Ocular Manifestations Associated with Brucellosis: A 26-Year Experience in Peru

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Background. Brucellosis has unusual clinical manifestations. Ocular involvement caused by brucellosis remains poorly recognized in areas in which brucellosis is endemic.

Methods. A prospective study was performed to evaluate patients attending the Instituto de Medicina Tropical “Alexander von Humboldt” and the Hospital Nacional Cayetano Heredia (Lima, Peru) from January 1980 through December 2005 who received a diagnosis of brucellosis with ocular involvement. Diagnosis was made on the basis of clinical findings as well as agglutinations and/or culture positive for Brucella melitensis.

Results. During a period of 26 years, 1551 patients with brucellosis were seen, including 52 patients with ocular brucellosis. We found that 7 (0.7%) of 965 patients with acute brucellosis and 45 (7.9%) of 570 patients with chronic brucellosis had ocular brucellosis (P < .001). In 16 patients with brucellosis, the disease stage was unclassified. The most frequent ocular presentation was uveitis, which was found in 43 (82.7%) of the 52 patients with ocular brucellosis. Posterior uveitis was the most frequent uveal syndrome (21 cases; 45.7%). Patients with panuveitis had the worst visual prognosis: 8 of 9 patients with panuveitis were legally blind, including 5 patients with no light perception.

Conclusions. Brucellosis may involve the eye and can lead to serious complications. In patients with brucellosis, early ophthalmologic evaluation can lead to prompt treatment and might prevent blindness from severe ocular damage.

Brucellosis is a zoonotic disease that can be found worldwide. Although it has been eradicated and is under control in most developed countries, it still represents an important health problem in many parts of the world, including the Middle East, the Mediterranean, Mexico, and Central and South America [1–3]. In some countries, such as Peru, Kuwait, and Saudi Arabia, brucellosis is endemic [3, 4].

In the genus Brucella, there are 6 classic pathogens, 4 of which have been recognized as human pathogens: Brucella melitensis, Brucella abortus, Brucella canis, and Brucella suis. Most cases in the world are caused by B. melitensis, which has been described as the most virulent Brucella species [1, 4, 5]. B. abortus is the most prevalent Brucella species in North America and Europe, whereas B. melitensis is more common in Latin America, the Mediterranean, and developing countries [1, 4]. In Peru, Brucella melitensis has been isolated in all cases in which cultures have been obtained.

Brucellosis is a systemic disease with a wide spectrum of clinical manifestations, which presents a diagnostic challenge. Even though classical symptoms of brucellosis are easy to recognize, some presentations are not well known, such as ocular brucellosis, and have to be considered when making a differential diagnosis. This could permit early diagnosis and treatment and, hopefully, reduce the number of complications [6].

The first case of ocular brucellosis in a human being was described by Lemaire in 1924 [7]. Cases involving uveitis, neuritis, optic neuritis, papilloedema, keratitis, and more-diverse ocular and neurological presentations associated with brucellosis have been reported [8].

With improved quality control of animal products and adequate livestock vaccination, the number of
acute brucellosis has been reduced in developed countries. Reported cases have been scarce, and in general, only anecdotal reports exist [9]. In those reports, ocular brucellosis has been described as an unusual presentation of the disease [2, 6, 10]. The aim of this study was to report ocular brucellosis presentations in a clinical series of ≥1500 patients with brucellosis.

PATIENTS, MATERIALS, AND METHODS

We prospectively included all patients with a diagnosis of systemic brucellosis attending the Instituto de Medicina Tropical “Alexander von Humbolt” and the Hospital Nacional Cayetano Heredia (Lima, Peru) from January 1980 through December 2005. We selected all patients with a diagnosis of brucellosis who had ocular involvement and all patients referred to our clinic for ocular lesions who were subsequently diagnosed as having brucellosis.

Patients with a diagnosis of brucellosis received evaluation by an infectious diseases specialist (E.G.) and a clinical microbiologist (C.C.). When ocular abnormalities were found, patients were referred to an ophthalmologist (I.R.) who systematically observed those patients with ocular involvement.

The inclusion criteria for our study were (1) agglutination test results positive for Brucella melitensis in blood (serum agglutination titer ≥1:160, 2-mercaptoethanol titer ≥1:80, and blocking antibody titer ≥1:80) and/or (2) isolation of B. melitensis from blood or bone marrow cultures [11].

Patients with ocular involvement were tested using the Venereal Disease Research Laboratory assay and/or the Fluorescent Treponemal Antibody Absorption assay, and they underwent serological testing for toxoplasmosis. Active tuberculosis was ruled out by clinical examination, tuberculin skin testing, and examination of chest radiographs.

Two different clinical courses were recognized for the disease: acute brucellosis (<8 weeks in duration) and chronic brucellosis (≥8 weeks in duration). We considered cases with a subacute or recurrent course to be cases of chronic brucellosis for the purpose of simplifying the statistical analysis.

The following presentations of uveitis were identified: (1) anterior uveitis, including iritis, iridocyclitis, and anterior cyclitis; (2) intermediate uveitis, including pars planitis, posterior cyclitis, and hyalitis; (3) posterior uveitis, including choroiditis, chorioretinitis, retinitis, and neuroretinitis; and (4) panuveitis, including inflammation of all 3 components of the uveal tract [12]. The following complications were identified: cataracts, glaucoma, maculopathy, vitreal alterations, phthisis bulbi, optic atrophy, neovascular retinal membrane, tractional retinal detachment, Behcet syndrome, Harada syndrome (posterior uveal inflammation with retinal exudations and meningeal irritation), and Vogt-Koyanagi-Harada syndrome (anterior segment inflammation associated with vitiligo, poliosis, disacusia, and meningeal irritation) [13].

All patients received standard therapy with doxycycline (100 mg twice per day for 6 weeks) in combination with rifampin (600–1200 mg/day for 6 weeks) or an aminoglycoside (administered intramuscularly once per day for 2 weeks), which was usually streptomycin (15 mg/kg or 1 g per day). If ocular inflammation was present, systemic and topical steroids were also prescribed for 2–4 weeks.

Data was tabulated in a Microsoft Excel spreadsheet with a unique identification code for each patient. Variables included were sex, age, systemic manifestations, and clinical course. In patients with ocular involvement, we considered ophthalmologic symptoms, initial and final visual acuity, unilateral or bilateral ocular involvement, uveal presentation, ocular complications, serum agglutination test results, and culture results. Data were analyzed using Stata, version 7.0 (Stata). For statistical analysis, independent variables were compared using the χ² test. P < .05 was considered to be statistically significant.

RESULTS

Fifty-eight of 1551 patients with systemic brucellosis had ocular involvement. Six of the patients with ocular involvement did not meet inclusion criteria for this study (5 patients had serum agglutination titers that were too low for inclusion, and 1 patient had ocular toxoplasmosis). Over a 26-year period, 52 patients with ocular brucellosis were registered; of these, 34 (65.4%) were women, and 18 (34.6%) were men (table 1).

### Table 1. Incidence of brucellosis and ocular brucellosis, by sex and clinical course.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Systemic brucellosis (n = 1551)</th>
<th>Ocular brucellosis (n = 52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>658</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>893</td>
<td>34</td>
<td>.24</td>
</tr>
<tr>
<td>Clinical coursea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>965</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>570</td>
<td>45</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*a Clinical course was undefined for 16 patients.

### Table 2. Systemic signs and symptoms of patients with ocular brucellosis.

<table>
<thead>
<tr>
<th>Systemic sign or symptom</th>
<th>No. (%) of patients (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias</td>
<td>26 (50)</td>
</tr>
<tr>
<td>Fever</td>
<td>24 (46.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Sweating</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Testicular paina</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>15 (28.8)</td>
</tr>
</tbody>
</table>

*a Three of 18 male patients reported testicular pain.
Table 3. Types of ocular involvement in patients with ocular brucellosis.

<table>
<thead>
<tr>
<th>Type of ocular involvement</th>
<th>No. (%) of patients (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ophthalmologic manifestation</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>48</td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>43b (82.7)</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>8</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>21</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>8</td>
</tr>
<tr>
<td>Panuveitis</td>
<td>9</td>
</tr>
<tr>
<td>Keratitis</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td><strong>Neuro-ophthalmologic manifestations</strong></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>7</td>
</tr>
<tr>
<td>Papilloedema</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Papilitis</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Third cranial nerve paresis</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

* Three patients had >1 ocular manifestation.
  b Three patients had different uveal involvement in both eyes.

Thirty-six cases of brucellosis (69.2%) were diagnosed using serum agglutination titers only. Four cases (7.7%) were diagnosed using only culture results. Diagnosis was made with both methods in 12 cases (23.1%). Bone marrow and/or blood samples were cultured in 35 cases, and B. melitensis was recovered in 16 (45.7%). Ocular involvement was reported for 7 (0.7%) of 965 patients with acute brucellosis, whereas 45 (7.9%) of 570 patients with chronic brucellosis had ocular involvement (table 1). Among the 52 patients with ocular brucellosis, age distribution was as follows: 26 (50%) were 16–35 years of age, 14 (26.9%) were >55 years of age, 11 (21.2%) were 36–55 years of age, and 1 (1.9%) was ≤15 years of age.

Systemic symptoms were present in 37 cases (71.2%) and absent in 15 cases (28.8%) (table 2). The most frequent ocular symptom reported was blurred vision (36 cases [69.2%]), followed by red eyes (9 cases [17.3%]), eye pain (6 cases [7.7%]), foreign body sensation (3 cases [5.8%]), scotoma in (3 cases [5.8%]), loss of vision (2 cases [3.9%]), double vision (2 cases [3.9%]), and lacrimation (1 case [1.9%]). Ten patients (19.3%) did not present with ocular symptoms but had abnormal findings of ophthalmologic examinations (5 of these 10 patients had visual acuity impairment).

Unilateral ocular involvement was reported for 32 (61.5%) of the patients, and bilateral ocular involvement was reported for 20 (38.5%). Ophthalmologic and neuro-ophthalmologic abnormalities were reported. Forty-three patients (82.7%) had cases of uveitis; among these patients, the posterior presentation was the most frequent (21 patients; 45.7%) (table 3).

A total of 56 ocular complications were present in 36 patients (69.2%). Some patients experienced >1 complication, and 16 patients (30.8%) did not have any complications (table 4).

Visual prognosis in patients with ocular brucellosis was based on visual acuity after treatment. Data on the visual acuity of 2 patients, 1 with anterior uveitis and 1 with intermediate uveitis, were not available. Eleven of 14 patients with anterior and intermediate uveitis had a visual acuity better than 20/50 after treatment; 4 of 21 patients with posterior uveitis and 8 of 9 patients with panuveitis were legally blind after treatment. The latter group included 5 patients with no light perception. The worst prognosis was observed for patients with panuveitis and posterior uveitis (table 5).

**DISCUSSION**

Since the start of the twentieth century, a number of ocular presentations associated with brucellosis have been reported [14, 15]. Nevertheless, there is no data on the incidence of this pathology, because most citations in the literature refer to case reports. In this study, ocular involvement due to brucellosis was reported in 52 (3.4%) of 1551 patients with brucellosis. Güngür et al. [16] reported that 38 (26%) of 147 patients with brucellosis had ocular involvement. Puig Solanes et al. [8] reported 60 (14.5%) cases out of 413 patients, and Rolando et al. [17] reported 14 (20%) out of 70 patients.

In this study, a higher proportion of ocular brucellosis was found in women (65.4%). This is consistent with previous findings by Puig Solanes et al. [8] and Rolando [18], who reported that 66% and 86.7% of patients with ocular brucellosis were female, respectively.

Many Peruvian studies of brucellosis report that female patients experience a larger number of symptoms and increased severity of symptoms [19, 20]. Most clinical studies of uveitis...
Figure 1. Ocular presentations associated with brucellosis. A, Phthisis bulbi. B, A and B ultrasound of the patient shown in A. Retinograph (C) and retinal angiogram (D) with window defect in the retinal pigment epithelium secondary to chronic edema in the macular area, showing evidence of septic emboli in a patient with brucellar endocarditis and focal choroiditis. E, Retinograph showing serous macular retinal detachment secondary to juxtapapillary choroidal granuloma in a 33-year-old man with chronic brucellosis. F, Retinograph of the patient shown in E, showing juxtapapillary chorioretinal scar 4.5 years after diagnosis of choroidal granuloma and 3 months of laser treatment. G, Anterior uveitis and secondary cataracts. H, Blue toluidine stain of iris biopsy sample from the patient shown in G, with granulomatous inflammatory reaction. The presence of Russell bodies (arrow) is the evidence of local production of specific immunoglobulins.

report a similar incidence in both sexes [21]. Although our study found that more women than men were affected, the difference was not statistically significant.

In this study, patients 16–35 years of age were encountered more frequently than patients in other age groups. This is consistent with the findings of Puig Solanes et al. [8], who found a higher prevalence of ocular brucellosis among young adults (21–30 years of age). We had only 1 patient ≈15 years of age, whereas 13.3% of the cases reported by Puig Solanes et al. [8] occurred in patients who were ≈15 years of age.
Ocular presentations of brucellosis can appear in either the acute phase or the chronic phase of the disease. In this study, a larger proportion of ocular manifestations was found in the chronic phase ($P < .001$) (figure 1A–G). This is consistent with other reports, such as that by Woods [22], who described ocular brucellosis only in the chronic phase of the systemic disease. Rolando et al. [23] and Puig Solanes et al. [8] concluded that uveitis develops more frequently in individuals with the subacute and chronic forms of brucellosis. Gungur et al. [16] also found that ocular brucellosis was more frequent during the chronic phase of the disease (accounting for 71% of cases of ocular brucellosis). In 1985, Rolando et al. [18] found that 4 (26.7%) of 15 patients presented during the acute phase of the disease, whereas 11 (73.3%) presented during the chronic and undulating phase. Moreover, Green [14], reporting on the work of 23 authors, stated that all ocular compromise appeared during the chronic phase of the systemic disease.

Many factors influence the presentation of ocular compromise during the chronic phase of brucellosis. In developing countries, patients frequently do not seek medical care until the disease has reached an advanced stage, and limited knowledge of disease pathology by health care providers often results in a late diagnosis.

We observed 2 types of ocular involvement: ophthalmologic and neuro-ophthalmologic. Of the ophthalmologic pathology caused by *Brucella* species, the most frequent form that we encountered was uveitis. It has been recognized as an important manifestation in ocular brucellosis [24] and widely described as being the most common form of ocular brucellosis [8, 25–28]. Only rarely do studies report another presentation as being

<table>
<thead>
<tr>
<th>Visual acuity</th>
<th>Anterior uveitis ($n = 7$)</th>
<th>Intermediate uveitis ($n = 7$)</th>
<th>Posterior uveitis ($n = 21$)</th>
<th>Panuveitis ($n = 9$)</th>
<th>Total ($n = 44$)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–40</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>50–200</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>400–LP</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>NLP</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

**NOTE.** LP, light perception; NLP, no light perception.
* Visual acuity was not obtained for 2 patients.

![Figure 2. Choroidal neovascular membrane. A, Black and white retinal image before contrast with extensive macular edema from the patient shown in figure 1E and 1F. B, C, and D, Retinal angiogram showing intermediate and late-phase serous macular detachment secondary to choroidal neovascular membrane (arrow) in a juxtapapillary chorioretinal scar. After 9 weeks of laser treatment, visual acuity improved to 20/20.](https://academic.oup.com/cid/article-abstract/46/9/1338/327612/26712)
Figure 3. Retinal detachment in a 59-year-old woman with a paravertebral abscess and classic dorsal brucellar spondylitis. A, A and B ultrasound of the right eye showing total serous retinal detachment. When systemic steroids were discontinued, a relapse of the retinal detachment occurred (B). Retinopexy with a 360–silicon band achieved definitive anatomical reattachment (C). Serum agglutination titer was 1:2560, and 2-mercaptoethanol in aqueous humor titer was 1:20. \textit{B. melitensis} was isolated from a bone marrow culture.

The most frequent uveal syndrome was posterior uveitis, followed by panuveitis. This is consistent with findings reported by Rolando et al. [23], who found that 9 (35%) of 25 patients with brucellosis had cases of posterior uveitis (35%), and 8 (32%) had cases of panuveitis.

The compromise of the optic nerve and of cranial nerves involved in ocular movements has been previously described in association with brucellosis [8, 25]. These neuro-ophthalmologic cases represent a small proportion of our cases. However, Puig Solanes et al. [8] reported 48 cases of neuro-ophthalmologic brucellosis in a 60-patient series. Most of the literature on neuro-ophthalmologic involvement in brucellosis consists of isolated case reports [8, 33–35]. Nevertheless, a study has reported a frequency of optic nerve involvement of 10.7% [25].

Optic nerve compromise is believed to be secondary to transient meningeal inflammation. Other studies have suggested that changes to the optic nerve follow an axonal degeneration secondary to inflammation caused by brucellosis [8, 33]. These studies also mention the possibility of ischemic and vasculitic factors, because visual acuity improvement was found after steroid treatment. This might be mediated through immune complexes [8, 33].

Etiological diagnosis of brucellosis is confirmed through the isolation of the microorganism. A positive culture result is more frequent in acute cases [26]. The tryptic soy broth (Ruiz-Castañeda biphasic medium) is of great importance for isolation of brucella, although it requires up to 6 weeks for the microorganism to grow. Isolation rates are greatly increased when this medium is used [20]. \textit{Brucella} species grow faster when cultured from bone marrow aspiration samples, which is consistent with the fact that the bacteria localizes itself in the phagocytic cells of the reticuloendothelial system organs [36].

New techniques have been developed, such as PCR, that are fast and have a high specificity and sensitivity [37–39]. These techniques, combined with serological testing, can be used in any phase of the disease [38]. Still, no standardized diagnosis for brucellosis has been established [37]. In addition, PCR has been described as useful for testing samples of fluids other than blood [5]. To date, there are no reports of PCR used to test ocular fluids.

Complications of ocular brucellosis can occur [23]. We found a high proportion of cataracts, followed by vitreal alterations, phthisis bulbi, maculopathies, glaucoma, neovascular retinal membrane (figure 2), tractional retinal detachment (figure 3), and other less frequent complications. In other reports, cata-
racts, glaucoma, and maculopathies have been described as being the most frequent complications of uveitis [40]. Recent studies have demonstrated that these 3 complications are the main causes of different levels of visual loss [40]. Therefore, early diagnosis of ocular manifestations of brucellosis has to be emphasized. In our study, only 16 patients did not develop complications. This stresses the importance of an ophthalmologic evaluation in patients with ocular brucellosis.

With regard to the visual prognosis of uveitis, we found worse acuity in patients with cases of panuveitis and posterior uveitis. Rolando et al. [23] reported that panuveitis cases were associated with a poor prognosis, compared with cases of anterior uveitis, which had a better prognosis. In our series, 13 of 52 patients lost vision, which emphasizes the importance of brucellosis as a cause of blindness in areas of endemcity [33].

This prospective study has some limitations. The study design did not allow for follow-up of all patients; only those patients with ocular involvement had ophthalmic follow-up. Patients who may have later developed ocular involvement may have been missed. In addition, it is possible that many cases of ocular brucellosis might not have been included as a result of not complying with the inclusion criteria. These cases mainly occurred in patients with ocular involvement and associated low agglutination titers (≤1:80).

We can conclude from this study that the most frequent manifestation of ocular brucellosis is uveitis, with posterior uveitis being the most frequent type of uveitis. Ocular damage occurs mainly in the chronic phase of the disease, and brucellosis with ocular involvement is infrequent in children. We found that 1 (0.003%) of every 300 children with a diagnosis of systemic brucellosis had ocular involvement. Children rarely develop the chronic form of the disease.

In conclusion, brucellosis, like tuberculosis, is a clinical condition that may present in any clinical form. There are no key diagnostic features that may suggest ocular compromise caused by brucellosis. Thus, complications of ocular brucellosis must be considered in an area of endemcity, with brucellosis in the differential diagnosis for patients with infectious uveitis. Every patient with a diagnosis of systemic brucellosis should undergo a routine ophthalmologic evaluation, particularly in an area of endemcity, such as Peru. This could reduce the possibility of blindness associated with brucellosis.

Acknowledgments

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Potential conflicts of interests. All authors: no conflicts.

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