Chapter 5

Ocular Manifestations of Brucellosis

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Abstract

Brucellosis is considered a zoonotic disease which is still an important health problem in endemic areas such as the Middle East, the Mediterranean, and Asia. Brucellosis is a systemic infection that might affect any organ or system in the body. Ocular involvement has been reported in 21% of brucellosis patients. The most common ocular manifestations of brucellosis were considered as anterior uveitis and choroiditis. The patients with anterior uveitis were reported to be usually in the acute stage and the patients with choroiditis, papilledema, and posterior uveitis were reported to be usually in the chronic stage of the disease. Ocular manifestations of brucellosis might also involve dacryoadenitis, conjunctivitis, episcleritis, scleritis, nummular keratitis, cataract, glaucoma, exudative retinal detachment, maculopathy, and neuro-ophthalmic defects including papilledema, papillitis, and cranial nerve paresis. Optic nerve involvement in brucellosis is considered secondary to meningeal inflammation, and it usually involves both optic nerves. Premacular hemorrhage related to *Brucella* endocarditis was reported as a rare ocular manifestation. Since ocular brucellosis has a wide spectrum of clinical manifestations, the diagnosis is considered to be mainly dependent on positive bacteriological and serological tests. Agglutinations and/or culture has been widely used for diagnosis of brucellosis. *Brucella* agglutination test over 1/160 titer and positive blood culture are considered as diagnostic factors for brucellosis. Early diagnosis and prompt treatment are considered to be effective for preventing blindness from severe ocular damage. Systemic antibiotics including streptomycine, rifampicin, doxycycline along with topical or systemic corticosteroid treatment have been recommended for at least 2 months. The purpose of this chapter is to describe the ocular manifestations of brucellosis, early diagnostic procedures, and treatment with reviewing the literature.

Keywords: brucella, uveitis, optic neuritis, preretinal hemorrhage

1. Introduction

Brucellosis is considered a common zoonotic disease that has been reported to cause more than 500,000 new human cases worldwide annually [1,2]. It is still more prevalent in some parts of

the world, especially Middle East countries including Iran, Saudi Arabia, Kuwait, Turkey, the Mediterranean, Mexico, and Central and South America [3-6]. *Brucella melitensis* has been reported as the most common and virulent species in endemic countries [7]. *B. abortus* has been seen mostly in Europe and North America [7]. *B. canis* causes canine brucellosis with intraocular inflammation, and *B.* suis infects domestic pigs [7].

2. Ocular manifestations

Brucellosis has unusual clinical manifestations, and the clinical presentation might vary from asymptomatic infection to a full-blown clinical picture of fever, night sweats, and joint manifestations; rarely, there is hepatic, cardiac, ocular, or central nervous system involvement [8]. Since there is no pathognomonic sign of ocular involvement caused by brucellosis, it remains poorly recognized in areas where brucellosis is endemic [9]. In a large series including 1551 patients with brucellosis from Peru during a period of 26 years, 52 (3.3%) patients have been diagnosed with ocular brucellosis [10]. Both acute and chronic brucellosis have been reported to cause ocular involvement [10]. All the ocular structures might be affected by brucellosis [9,11]. However, the most frequent ocular presentation has been reported as uveitis [12,13]. Uveitis has been reported between 21 and 67% of patients with ocular brucellosis in the previous studies [12-14]. The following presentations of uveitis might be identified: anterior uveitis, including iritis, and iridocyclitis; intermediate uveitis, including pars planitis and vitritis; posterior uveitis, including choroiditis, chorioretinitis, retinitis, and neuroretinitis; and panuveitis, including inflammation of all 3 components of the uveal tract [11-15]. The most frequent presentation of uveitis in ocular brucellosis has been considered as posterior uveitis [16]. Patients with panuveitis had the worst visual prognosis [16,17]. In a case series, 8 of 9 patients with panuveitis were legally blind, including 5 patients with no light perception [17]. In a cohort study from Turkey including 132 patients with brucellosis, anterior uveitis was the most frequent manifestation with a frequency of 41%, followed by choroiditis (32%), panuveitis (9%), papilledema (9%), and retinal hemorrhages (9%) [12]. 41% of the patients with ocular involvement were found in the acute stage and 59% were in the chronic stage of brucellosis [12]. In this study, all the patients with anterior uveitis were reported to be in the acute stage, and all the other patients with choroiditis, papilledema, and retinal hemorrhages were reported to be in the chronic stage of the disease. [12] In another cohort study from Turkey including 147 patients with the diagnosis of brucellosis, 38 patients (26.0%) had ocular manifestations including conjunctivitis in 26 (17.7%), anterior uveitis in 6 (4.1%), posterior uveitis in 1 (0.7%), dacryoadenitis in 2 (1.4%), and episcleritis in 3 (2.1%) of patients [18]. Brucellosis might have unusual ocular manifestations [17,19,20] such as: recurrent episcleritis associated with brucellosis has been reported as a rare occurrence from Turkey and France [19,20]. A rare presentation of brucellosis has also been reported as bilateral optic nerve, right abducent nerve involvement, and endocarditis complicated by right premacular hemorrhage in a 28-year-old white female from Turkey [21]. Bilateral multifocal choroiditis with serous retinal detachment in a patient with *Brucella* infection has been reported from USA considering

Vogt-Koyanagi-Harada (VKH) syndrome, which is characterized by bilateral panuveitis associated with bilateral retinal detachments spontaneously resolving, as differential diagnosis [17].

3. Pathogenesis and diagnosis

The infection was rapidly controlled at the site of inoculation but resulted in a local and systemic dissemination of *Brucella* mainly in the pharyngeal tonsil, local and peripheral lymph nodes, and the spleen [24]. The control of the infection is considered to be associated with the induction of a specific immune response characterized by an increase in IgG producing B-cells, the production of IFN- gamma, and IL-10 by cells from draining parotid, retropharyngeal, and submaxillary lymph nodes, but also from more distant peripheral lymph nodes.[24] IFN-gamma is produced by CD4+, CD8+, and CD4(-)CD8(-) gamma delta(-) cells, and probably contributed to the control of both local and systemic infection [25]. Human brucellosis is diagnosed by clinical criteria, isolation of the causative agent from blood or tissue cultures with a positivity rate of 40-70%, or by using serologic techniques as complementary tools. Rose Bengal Plate Test (RBPT) and serum agglutination test (SAT) are the most widely used serologic tests [26]. The sensitivity of RBPT is considered high, but its specificity is low for testing individuals residing in an endemic area [26]. SAT is used to confirm RBPT results. It has limitations of lack of sensitivity as well as specificity [27-29]. Recently, molecular biology diagnostic techniques have been developed, intending to optimize the etiological confirmation [30]. Polymerase chain reaction (PCR) amplification-based methods are being used effectively in the detection of brucellosis [31]. They are considered safer than culture-based methods for the staff [31]. Intraocular serological tests are used to support the diagnosis of ocular brucellosis [14,32]. The Goldmann-Witmer coefficient, which is the ratio of intraocular to serum IgG production against the *Brucella* organism, is usually determined by analyzing the serum and intraocular fluid agglutinations for *Brucella* [14,33,34]. The diagnosis is usually confirmed with a high *Brucella* agglutination titer in the vitreous specimen [33]. The sensitivity of the Goldmann-Witmer analysis has been reported as 66.7% and the specificity was 100% [14].

4. Differential diagnosis

Ocular involvement of brucellosis should be differentially diagnosed from tuberculosis, syphilis, toxoplasmosis, toxocariasis, sarcoidosis, behcet's disease, Vogt-Koyanagi-Harada syndrome, and multifocal choroiditis [16,17,32]. No pathognomonic sign of ocular involvement of brucellosis has been reported. However, acute form of brucellosis is usually presented as fever, headache, sweating, lower back pain, and organomegaly [9]. Ocular involvement in acute form has been reported usually in the form of bilateral acute anterior uveitis, which might be associated with episcleritis and scleritis [10]. Posterior uveitis followed by panuveitis associated with papillitis and retinal hemorrhages were considered the most common ocular manifestations of chronic brucellosis [10]. Neuro-ophthalmologic signs, including the cranial

nerves involved in ocular movements, were also reported to be more common in chronic brucellosis [34].

5. Complications

Ocular brucellosis might lead to blindness from severe ocular damage in patients having late diagnosis and improper treatment. The following complications have been reported: cataracts, glaucoma, maculopathy, vitreal alterations, phthisis bulbi, optic atrophy, neovascular retinal membrane, and tractional retinal detachment [18,32].

6. Treatment

Ophthalmic manifestations of brucellosis are usually treated with both antibiotics and steroids [35]. Cavallarro et al. reported a patient with papilledema due to brucellosis that was treated with sole anti-brucellosis treatment without steroid administration [36]. Abd Elrazak reported a case of bilateral optic neuritis caused by brucellosis that resolved following anti-brucellosis and steroid administration [37]. Sahin et al. reported the resolution of unilatreral papillitis and premacular hemorrhage with antibiotics and intravenous high-dose steroid followed by oral steroid administration for 3 months [21]. The tetracyclines remain the most active and clinically effective antibiotics for the treatment of brucellosis [38]. Doxycycline is now the preferred tetracycline analogue for treating human brucellosis [38]. The use of tetracyclines as monotherapy for human brucellosis is complicated by a relapse rate between 8 and 39% [38]. The high relapse rates are dramatically reduced when doxycycline is combined with other drugs, such as streptomycin (relapse rate 4.5%) or rifampicin (relapse rate 8.4%) [38]. Streptomycin in combination with tetracycline or doxycycline has been the "gold standard" for comparison of other antibiotic regimens for the treatment of human brucellosis [38]. A major drawback to the use of tetracyclines is the permanent staining of teeth in young children [39]. Consequently, tetracyclines are contraindicated for brucellosis in pregnant women and children under 8 years of age [39,40]. In this regard, doxycycline binds less to calcium than do other tetracyclines and may cause dental complications less frequently [41]. Cotrimoxazole is a useful alternative in the treatment of brucellosis when the use of tetracyclines is contraindicated [42,43]. Although, rifampin has been used as monotherapy in brucellosis relapses, and the emergence of rifampin-resistant strains have led to its use primarily in combination with other drugs [38]. Results have been generally disappointing in monotherapy with quinolones, which were used to treat human brucellosis [38]. In a study from Turkey, 21 patients received ofloxacin (200 mg twice daily) for varying periods of time; the relapse rate was 16% [44]. In contrast, a group of patients in Israel treated with ciprofloxacin (750 or 1000 mg twice daily) for 6 weeks had a relapse rate of 66% [45]. Similarly, another study from Turkey reported 12 patients treated with ciprofloxacin (500 mg thrice daily) for 3 to 6 weeks, with a relapse rate of 21% [46]. Consequently, monotherapy of brucellosis with quinolones is not recommended, and they should be used in combination with other antimicrobials [38, 47]. The combination of doxycycline for 6 weeks

plus streptomycin for 2 to 3 weeks remains the most frequently used and most effective treatment for human brucellosis [47]. Most authorities consider that gentamicin (5 mg/kg/day) intravenously or intramuscularly as a single injection can be used in place of streptomycin; however, the duration of gentamicin administration is unclear [48]. Although 5- and 7- day regimens of gentamicin have been used, we advise no fewer than 10 days [48]. In summary, many clinicians prefer to administer rifampin (600-900 mg/day orally) for the remainder of the 6 weeks after discontinuing gentamicin, but this regimen has not been studied in comparative trials. The second-choice regimen consists of doxycycline (200 mg/day orally) plus rifampin (600-900 mg/day orally), with both drugs administered for 45 days.

7. Conclusions

Ocular involvement in acute or chronic brucellosis is still prevalent in endemic countries. A wide range of ocular manifestations have been described for brucellosis. However, uveitis and neuro-ophthalmic manifestations are the most common presentations. Diagnosis of ocular brucellosis mainly depends on culture and serology of blood and intraocular fluids. Early diagnosis and prompt treatment might restore the vision in ocular involvement.

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