

Brucella Endocarditis

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Brucella endocarditis is a rare, and life threatening complication of human brucellosis. Children are usually infected by consumption of contaminated dairy product. Clinical presentation is similar to rheumatic fever. Aortic valve is most commonly involved. Clinical manifestations of fever, arthritis/arthritis, aortic insufficiency, echocardiographic evidence of vegetation, and negative findings of blood culture, in a case with suspicious contact should suggest the diagnosis. Perioperative antibiotics combined with surgical treatment are an effective management. In pediatric age group, surgical techniques using biologic valves and preservation of native valves are preferred.

Keywords: Aortic Valve Insufficiency; Brucellosis; Endocarditis; Therapeutics; General Surgery

1. Introduction

Brucellosis is a common public-health problem. Human beings are incidental hosts and acquire the disease by direct contact with infected animals or consumption of their products, particularly unpasteurized dairy productions. *Brucella* is a fastidious, intracellular gram-negative coccobacillus. Brucellosis is an endemic disease in Mediterranean area, Persian Gulf borders, India, and South or Central America countries. Infants and children are affected by ingestion of unpasteurized raw milk. Brucellosis is a systemic disease, and diagnosis may be difficult in the absence of contact-history with infected animal or contaminated food. The common presentation is fever of unknown origin, and symptoms usually begin 2-4 weeks after the inoculation. Isolation of organism from blood culture may require 4 weeks of incubation. It is important to inform the microbiology laboratory that infection with *Brucella* is suspected (1).

Infective endocarditis is a microbial infection of heart endocardium. Native and mechanical cardiac valves are the most common sites of involvement. In all age groups those with structural heart disease are usually affected. Endocarditis can involve septal defects, intracardiac surgical patches, surgical and nonsurgical intracardiac shunts. Neonatal endocarditis most often occurs in the normal heart. Other reasons include: surgical or nonsurgical cardiovascular interventions, increased use of intracardiac prosthetic devices, and prolonged insertion of central venous catheter.

A limited number of pathogens are responsible for most cases with endocarditis. Gram positive cocci account for

over 90% of bacteria, of which *Streptococcus viridans* and *Staphylococcus aureus* are the most common. Studies indicate that these two microorganisms have a special propensity for adherence to the heart valves of humans and canine animals. In contrast, gram negative bacteria have poor adherence to this system and are isolated in less than 10% of patients with endocarditis: these include: *Enterococci*, *Pseudomonas*, *Neisseria*, and *Haemophilus* species (2).

Brucella endocarditis is a rare complication of *Brucella* systemic disease. The aim of this article is to discuss the various aspects of this combined disease.

2. Discussion

Endocarditis is a rare complication of brucellosis; it develops in 1-2% of patients. This complication is responsible for 80% of mortality rate in brucellosis (3, 4). In a research by Keshtkar et al. all the English, and French articles about "*Brucella*", "endocarditis", and "*Brucella* endocarditis" in PubMed, Google, and SCOPUS search engines were reviewed from January 1966 to July 2011. They found 121 articles with 308 cases of brucella endocarditis. Turkey and Iran had reported most of the cases (41.9%, 10.1% respectively), and 95 % of cases were from the Middle East or Mediterranean countries. Diagnosis was confirmed with culture or serology tests and in one patient with PCR (polymerase chain reaction), 82.5% of patients were infected with *Brucella melitensis*, and 14% with *Brucella abortus*. The age of patients ranged from 5 to 77 years with a mean of 41 years, and 75.3% were male. Predisposing cardiac condition was evaluated in 233 patients. No underly-

Implication for health policy/practice/research/medical education:

Brucellosis is a common infection in Iran, and brucella endocarditis is a fatal cardiac involvement. Recognizing this life threatening complication is useful for pediatricians.

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ing condition was found in 32.6%, followed by prosthetic valve involvement in 21.0%, and rheumatic heart disease in 15.5%. Aorta was the most commonly involved valve and usually needed emergency replacement with a mechanical valve. Surgery improved outcome by decreasing mortality from 32.7% in patients who received only medical therapy to 6.7% in those who received combination of medical and surgical treatment ($P < 0.001$) (5). Mitral valve is less frequently involved. Brucella endocarditis can affect either native or prosthetic valves. Diagnosis needs a high index of suspicion in culture negative endocarditis especially in patients with close contact with farm animals. A culture with positive results in a susceptible patient confirms the diagnosis with 91% sensitivity. Early diagnosis and prompt treatment with appropriate antibiotics can return the integrity of valve's structure with minimal damage (6). Other cardiovascular complications of brucellosis such as myocarditis, and pericarditis are rare especially in the absence of endocarditis. In endemic area it is important to consider brucellosis in differential diagnosis of disorders which affect pericardium or myocardium even in the absence of concomitant endocarditis (7). Gastelis et al. conducted a search in the Medline database for articles published between 1984 and 2010 using the words "pericarditis", "myocarditis", and "brucellosis". They found only 11 reports including 14 adult patients in English literature. These 14 patients had pericarditis or myocarditis in the absence of simultaneous involvement of endocardium. In recent data of more than 200 cases of brucellosis, pericarditis or myocarditis was not reported (7). In a study from Spain (Malaga), 1.5% of 530 patients with Brucella had cardiac involvement. There was one case with pericarditis and one case with myocarditis, and both of these involvements were without endocarditis (8). In a report of 400 cases of brucellosis from Kuwait, there were 2 cases with endocarditis and six with other cardiac involvement including one patient with myocarditis (9).

Brucella endocarditis is due to direct invasion of organism to the endocardium. Valvular injuries include micro abscesses within the cusps, destruction of commissures, rupture of chordae, myocardial abscess, and calcified nodular deformation. Brucella endocarditis is a destructive process with high tendency to tissue ulceration, leading to severe injury of valves, and large vegetations which are difficult to treat with medical therapy alone. This destructive process has a tendency for fibrosis, hyalinization and calcification (5). Jeroudi et al. from Saudi Arabia reported 4 adult patients with normal hearts who developed severe aortic regurgitation after infection with *Brucella*, and in one of them mitral valve was also affected. Medical treatment did not cure the patients and all needed valve replacement. At operation all patients had aortic valve vegetation and combination of severe destruction of valves structures. Three patients had cusp

perforation, 2 detached leaflets, and one aortic root abscess. The patient with mitral valve involvement had tearing of the anterior leaflet and ruptured chordae tendineae. Three months after the operation, all the patients showed significant drop in anti-brucella antibody titers. Medical therapy continued until 6 months after the operation (10). The aortic valve was affected in 75-85% of cases, and the incidence of endocarditis associated with cardiac abscesses was 20.5% (5, 10). There are 4 species of Brucella which are pathogenic for humans including; *melitensis*, *abortus*, *canis*, and *suis*. The low incidence of Brucella endocarditis in western countries is not surprising because most cases are due to *Brucella abortus*. This species accounts for mild disease with very few severe complications. *Brucella melitensis* in eastern societies is responsible for severe suppurative and disabling complications (10). There are several reasons for low incidence of positive blood culture in Brucella endocarditis such as intracellular location and fastidious nature of organism, previous treatment with antibiotics, and long duration between beginnings of symptoms and the diagnosis (10). The intracellular location of the organism makes it unavailable for antibiotics.

Reports indicate that most cases of Brucella endocarditis in adults had a fulminant course ended with aortic valve replacement by surgery. It seems that cardiac involvement in pediatric brucellosis does not follow the fulminant course of adult patients. In a survey by Lubani et al. from Kuwait, 5 children aged 6 to 11 years with cardiac involvement were found among 300 pediatric patients with brucellosis. This gives an incidence of 1.7% for this complication in the pediatric age group. Echocardiography revealed mitral valve vegetation in one patient, functional mitral valve incompetence in two, decreased myocardial performance in two, and decreased myocardial performance accompanied with prolonged PR interval in one (11). Electrocardiographic changes in *Brucella carditis* usually include conduction pathway and result in prolonged PR interval. In the Lubani's study 3 patients had myocarditis and two had mitral valve involvement. Asymptomatic pericardial effusion can be detected by echocardiography and underscores the importance of echocardiography for evaluation of heart implications in brucellosis. Other evidences for cardiac involvement can be found in routine tests such as chest radiography and electrocardiography. Differential diagnosis of Brucella from acute rheumatic fever is difficult, especially when heart involvement is concerned (11, 12). Both diseases present with fever, and arthralgia/arthritis as well as high sedimentation rate. Findings like leukocytosis and increased anti streptolysin O titer in ARF would help to distinguish ARF from brucellosis with leukopenia and increased anti-brucella antibody titers (11, 12).

Severe injury of native valves due to rheumatic heart disease usually results in valve replacement with pros-

thetic valves, and these mechanical valves can be infected with *Brucella* species. An episode of rheumatic fever during childhood followed by rheumatic heart disease can be considered a predisposing factor (12). Approximately 50% of patients with *Brucella* endocarditis have underlying valvular diseases (3). Both biologic and mechanical valves have been affected frequently. In endemic area such as Saudi Arabia 10% of prosthetic valves endocarditis are due to *Brucella*, and vegetations usually appear like a bulky mass. All reports recommended a combination of antimicrobial agents and replacement of the prosthetic valve (13, 14). Valve replacement in acute phase of infection may lead to paravalvular leakage. *Brucella* may be detected in culture of the infected valve even after 8 weeks of adequate treatment (15). Presence of bacteremia after adequate antimicrobial treatment in patients with prosthetic valves infected with *Brucella*, should awaken suspicions of endocarditis (16). Growing up in children with implanted prosthetic valve results in malfunction and stenosis of valve, which may need reoperation for valve replacement. Another problem is the paucity of appropriate-size mechanical valve for this age group of patients. For this reason biologic valves are preferred for children. Kazuz et al. from Turkey (2005) reported a 10-year-old girl with normal heart who was affected with *brucella* endocarditis. Echocardiography revealed mitral regurgitation with 3 mobile vegetations on the valve surface. On the 4th day of treatment the patient experienced loss of consciousness. Brain magnetic resonance angiography showed acute ischemic infarct in the right parietal region. The patient underwent surgery. Resection of vegetations combined with annuloplasty with a biologic ring and preservation of the rest of native valve was performed. Medical therapy continued for 10 weeks after the operation until normalization of Wright agglutination titer (17). Another report from Turkey presented a child who required aortic valve replacement after *brucella* endocarditis (18).

Even with appropriate treatment the incidence of relapse is high and ranges from 5% to 40 % (19, 20). Obrenovic-Kirenski et al. from Serbia (2012) reported an adult case of mitral valve endocarditis during *brucellosis* relapse. Mitral valve involvement was complicated by perforation of anterior leaflet of mitral, severe mitral insufficiency, and pulmonary hypertension. The patient improved by mitral valve replacement accompanied with a 6-month postoperative medical therapy. Prior to this report, no cardiovascular involvement during the relapse episode had been described in a study reported the largest series of patients with *brucellosis* (21). Infection of tricuspid valve in *brucella* endocarditis is extremely rare. Yazici hu et al. (2012) presented a female patient with fever, fatigue, and severe right heart failure. Echocardiography showed large vegetation on the tricuspid valve. Blood culture had negative results and the titer of anti

brucella antibody was 1/640. The patient recovered on an eight-week medical therapy (22).

Brucella antigen is capable of affecting the endothelial cells of vascular system. This infection produces a potent inflammatory response. The inflammatory response and the reaction of host immune system are suggested as the basis for vascular involvement. Activation of endothelial cells in response to infection accompanied by upregulation of adherent molecules and secretion of proinflammatory chemokines may play an important role in vascular damage. Vascular complications are quite rare and include; arterial aneurysm formation in different vessels, peripheral arteritis, arterial thrombosis, cutaneous vasculitis, deep venous thrombosis, and cerebral vein thrombosis (23). Colomba et al. from Italy (2012) presented a man with *brucella* endocarditis and manifestations of aortic valve regurgitation as well as subclavian artery thrombosis. Wright agglutination test had positive results, and *Brucella melitensis* was isolated from blood culture. The aortic valve was replaced with prosthesis by surgery. Medical treatment was administered for 45 days and heparin was given for 10 days (24). McKee et al. from the USA reported a 15-year-old boy infected with *Brucella canis* after scratch by domestic dog. Echocardiography and cardiac catheterization demonstrated severe aortic regurgitation. Ultra sound examination revealed bilateral aneurysms of the tibioperoneal arteries. Aortic valve was repaired by the Ross procedure and aneurysms were excluded by surgery. Vascular continuity was restored by saphenous vein graft. There was no previous case report of peripheral mycotic aneurysms in children (25).

Treatment of choice in *brucella* endocarditis is combined medical and surgical therapy. Kose et al. from Turkey (2012) reported an adult woman with vegetation on mitral valve treated with medical therapy alone. To their knowledge only 16 cases have been reported in literatures treated with medical therapy alone. Medical treatment alone can be used for mild cardiac involvement and within a short duration of symptoms onset (26). The recommended treatment for bacterial endocarditis in pediatric age group is as follows: doxycycline (2-4 mg/kg/d) maximum 200 mg/d (PO for 4-6 months) plus gentamicin (3-5 mg/kg/d) IM or IV for 2 weeks \pm rifampicin (15-20 mg/kg/d: maximum 600-900 mg/d PO) for 4-6 months. Several factors are important for successful treatment including: antimicrobial agent with intracellular killing effect, long-term treatment, and compliance of patient for long-term therapy. Doxycyclines combined with aminoglycosides are the most effective drugs for treatment, and are associated with decline in the recurrence rate (1). There is no specific recommendation for duration of antimicrobial therapy. A combination of clinical, serologic and microbiologic findings helps physicians to decide about the duration of treatment. Normalization of anti-*brucella* antibody titer is recommended as the end point

of effective treatment. Periods of treatment reported by different authors vary from 2 to 13 months (26, 27). Indications for surgery are as follows: large vegetation, abscess formation, aneurysm, severe valvular insufficiency, malfunction of prosthetic valve, intractable heart failure, and multiple peripheral emboli (27, 28). Many authors recommended that specific antimicrobial therapy should be continued after the operation until complete clinical recovery occurred, and serum antibody titers and agglutination test reached the normal levels.

Conclusion: Endocarditis due to brucellosis is considered a rare incident involving native, and prosthetic valves. Prompt diagnosis combined with medical and surgical treatment is lifesaving.

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