand. So far, *Leptospira* uveitis was
predominantly observed during the chronic stage of systemic *Leptospira* infection. Only one HIV-negative patient with chronic bilateral panuveitis was proven to have a current infection with *Leptospira australis*, a strain being most commonly found in a survey of suspected leptospirosis cases in northeast Thailand. His eye examination revealed panuveitis characterized by anterior chamber and vitreous cells, fine keratic precipitates, but no retinal lesions, clinical features that are compatible with the diagnosis of ocular leptospirosis. The higher prevalence of *Leptospira* serology in HIV-positive patients is a surprising finding as *Leptospira* infection is not previously reported to be common in the HIV population. The majority of patients with uveitis are of working age and a significant percentage suffer from associated systemic diseases, including poverty-associated infections. Many infections can be treated and, therefore, it is important to identify the causative agents. Our finding of positive *T. gondii* serology in 43% of patients with posterior uveitis indicates that *T. gondii* may be responsible for a significant number of posterior uveitis cases in non-HIV-infected patients in Thailand and that infections with *T. pallidum* and *Leptospira* are less common causes of uveitis in the non-HIV-infected population. However, occasional uveitis patients might suffer from these infections, as in our series 1 HIV-negative patient had syphilis and 1 additional patient suffered from leptospirosis.

The best assessment of the definitive diagnosis of infectious uveitis currently lies in the analysis of intraocular fluid samples for DNA/RNA and antibodies by PCR and Goldmann-Witmer coefficient (GWC) analysis, respectively. These diagnostic possibilities (and consequent treatments) are, however, not widely available, even in so-called developed countries, and their widespread implementation is challenging. Our data provide an insight into the etiology of infectious uveitis in Thailand and form a firm basis for future laboratory investigations for potentially causative microorganisms by the molecular and serological analyses of intraocular fluids.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**REFERENCES**


