Early Aqueous Humor Analysis in Patients with Human Ocular Toxoplasmosis

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To evaluate the diagnostic sensitivity of a panel of laboratory tests for ocular toxoplasmosis performed at the time of presentation, paired samples of aqueous humor and serum were collected from 49 consecutive episodes of ocular toxoplasmosis with a clinical course of less than 3 weeks. Total immunoglobulin G (IgG) and Toxoplasma gondii-specific IgG, IgM, and IgA were quantified by enzyme-linked immunosorbent assay. The avidity of T. gondii-specific IgG was determined, and DNA extracted from aqueous humor was amplified for detection of a glycoprotein B gene sequence of T. gondii. The diagnosis was confirmed for 73% (36 of 49) of the patients; this rate rose to 79.5% if data from a later analysis of aqueous humor derived from five of the negative patients were included. The analysis of serum (detection of T. gondii-specific IgM and analysis of consecutive serum samples) alone did not contribute to the diagnosis. Calculation of local antibody production lacked diagnostic sensitivity when it was determined less than 3 weeks after the manifestation of clinical symptoms (28 of 49 patients [57%]), but this rate rose to 76% after an analysis of a second aqueous humor sample. The antibody avidity index attained diagnostic significance in only 8 of 43 instances (19%), and T. gondii DNA was amplified from no more than 6 of 39 (16%) aqueous humor samples. However, T. gondii-specific IgA was found within the aqueous humors of 11 of 43 patients (26%); measurement of the T. gondii-specific IgA level thus contributed substantially to the diagnostic sensitivity of the laboratory tests.

Ocular toxoplasmosis is allegedly the most common cause of posterior uveitis in immunocompetent individuals (29, 42, 60). In most patients it is presumed to be a reactivated congenital condition (43, 53), but instances of acquired infection have also been reported (56). Clinical diagnosis is based on the manifestation of characteristic biomicroscopic features (13, 58, 61). A white, sharp-edged but irregular neuroretinal inflammatory focus (0.5 to 2 optic disc diameters in size) is usually seen, frequently in association with an old scar. When revealed by fluorescein angiography, this lesion may appear to be much larger than the same lesion viewed directly (2, 13, 46, 60). A largely cellular vitreal infiltration is regularly observed, with maximal density over the inflamed area, often in association with a moderate focal vasculitis. In recurrent ocular toxoplasmosis, acute inflammation may be restricted to a discrete zone at the margin of an old scar. The latter, as well as the small neuroretinal inflammatory satellites, are best detected by means of red light-free illumination (2, 61). The biomicroscopic indications of ocular toxoplasmosis are not, however, always so obvious, as signified here. Indeed, the clinical picture may often be far from typical, particularly in elderly patients (13, 26, 30).

Over the past three decades, many different serological tests have been introduced to confirm past infection with Toxoplasma gondii by the detection of T. gondii-specific immunoglobulin G (IgG) antibodies (27). According to current understanding, the presence of T. gondii-specific IgM is the hallmark of a recently acquired systemic or, possibly, ocular infection, although the rate of false-positive results due to persisting antibodies of this type is known to be fairly high (39). Given the absence or low levels of T. gondii-specific IgM in patients with reactivated ocular toxoplasmosis, it cannot therefore serve as a reliable marker of this disease (19, 34, 36, 56, 62).

Laboratory confirmation of ocular toxoplasmosis may be achieved in 50 to 80% of patients by analyzing paired samples of aqueous humor and serum for the accelerated local production of anti-Toxoplasma IgG (6, 12, 14, 32, 49) and, with late onset, of specific IgA also (28, 43, 59) but, possibly except in cases of acquired ocular disease, not of anti-Toxoplasma IgM in the aqueous humor (19, 34, 36, 56, 62).

On the basis of published data and our own observations, we have gained the impression that the rate of laboratory confirmation of ocular toxoplasmosis increases as a function of the time interval between the onset of symptoms and sample collection, which spans 4 to 52 weeks in the literature (11, 14, 49, 56). Since timely laboratory verification of the disease may be of therapeutic relevance, we wished to ascertain whether an early analysis (at less than 3 weeks after the onset of symptoms) substantially reduced the rate of confirmation rate of ocular toxoplasmosis.

MATERIALS AND METHODS

Patients. Forty-nine consecutive episodes of ocular toxoplasmosis in 45 patients who manifested the typical clinical picture (as outlined above) were included in this study from the time of their first presentation. Twenty-four (53%) of the patients were female, and their ages spanned 12 to 83 years (mean age, 27.9 years). Each patient presented at the clinical activation stage of the disease, as revealed by the presence of vitreal floaters, with this state being followed by a drop in visual acuity, usually within 14 days but occasionally after a delay of up to 3 weeks (mean ± standard deviation, 9.7 ± 8.4 days; range, 1 to 42 days; median, 7 days). Patients with symptoms that were not obviously attributable to newly reactivated ocular toxoplasmosis, as well as those with underlying inflammatory diseases or immunodeficiency syndromes, were excluded from the study. Patients were subjected to a thorough ocular examination, which included binocular funduscopy with pupillary dilation, on their first presentation and after 2 and 6 weeks. A 50° fundus photograph was taken to document the course of the disease, and blood was drawn for the quantification of specific antibodies and to determine whether the therapy was causing toxic side effects. A sample of aqueous humor was taken at the first presentation (prior to the onset of treatment) and thereafter at 6 weeks, on a voluntary basis, if the initial analysis had
TABLE 1. Standard therapeutic protocol for reactivated ocular toxoplasmosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of doses, dose</th>
<th>Length of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimethamine</td>
<td>2, 25 mg/day</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>1, 25 mg/day</td>
<td>6 wk</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>3, 1 g/day (4, 1 g for body weights above 75 kg)</td>
<td>4 wk</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>3, 15 mg/wk</td>
<td>6 wk</td>
</tr>
</tbody>
</table>

failed to confirm the clinical diagnosis or if an adequate scarring of the active zone had not occurred during the treatment period. All patients received a standard therapy; i.e., they were administered pyrimethamine, sulfadiazine, and leucovorin (Table 1).

Analyses of blood and aqueous humor samples. Serum was obtained from centrifuged blood samples and was stored for a maximum of 24 h at 4°C prior to the analysis of immunoglobulins. Aliquots of aqueous humor of 150 to 250 μl were withdrawn after anterior chamber paracentesis. The sediments obtained after the centrifugation of these samples were dissolved in 50 μl of proteinase K buffer, and the solution was used for the amplification of T. gondii DNA (18); supernatants were used for the analysis of immunoglobulins.

Immunassay procedures. The total IgG concentrations within the aqueous humor supernatants (dilution, 1/10) and serum samples (dilution, 1/100) were estimated by high-sensitivity nephelometry (detection limit, 4 mg/liter), the levels of T. gondii-specific IgG, IgM, and IgA were determined with commercial available test system (Platelia Toxo; Sanofi-Diagnostics Pasteur, Marnes la Coquette, France; dilutions, 1/20 [aqueous humor supernatants] and 1/100 [serum samples]). The positive cutoff for the T. gondii-specific IgG test corresponds to 6 IU/ml on a scale set with World Health Organization-standardized samples of control sera containing defined concentrations of specific antibodies (devised according to the manufacturer’s instructions).

The Goldmann-Witmer coefficient, also known as the antibody ratio (C), was calculated by using the Goldmann-Witmer formula, where C = anti-T. gondii-specific IgG (IgG level in aqueous humor/IgG level in serum)/total IgG (IgG level in serum/IgG level in aqueous humor) (21), as described by Desmons (14).

The estimation of T. gondii-specific Ig avidity was based on the method described by Vinhal et al. (63) and Lecolier and Pucheu (38), but we incorporated a modification of our own to effect the dissociation of antigen-antibody complexes with 6 M urea. Duplicate aliquots withdrawn from each of two different dilutions of each sample (1/20 and 1/100 for aqueous humor; 1/100 and 1/1,000 for serum) were processed in parallel. During the washing phase, wells containing duplicate aliquots were treated differently, with one being rinsed with the kit’s standard solution (Tris–NaCl buffer [pH 7.4]) containing Tween 20 and 0.01% sodium deoxycholate and the other being rinsed with the same solution containing 6 M urea to dissociate antigen-antibody complexes. The wells were washed three times, each for a 5-min period, with the appropriate solution, and the entire plate was then finally rinsed with the standard solution. All other steps in the enzyme-linked immunosorbent assay procedure were performed according to the manufacturer’s protocol (Platelia Toxo; Sanofi-Diagnostics Pasteur). Optical densities were measured at an emission wavelength of 492 nm (Microwell reader’s system, model LP 400; Sanofi Diagnostics Pasteur). Two readings for each dilution of aqueous humor and serum were performed: one for the well with the standard solution and the other for the well with the same solution containing 6 M urea to dissociate antigen-antibody complexes. The antibody ratio was calculated from the optical density quotient: optical density for the well with urea/optical density for the well with the standard solution. Each enzyme-linked immunosorbent assay run included internal controls (low- and high-avidity samples) for which the avidity index values differed by less than 10% from the expected avidity index values. An avidity index equal to or less than 0.3 was considered to be indicative of the clinical diagnosis if numerical values were below the positive (i.e., confirmatory) cutoff level, as defined above, for each test. Data were held to be indicative of the clinical diagnosis if numerical values were substantially above the negative cutoff point but below the level required for confirmation in each specific test (defined above). Values that fell within this “indicative” category afforded evidence of the existence of infection activity.

RESULTS

Confirmation of diagnosis at the time of presentation. Among the 49 consecutive episodes of ocular toxoplasmosis that satisfied the inclusion criteria, the clinical diagnosis was supported by indicative laboratory results for 9 episodes (18.4%) and was confirmed for 27 episodes (55.1%) at the time of presentation. Positive results for paired aqueous humor and serum samples by only one of the various laboratory tests supported the clinical diagnosis for 21 episodes (42.9%), whereas positive findings by two or more were indicative of or confirmative for 15 episodes (30.6%). For the remaining 13 episodes (26.5%), specific antibodies were found in the serum, but neither these nor parasitic DNA was detected within the aqueous humor (Table 2). Neither the length of time between the onset of symptoms and presentation nor the absence or presence of scars influenced the laboratory confirmation rates (P = 0.1).

A threefold rise in the concentration of specific IgG in serum was found in only 1 of the 30 patients (3%) from whom blood had been withdrawn after 2 and 6 weeks. In this case, the antibody ratio for T. gondii-specific IgG was confirmatory, as was the level of T. gondii-specific IgA in the aqueous humor. T. gondii-specific IgM was detected in the sera of five patients; in two of these, it was present in the aqueous humor as well, with a higher index in the latter. Since, however, T. gondii-specific IgM may persist for long periods in an as yet undetermined proportion of patients, these results were not included in the rate-of-success analysis.

The antibody ratio was found to be indicative of the diagnosis if (i) the concentrations of specific marker antibodies (IgG) in serum were at least threefold higher than the baseline levels 6 weeks after the onset of symptoms; (ii) the levels of T. gondii-specific IgA in the aqueous humor and serum were equivalent or if the local index level of T. gondii-specific IgA was 0.5 or more in the absence of detectable IgA (lower local levels of specific IgA, in combination with negative readings for serum, were taken to be indicative of but not confirmatory for the clinical diagnosis); (iii) the IgG C value was 8 or above (a C value that ranged between 3 and 8 was taken to be indicative of but not confirmatory for the clinical diagnosis; one below 3 was judged to confute the clinical diagnosis); (iv) the specific IgG avidity ratios for aqueous humor and serum differed by 0.2 or more (differences between 0.15 and 0.2 indicated that the patterns of antibody turnover in the two media were dissimilar; if the lower value was detectable in the aqueous humor, local antibody consumption was assumed to have taken place; if the antibody avidity ratio was greater than 0.6, the infection was presumed to have existed for more than 6 months; a value below 0.4 suggested that the infection was newly acquired rather than reactivated; and (v) the DNA of T. gondii parasites could be amplified from aqueous humor sediments by PCR.

The results of laboratory tests were deemed to be negative, i.e., nonsupportive of the clinical diagnosis, if numerical values were below the positive (i.e., confirmatory) cutoff level, as defined above, for each test. Data were held to be indicative of the clinical diagnosis if numerical values were substantially above the negative cutoff point but below the level required for confirmation in each specific test (defined above). Values that fell within this “indicative” category afforded evidence of the existence of infection activity.

TABLE 2. Laboratory confirmation of ocular toxoplasmosis at time of presentation

<table>
<thead>
<tr>
<th>No. of tests with indicative and confirmatory results*</th>
<th>No. (%) of paired aqueous humor and serum samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13 (26.5)</td>
</tr>
<tr>
<td>1</td>
<td>21 (42.9)</td>
</tr>
<tr>
<td>More than 1</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>Indicative</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Confirmatory</td>
<td>27 (55.1)</td>
</tr>
</tbody>
</table>

* Indicative and confirmatory are defined in Materials and Methods section under “Criteria for laboratory support of the clinical diagnosis.”
nosis for 8 patients and confirmatory for 20 patients, with the levels of specific IgA in the aqueous humor likewise being indicative of or confirmatory for the diagnosis for three and eight of these patients, respectively. The antibody avidity ratio was indicative of the diagnosis for five patients and confirmatory for three patients. It supported a suspicion of newly acquired toxoplasmosis with ocular involvement in two patients; one of these patients had suffered an episode of highly febrile systemic disease involving the liver and lungs 3 months prior to presentation for the ocular disease. Detection of parasitic DNA by PCR supported the diagnosis in six patients (16%); in three of these patients it constituted the only positive laboratory test (Table 3). Of these three patients, two consented to analysis of a second aqueous humor sample within 6 weeks. In one of these patients no further laboratory evidence for the diagnosis was revealed; in the other, a delayed onset of local antibody production was revealed, thus confirming the diagnosis.

**Confirmation of the diagnosis by analysis of a second aqueous humor sample.** In five patients, a second anterior chamber puncture was performed within 6 weeks of the first one to confirm the late onset of a humoral immune response. Four additional cases patients granted a request for a second puncture at 10, 21, 22, or 53 weeks (Table 1) owing to the persistence of inflammatory activity, even with standard therapy. In three of the five patients with no initial evidence of local antibody formation (including the two who were positive for parasitic DNA), the diagnosis was finally confirmed by a positive antibody ratio. In one of the patients in whom parasitic DNA was detected and in one patient with no laboratory evidence of active ocular toxoplasmosis, no laboratory confirmation was obtained, despite the manifestation of a typical clinical picture in each patient (Table 4).

In summary, the performances of all available tests with paired samples of aqueous humor and serum derived at the

### Table 3. Independent efficacy of each laboratory test performed with paired samples of aqueous humor and serum for confirming the diagnosis of ocular toxoplasmosis

<table>
<thead>
<tr>
<th>Laboratory test result</th>
<th>Increase in level of T. gondii-specific IgG</th>
<th>C</th>
<th>T. gondii-specific IgA in aqueous humor</th>
<th>T. gondii-specific IgG avidity</th>
<th>Detection of T. gondii DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>29 (97)</td>
<td>21 (43)</td>
<td>32 (74)</td>
<td>35 (78)</td>
<td>32 (84)</td>
</tr>
<tr>
<td>Indicative</td>
<td>1 (3)</td>
<td>8 (16)</td>
<td>3 (7)</td>
<td>5 (11)</td>
<td>—</td>
</tr>
<tr>
<td>Confirmatory</td>
<td></td>
<td>20 (41)</td>
<td>8 (19)</td>
<td>3 (7)</td>
<td>6 (16)</td>
</tr>
</tbody>
</table>

* The various results are defined in Materials and Methods under “Criteria for laboratory support of the clinical diagnosis.”

**Table 4. Comparison of laboratory test results with paired samples of aqueous humor and serum collected at time of presentation and 2 to 53 weeks thereafter**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time interval (wk)</td>
<td>1 2 3 4 5 6 7 8 9</td>
</tr>
<tr>
<td>Anti-Toxoplasma IgG level in serum/anti-Toxoplasma IgG level in aqueous humor (IU)</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>392/0 86/0 320/127 10/0 285/0 350/280 50/12 22/0 2,000/1,500</td>
</tr>
<tr>
<td>i</td>
<td>31/0 86/17 350/280 15/73 228/0 350/80 34/6 26/0 308/1,490</td>
</tr>
<tr>
<td>C</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>0 0 5.9 0 0 3.7 16.8 0 0.33</td>
</tr>
<tr>
<td>i</td>
<td>0 20.6 3.7 428 0 5.2 14.5 0 18.7</td>
</tr>
<tr>
<td>Aqueous humor IgA (index)</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>0 0 4 0 0 0 0 0 0</td>
</tr>
<tr>
<td>i</td>
<td>0 0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Antibody avidity (index)</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>— — 0.4 — — 0.45 0.8 — 0.7</td>
</tr>
<tr>
<td>i</td>
<td>0.75 0.45 0.55 — 0.15 0.55 — 0.8</td>
</tr>
<tr>
<td>DNA amplification,</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>1 0 0 0 0 0 0 0 1 (vitreous)</td>
</tr>
<tr>
<td>Confirmatory test</td>
<td>PCR C C?, IgA C Not confirmed C? C PCR vitreous C, PCR, Toxoplasma-specific IgG in serum</td>
</tr>
</tbody>
</table>

* Confirmatory results are indicated in boldface type. Abbreviations and symbols: d, sample collection at the time of presentation; i, sample collection at the indicated time after presentation; —, if no specific antibodies were detected, it was not possible to determine antibody avidity in the aqueous humor. For two patients (patients 1 and 8) with clinically typical cases, the laboratory diagnosis relied solely on PCR results.

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time of presentation and at 2 to 53 weeks for 9 patients yielded no laboratory support for the clinical diagnosis for 10 patients (20.4%); the results were indicative of the diagnosis for 9 patients (18.4%) and confirmatory for the diagnosis for 30 patients (61.1%) (Table 5).

**DISCUSSION**

Biomicroscopic signs of ocular toxoplasmosis are regarded as the “gold standard” for the clinical diagnosis of toxoplasmosis, with the proportion of false-positive and false-negative results depending largely upon the relative experience of the ophthalmologist (27). Any investigation that addresses the sensitivities and specificities of laboratory tests instigated to confirm a diagnosis of presumed ocular toxoplasmosis will inevitably draw on a group of patients defined according to the clinical picture. Although we included only those individuals who manifested a very typical clinical picture, it should nonetheless be borne in mind that any such study will carry the risk that the results were only indicative, consent for a second anterior chamber puncture was obtained from only five patients; for three of these patients laboratory tests confirmed the diagnosis.

Application of T. gondii DNA is known to be a sensitive index of acute fetal infection when it is performed with samples of amniotic fluid (22) and to be helpful in the diagnosis of cerebral toxoplasmosis when it is conducted with aliquots of cerebrospinal fluid derived from immunocompromised patients (9, 50); it has also been claimed to be of value in the diagnosis of ocular toxoplasmosis when it is carried out with samples of aqueous humor (1, 8; A. P. Brezin, C. E. Eqwuagu, C. Silveira, P. Thulliez, M. C. Martins, R. M. Mahdi, R. Belfort, Jr., and R. B. Nussenblatt, Letter, N. Engl. J. Med. 324:699, 1991). However, even when precautionary measures are taken to prevent false-positive results generated by the incorporation of stray DNA (35) and to digest amplified target DNA fragments prior to amplification, which is now the routine practice in most laboratories (40), the amplification of T. gondii DNA from samples of aqueous humor is of little diag-

**TABLE 5. Definitive laboratory support for clinical diagnosis**

<table>
<thead>
<tr>
<th>Laboratory contribution</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitively negative(ab)</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>Indicative</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>Confirmatory</td>
<td>30 (61.2)</td>
</tr>
</tbody>
</table>

\(a\) The various results are defined in Materials and Methods under “Criteria for laboratory support of the clinical diagnosis.”

\(b\) Of the 15 patients for whom the clinical diagnosis was not confirmed by laboratory results at the time of presentation and the 9 patients for whom the results were only indicative, consent for a second anterior chamber puncture was obtained from only five patients; for three of these patients laboratory tests confirmed the diagnosis.
nostic value for immunocompetent patients with ocular toxoplasmosis (12, 19, 57). Only in immunodeficient patients, e.g., in patients with AIDS (4, 10, 51), and in individuals with what is presumed to be recently acquired ocular toxoplasmosis (41) is it a useful index of this disease. These findings are not perhaps surprising, since immunodeficient patients have markedly higher parasite DNA copy numbers and manifest a feebler immunological degradation of target DNA than immunocompetent patients. Furthermore, the ocular disease in immunodeficient individuals is an acute form of a generalized infection, which is not immunologically controlled. Consequently, the probability of detecting parasites or their DNA in any bodily compartment of immunodeficient patients is much higher than that for immunocompetent individuals with a previous or chronic infection (17, 23), such as reactivated ocular toxoplasmosis, a condition in which local reactivation of the chronic infection is confined almost exclusively to the region abutting a preexisting retinal scar and only rarely spreads into the anterior segment of the eye. Hence, the chances of detecting target DNA within the aqueous humors of immunocompetent individuals are fairly remote. Amplification of T. gondii DNA from samples of vitreous might possibly prove to be of diagnostic value, since the turnover, and thus clearance, of parasitic DNA in this medium is much slower than that in the aqueous humor (3, 12, 45). However, the potential complications associated with vitreal puncture are too severe to justify this undertaking on a routine basis.

In evaluating the data reported in the literature, it is also necessary to bear in mind that the detection sensitivity of DNA amplification varies between laboratories, since not all of these use standardized procedures or adopt those performed in certified reference establishments (24, 52). Our own low detection rates were not, however, attributable to this cause, since the PCR method that we used complied with the one-copy-per-sample standard set by reference laboratories (52) and included measures for the internal inhibition of amplification as well as for the destruction of stray DNA (44).

Relatively little is in fact known about the time dependence of antibody production in the eye (16, 26), and existing data pertaining thereto do not always fit into our current immunopathophysiological understanding of this phenomenon. In necrotizing viral retinopathy, for example, local antibody production is regularly observed at about the time of clinical presentation in immunocompetent individuals (11), whereas in ocular toxoplasmosis, a delayed response of up to 4 weeks can be expected (12, 14, 49, 56). This delay in local antibody production is not consistent with the more rapid development of clinical symptoms in the latter case than in the former (11), nor is it consistent with the circumstance that necrotizing viral retinopathy is believed to be a first-episode ocular disease, whereas ocular toxoplasmosis is a recurring one. These observations can be partially reconciled with our current understanding by allowing for differences in the rate of local antibody consumption or in the severity of the local inflammatory response (15), but not entirely. A severe inflammatory reaction, such as the one characteristic of necrotizing viral retinopathy, would be expected to give rise to a high proportion of false-negative results, which is not the case for this disease (33).

Host immune responses are subject to interindividual differences in the rate of activation of immunological mechanisms (and eventually also of immunogenetic mechanisms) (5, 26, 47). Until these mechanisms are more fully understood, a meaningful interpretation of laboratory findings would be greatly facilitated by devising scoring systems for the different diagnostic strategies, with the scoring systems based on the pooled data of nominated reference laboratories. Until such databases are established, we cannot judge whether the cases of disease in the 20% of patients with unconfirmed ocular toxoplasmosis were attributable to a mismatch between the clinical and laboratory diagnoses.

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