

## Review Article

# Ocular Brucellosis: A Brief Update

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### Abstract

Brucellosis is a zoonotic disease of important health significance in endemic areas such as Iran. Brucellosis can affect any organ or system in the human body. Ocular involvement is rare and can lead to poor visual prognosis if not treated early. The most common ocular manifestation of brucellosis is uveitis, although any ocular structure can be involved. The diagnosis of ocular brucellosis is based on clinical examination as well as culture and serological tests. The classical treatment regimen includes doxycycline and rifampin. Early diagnosis and prompt treatment are effective in preventing blindness. Here we briefly review the manifestations, diagnostic tools, and treatment of ocular brucellosis.

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## Introduction

Brucellosis, also known as undulant fever, Malta fever, and Mediterranean fever, is a zoonotic infection which is prevalent worldwide. Brucellosis is mainly transmitted from cattle, sheep, goat, pig and camel either by direct contact with body fluids of infected animals (blood, placenta, fetuses or uterine secretions), or through ingesting of contaminated raw animal products, such as unpasteurized milk and soft cheese<sup>1,2</sup>. Although brucellosis is nearly eradicated in developed countries due to widespread livestock vaccination and safe food handling procedures; the disease is still endemic in the Mediterranean region as a major public health concern<sup>1,2</sup>. In patients with brucellosis any organ or system can be involved<sup>2</sup>. The symptoms of brucellosis are nonspecific with most patients complaining of fever, sweats, malaise, headache, arthralgia, and backache<sup>1</sup>. Ocular involvement is rare and is usually a complication of chronic brucellosis<sup>3-5</sup>. The most common ocular manifestation in brucellosis is uveitis; while other findings include keratoconjunctivitis, keratitis, iridocyclitis, choroiditis, optic neuritis, papilledema, and endophthalmitis<sup>4</sup>. Despite treatment, ocular brucellosis might cause severe complications and lead to blindness<sup>4</sup>. In this manuscript, we present a brief update on ocular brucellosis, its manifestations, diagnosis, and treatment methods.

## Bacteriology

Brucella species are small, aerobic, Gram-negative coccobacillary, nonmotile, not spore-forming microorganisms<sup>1</sup>. Four species have been recognized as causing infection in humans: brucella melitensis (transferred from goat, sheep, and camel), brucella abortus (transferred from cattle), brucella suis

(transferred from swine) and brucella canis (transferred from dogs)<sup>1</sup>. Brucella melitensis is the most common virulent species (70 % of cases). Brucella species grow relatively slowly and require 7-21 days to appear using the classic biphasic blood cultures<sup>1</sup>. Lysis centrifugation can detect organisms more quickly with higher sensitivity<sup>1</sup>. Growth is best seen on trypticase soy agar, brucella agar or serum dextrose agar at 37 °C. Brucella abortus and brucella suis require supplementary CO<sub>2</sub> for growth. The incubation period is highly variable, usually between 1 and 5 weeks<sup>1</sup>.

## Epidemiology

The true incidence of brucellosis is unknown because most cases remain undiagnosed. The World Health Organization (WHO) have stated that more than 500,000 new brucellosis cases are reported worldwide annually<sup>1,2</sup>. Brucellosis is still endemic in the Middle East countries including Iran, the Mediterranean region, Mexico, Central and South America<sup>3-5</sup>. Brucella melitensis is the most common virulent species in endemic countries and brucella abortus is mostly reported in Europe and North America<sup>3-6</sup>. Ocular involvement is relatively rare and is reported in 3 % - 26 % of cases<sup>3-6</sup>.

## Diagnosis

The diagnosis of ophthalmic brucellosis might be made clinically through eye examination. Ocular brucellosis is suspected when eye manifestations are present in a patient with fever, sweating, history of animal contact in endemic areas and consumption of unpasteurized dairy products. Ocular brucellosis may be misdiagnosed for years. Slit lamp biomicroscopic examination will reveal the extent of eye involvement while Brucella blood culture will confirm the

diagnosis of active systemic brucellosis. Culture of aqueous and vitreous samples may grow brucella and the brucella agglutinin titer may be raised. Serologic techniques such as Rose Bengal Plate Test (RBPT) and serum agglutination test (SAT) are the most widely used serologic tests<sup>7</sup>. Polymerase chain reaction (PCR) methods are also effective in detection of brucellosis<sup>8</sup>. The Goldmann-Witmer coefficient, which is the immune load ratio of intraocular to serum IgG production against the brucella organism, can help in the diagnosis<sup>9-11</sup>. B-scan ultrasonography, orbital CT scan and MRI might detect any abnormalities in the vitreous, choroid, uvea, sclera, retina, optic nerve and III, IV and VI cranial nerves.

### Clinical Manifestations

The clinical presentations of brucellosis include fever, night sweats and joint manifestations; though it can be asymptomatic. Rarely, multisystem disease with hepatic, cardiac, ocular, or central nervous system involvement can be encountered<sup>1</sup>. Unfortunately, since there is no pathognomonic sign of ocular brucellosis, most cases remain undiagnosed in endemic countries<sup>12</sup>. Considering the poor prognosis of undiagnosed ocular brucellosis, a high degree of clinical suspicion is of high importance, especially in endemic areas. Ocular involvement in brucellosis can occur both in the acute and chronic phase<sup>4</sup>. However, as Green<sup>13</sup> reported in 1938, most ocular manifestations of brucellosis occur in the chronic phase. Although any ocular structure might be involved in ocular brucellosis, the most frequent ophthalmic manifestation is uveitis<sup>5,12,14,15</sup>. Studies have reported uveitis manifestation in 21% - 67% of patients with ocular brucellosis<sup>5,9,14</sup>. Although the most

frequent reported type of uveitis is posterior uveitis<sup>4</sup>, any type can be seen<sup>16</sup>. Patients with panuveitis will have the worst visual outcomes<sup>4,16</sup>. The clinical findings of ocular brucellosis include conjunctival injection, decreased vision, eye pain, tearing, foreign body sensation, diplopia, cotton wool spots, exudative retinal detachment, and retinal hemorrhage<sup>4,11,17,18</sup>.

Rolando et al.,<sup>4</sup> reported a large series of 1551 Peruvian brucellosis patients from 1980 to 2006<sup>4</sup>. Fifty-two patients (3.3%) had ocular brucellosis. Uveitis was present in 82.7% of patients with posterior uveitis (40.3%) as the common form, followed by neuro-ophthalmic complications (13%), keratitis (5.8%), and conjunctivitis (3.8%)<sup>4</sup>. Most patients with eye manifestations had chronic brucellosis (86%) and 65% of patients were females. Bilateral ocular involvement was found in 20 patients (38.5%)<sup>4</sup>. The poorest prognosis was seen among patients with panuveitis sometimes leading to blindness or light perception<sup>4</sup>. Sungur et al.,<sup>5</sup> reported ocular manifestations of 132 patients with brucellosis from Turkey. Ocular involvement was detected in 21% of patients and anterior uveitis was the most frequent ocular manifestation (41%), followed by choroiditis (32%), panuveitis (9%), papilledema (9%), and retinal hemorrhages (9%). Fifty-nine percent of patients with ocular involvement were in the chronic stage of brucellosis<sup>5</sup>. In contrast to the literature, they found that the anterior uveitis manifestation was only seen in the acute stage, and all posterior segment manifestations were seen in the chronic stage of the brucellosis. Güngür et al.,<sup>3</sup> also, from Turkey, reported a cohort of 147 patients with brucellosis of which 38 (26%) had ocular manifestations. The most frequent ocular findings were conjunctivitis (68.4%), anterior uveitis (15.7%), episcleritis (7.8%),

dacryoadenitis (5.2 %), and posterior uveitis (2.63 %). Seventy-one percent of patients had chronic brucellosis<sup>3</sup>. Brucellosis might have atypical ocular manifestations. Recurrent episcleritis associated with brucellosis has been reported<sup>19,20</sup>. Sahin et al.,<sup>21</sup> reported a 28-year-old female with brucellosis presenting with bilateral papillitis, right abducent nerve palsy, and premacular hemorrhage. Andisheh et al.,<sup>22</sup> reported a case of sixth nerve palsy as an unusual presentation of neurobrucellosis in a young patient. Mete et al.,<sup>23</sup> reported a case of unilateral brucella dacryoadenitis. Oray et al.,<sup>24</sup> reported a young female with a 6-month history of visual loss in the left eye, presenting with dense vitreous haze, posterior hyaloid opacities, and retinochoroiditis. The vitreous sample demonstrated brucella melitensis growth and the patient was diagnosed with endogenous endophthalmitis leading to poor visual outcome<sup>24</sup>.

### Treatment

According to the World Health Organization (WHO) guidelines, the classical treatment of brucellosis in adults and children above 8 years is a combination of doxycycline (100 mg PO twice daily) and rifampin (600-900 mg/day PO) for 6 weeks<sup>25</sup>. Doxycycline for 6 weeks plus streptomycin (1g/day IM) for 2-3 weeks is believed to be more effective in preventing relapse<sup>15</sup>. Gentamicin can be used as a substitute for streptomycin with equal efficacy<sup>26</sup>. Ciprofloxacin can also replace doxycycline with similar efficacy<sup>25</sup>. A Cochrane meta-analysis found that doxycycline for 6 weeks plus streptomycin for 2-3 weeks was more effective than doxycycline plus rifampin for 6 weeks<sup>27</sup>. Tetracyclines are contraindicated in pregnant women and children below 8 years<sup>28,29</sup>. For

brucellosis in children younger than 8 years, rifampin and TMP-SMZ for 6 weeks is the current best therapy<sup>30</sup>. Also for brucellosis in pregnant women, the recommended therapy is rifampin, either alone or in combination with TMP-SMZ<sup>31</sup>. Note that TMP-SMZ might increase the risk of kernicterus at the end of pregnancy<sup>31</sup>.

Cavallaró et al.,<sup>32</sup> reported a case of bilateral papilledema in a child with brucellosis. The patient was treated with rifampin and minocycline with complete recovery. Abd Elrazak<sup>33</sup> successfully treated a 13-year-old child with bilateral brucella optic neuritis using tetracycline, streptomycin, and prednisolone. Sahin et al.,<sup>21</sup> reported a case of brucellosis complicated by papillitis, gaze palsy, endocarditis and premacular hemorrhage. The patient underwent surgical replacement of the aortic valve and was treated with rifampin 600 mg/day and doxycycline 200 mg/day for 6-month with resolution of her symptoms and restoration of vision<sup>21</sup>.

Most patients with ocular brucellosis respond well to the antibiotic treatment alone. However, additional surgical treatments such as abscess drainage, cataract extraction and vitrectomy may be necessary. Brucellosis complicated by panophthalmitis is difficult to treat and resistant to classic antibiotic regimens and may require ocular enucleation, while optic neuritis and ophthalmoparesis due to neurobrucellosis usually respond well to antibiotics alone.

### Conclusion

Ophthalmic manifestation of brucellosis is a rare entity but should be investigated in all patients with brucellosis, especially in endemic areas. Uveitis is the most common presentation and most cases of ocular involvement present in the chronic phase of brucellosis.

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### Footnotes and Financial Disclosures

#### Conflict of interest:

The authors have no conflict of interest with the subject matter of the present study.