Successful management of *Brucella mellitensis* endocarditis with combined medical and surgical approach

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Abstract

**Objectives:** *Brucella* endocarditis is an underdiagnosed complication of human brucellosis, associated with high morbidity and mortality. We report the successful management of a number of cases of *Brucella mellitensis* endocarditis. **Patients and methods:** Seven consecutive cases of *Brucella mellitensis* endocarditis were treated over the last 20 years, based on high suspicious of the disease at first place. The early suspicion of *Brucella* endocarditis relied on medical history and a standard tube agglutination titer $\geq 1:320$. Blood and/or cardiac tissue cultures were positive in all patients, but available late following surgery. All patients were successfully treated with a combination of aggressive medical and early surgical therapy. All affected valves were replaced within 1 week from admission (five aortic and three mitrals). Medical treatment included co-trimoxazole, tetracyclines and streptomycin, before surgery, followed by co-trimoxazole and tetracyclines for a median of 12 months (range: 3–15 months) after surgery until the titers returned to a level $\leq 1:160$. **Results:** There were neither operative deaths nor recurrence of infection. One patient died two years after the operation due to massive cerebrovascular accident. Ten-year survival was 85.7 ± 13.2%. **Conclusion:** Although *Brucella mellitensis* endocarditis is a rare entity, its optimum management should be a combination of aggressive medical treatment and early surgical intervention, based on high degree of suspicion in areas with high incidence of the disease. © 2001 Elsevier Science B.V. All rights reserved.

**Keywords:** *Brucella melitensis*; *Brucella* endocarditis; *Brucella* complications

1. Introduction

Brucellosis continues to be prevalent in Greece. In contrast to the other usual causes of infective endocarditis that a physician frequently faces and easily detects, brucellosis still constitutes a major diagnostic and therapeutic problem. The diagnostic difficulties mainly lie in the need of epidemiological consideration for the suspicion of *Brucella*, due to the complexity of laboratory methods to identify the pathogen. Doctors may not suspect *Brucella* species, unless there is a history of occupational contact with an infected animal or of ingestion of infected milk, milk products, or tissues. The reported serious complications and high mortality associated with this clinical condition signifies the need for early diagnosis and treatment [1].

We report the timely and successful management of seven cases of *Brucella mellitensis* infective endocarditis with combined medical and surgical treatment.

2. Patients and methods

From January 1978 through January 1998, seven cases of *Brucella* endocarditis were diagnosed among 175 cases of endocarditis caused by various organisms. The suspicion of *Brucella* endocarditis was raised in patients reporting untreated milk and milk product ingestion from goat or cattle or skin contact with tissues and secretions of these animals. Standard tube *Brucella* agglutination test (Laboratory Diagnostics Company, INC, Morganville, N.J.) titer more than 1:160 in two consecutive samples drawn 1 week apart strengthened the suspicion for recent exposure to *Brucella*. Blood cultures and resected native valves during surgery were incubated in biphasic trypticase soy broth and agar medium (Ruiz–Castaneda medium) for 4 weeks. M-mode, cross sectional and Doppler echocardiography was preoperatively performed on all patients. The indication for valve replacement in *Brucella* endocarditis,
common between the involved departments, was the presence of a *Brucella* titer greater than 1 to 320 in the face of valvular dysfunction with or without vegetations. Patients’ follow-up included Standard tube *Brucella* agglutination test (STA) titers and blood cultures every 3 months over a period of 1 year and transthoracic echocardiograms every 2–3 months over 2 years.

The demographic characteristics, as well as the clinical, laboratory and operative findings are summarized in Table 1. All patients reported recent exposure to non-pasteurized goat milk or contact with sheep. Median duration of symptoms and signs before admission was 4 weeks (range: 4–7 weeks). On admission all patients were febrile with oral temperature greater than 38°C, dyspnoic and anemic (median hemoglobin 11 mg/dl, range: 10.4–13 mg/dl). Six patients had murmurs from the affected valves, apart from a 53-year-old female patient (patient 5) with aortic valve *Brucella* endocarditis. In the latter, the suspicion of endocarditis was raised due to dyspnea at rest and signs of congestive heart failure, and the diagnosis was confirmed by echocardiography. Two patients (2/7, 28%, patients 3 and 4) had a history compatible with rheumatic fever in childhood. Six patients (6/7, 86%) had signs of congestive heart failure, with prominent elevation of jugular vein pressure and hepatomegaly. Median white cell count was 4000/mm$^3$ (range: 2100–7700/mm$^3$) and erythrocyte sedimentation rate 74 mm/h (range: 47–91 mm/h). Electrocardiographic findings included left ventricular hypertrophy in two patients (2/7, 28%, patients 3 and 4) and biventricular hypertrophy in one patient (1/7, 14%, patient 7). Chest X-rays revealed cardiomegaly in five patients (5/7, 71%, patients 3, 4, 5, 6, 7) and bilateral pleural effusion in 1 patient (1/7, 14%, patient 5). All patients had significant valvular disease on echocardiogram (Table 1). Standard tube *Brucella* agglutination titers were elevated in all patients. Blood cultures obtained before the operation and/or cardiac tissue cultures obtained in the operation confirmed the diagnosis of *Brucella mellitensis* in all patients.

After admission and rise of the serologic suspicion of *Brucella* endocarditis all patients were started on an intravenous combination of co-trimoxazole, tetracyclines and streptomycin. The first four patients treated before 1988 received co-trimoxazole 960 mg twice daily IV, tetracycline 750 mg three times daily IV and streptomycin 16 mg/kg/day IM. The last three patients treated after 1988 received co-trimoxazole 960 mg twice daily IV, doxycycline 200 mg twice daily IV and streptomycin 16 mg/kg/day IM. All patients were operated within 1 week from admission. Indications for operation included mere valve dysfunction in patient (patient 1/7, 14%, patient 1), valve dysfunction and progressive heart failure in two patients (2/7, 28%, patients 2 and 5) and a combination of valve dysfunction, progressive heart failure and presence of valve vegetations in the rest (4/7, 57%). Two patients (2/7, 28%, patients 5 and 6) were operated on an urgent basis due to severe heart failure, secondary to aortic valve destruction.

### Table 1

Demographic characteristics- Clinical, laboratory and operative findings

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/ gender</th>
<th>Year of diagnosis</th>
<th>Symptoms &amp; signs</th>
<th>NYHA</th>
<th>Duration symptoms (weeks)</th>
<th>Affected cardiac valve</th>
<th>Echo findings</th>
<th>Operative findings</th>
<th>STA on admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26/F</td>
<td>1978</td>
<td>Malaise, SOB, fever, diastolic murmur</td>
<td>II</td>
<td>6</td>
<td>Aortic</td>
<td>Aol (2–3/4)</td>
<td></td>
<td>1:1000</td>
</tr>
<tr>
<td>2</td>
<td>41/M</td>
<td>1979</td>
<td>SOB, fever, sinus tachycardia, elevated JVP, diastolic murmur</td>
<td>III</td>
<td>4</td>
<td>Aortic</td>
<td>Aol (3/4)</td>
<td></td>
<td>1:640</td>
</tr>
<tr>
<td>3</td>
<td>36/M</td>
<td>1985</td>
<td>SOB, fever, elevated JVP, hepatomegaly, diastolic murmur</td>
<td>IV</td>
<td>6</td>
<td>Mitral</td>
<td>MS and vegetations</td>
<td>Mitral valve vegetations</td>
<td>1:2400</td>
</tr>
<tr>
<td>4</td>
<td>62/M</td>
<td>1986</td>
<td>Malaise, weight loss, SOB, fever, elevated JVP, hepatomegaly, diastolic murmur</td>
<td>III</td>
<td>5</td>
<td>Mitral</td>
<td>MS and vegetations on both leaflets of mitral valve</td>
<td>Mitral valve vegetations</td>
<td>1:1400</td>
</tr>
<tr>
<td>5</td>
<td>53/F</td>
<td>1988</td>
<td>Weakness, SOB, fever, elevated JVP, hepatomegaly</td>
<td>IV</td>
<td>7</td>
<td>Aortic</td>
<td>Aol (4/4)</td>
<td>Vegetations on right coronary cusp</td>
<td>1:480</td>
</tr>
<tr>
<td>6</td>
<td>49/F</td>
<td>1991</td>
<td>SOB, fever, elevated JVP, diastolic murmur</td>
<td>IV</td>
<td>6</td>
<td>Aortic</td>
<td>Aol (4/4) and vegetations</td>
<td>Aortic valve vegetations</td>
<td>1:2400</td>
</tr>
<tr>
<td>7</td>
<td>65/M</td>
<td>1998</td>
<td>SOB, fever, elevated JVP, hepatomegaly, systolic and diastolic murmur</td>
<td>III</td>
<td>5</td>
<td>Aortic + Mitral</td>
<td>Aol (3/4), MI (2/4) and vegetations</td>
<td>Vegetations on both mitral and aortic valves</td>
<td>1:2000</td>
</tr>
</tbody>
</table>

* M, male; F, female; SOB, shortness of breath; NYHA, New York Heart Association; JVP, jugular venous pressure; Aol, aortic valve incompetence; MS, mitral valve stenosis; MI, mitral valve incompetence; STA, standard tube agglutination titers.
Results were expressed as median and range for continuous variables. Kaplan–Maier analysis was used for survival analysis.

3. Results

Four patients (4/7, 57%, patients 1, 2, 5 and 6) underwent standard aortic valve replacement with Carbomedics prosthetic valves. They all had significant aortic valve incompetence and 2 of them (2/4, 50%, patients 5 and 6) had aortic valve vegetations. Patient 5 had vegetations in the right coronary cusp, which had not been shown by the preoperative echocardiogram. Two patients (2/7, 28%, patients 3 and 4) underwent standard mitral valve replacement with Carbomedics prosthetic valve. They both had mitral valve stenosis due to rheumatic valve disease and associated vegetations. One patient (1/7, 14%, patient 7) underwent standard aortic and mitral valve replacements with Carbomedics prosthetic valves. In the latter, both valves were incompetent with vegetations. Four patients in total (4/7, 57%, patients 1, 3, 4, 7) had changes in the affected valves compatible with rheumatic valve disease.

There were no operative deaths. One patient (1/7, 14%, patient 7) suffered hemiplegia due to cerebral infarction and low cardiac output in the early postoperative period. This patient died 2 years after the operation due to a massive cerebrovascular accident. No other patients experienced any complication in the early or late postoperative period. In the immediate postoperative period all patients continued their preoperative antibiotic treatment with co-timoxazole and tetracyclines until discharge, while streptomycin was discontinued. All patients were afebrile before discharge and their median hospital stay was 13 days (range: 11–26 days). After discharge all patients received a combination of co-trimoxazole 8 mg/kg four times daily p.o. and tetracyclines (tetracycline 750 mg three times daily p.o. or doxycycline 200 mg twice daily p.o. for the first four patients and the last three patients, respectively) for a median 12 months (range: 3–15 months). The end-point of antibiotic therapy was the normalization of \textit{Brucella} titers (≤1:160). All postoperative and follow up blood cultures grew no pathogens. Standard tube \textit{Brucella} agglutination titers presented gradual decrease in all patients (Fig. 1). Apart from some minor gastrointestinal upset in patients treated with doxycycline, no patient developed any significant complication related to antibiotic therapy i.e. hepatotoxicity, etc. Ten-year survival was 85.7 ± 13.2% (Fig. 2).

4. Discussion

Endocarditis may be a complication of systemic Brucellosis in countries with a high prevalence of \textit{Brucella} and rheumatic heart disease [2]. In our series \textit{Brucella} endocarditis was recognized in 4% of patients treated for endocarditis. \textit{Brucella} endocarditis incidence varies widely and ranges from 0.7 to 10.9% of endocarditis cases in different countries [3–5] having a higher prevalence in Mediterranean countries and Middle East as compared with Western countries. Dalrymple-Champneys [6] reported five cases of endocarditis among 1500 patients with Brucellosis in Britain over a 43-year period. The low incidence of \textit{Brucella} endocarditis in Western World is not surprising, as most of the cases are caused by \textit{Brucella abortus}, a species known to be responsible for mild disease and uncommonly associated with suppurative or disabling complications [7,8]. In Greece \textit{Brucella melitensis} is endemic. In our series, definite diagnosis was established in all patients and they all had \textit{Brucella melitensis}, which is known to cause acute severe disease with symptoms that may be disabling. \textit{Brucella melitensis} resists the bactericidal activity of normal serum and remains viable inside the human polymorphonuclear leucocytes [9] properties that account for its greater virulence [10]. The low white cell count encountered in our series may be compatible with the clinical presentation of brucellosis.

The diagnosis of endocarditis during the course of Brucellosis is difficult. Blood cultures although highly specific, present a quite low sensitivity (15–20%) [10].
This low yield of positive blood cultures may be due to the fastidiousness of the organism, previous antibiotic treatment and a long interval between the onset of symptoms and the final diagnosis [11,12]. However, treatment should be initiated on the ground of high clinical suspicion and not delayed until culture results are known, usually after 4 weeks, due to the fulminant course of the disease [13]. In our study all patients presented positive blood and/or cardiac tissue cultures, which confirmed the diagnosis late after surgery and the initiation of antibiotics. The high incidence of positive cultures in our study is probably due to the fastidiousness of the organisms and the short interval between the onset of symptoms and the cultures. Slide agglutination test’s specificity is 40–50% in acute brucellosis and its sensitivity is high (92–98%) in acute but low (45–59%) in chronic brucellosis [13]. Brucella immunologic tests (ELISA and others) have been reported highly sensitive and specific for acute and chronic brucellosis [10]; however, their diagnostic value is not fully established. In our patients Brucella endocarditis was suspected because of reported contact with sheep, goats or untreated milk products, although no exposure to infected animal or animal products was established. Persistently high serologic titers (>1:320) of Brucella were considered diagnostic and stimulated treatment for Brucella endocarditis. Rapid hemodynamic deterioration and congestive heart failure, common in Brucella endocarditis, were present in six out of seven patients. In one patient the high rising preoperative serologic titer of Brucella as well as post-treatment fall of agglutination titers confirmed the clinical suspicion and encouraged the continuation of treatment. Later the diagnosis was confirmed by the culture results.

Conservative antibiotic treatment alone is considered ineffective and therefore not recommended by most authors [1]. However, in selected patients with absence of congestive heart failure, prosthetic valve, relatively mild extravalvular cardiac involvement, and a somewhat shorter disease history before initiation of antibiotic treatment, conservative medical therapy may be a valid alternative to surgery [14,15]. It is worth noting, however, that most of the conservatively treated cases were caused by Brucella abortus [16,17]. In our series valvular dysfunction, presence of vegetations and congestive heart failure urged us to follow a more aggressive treatment policy, and so far we have not experienced cases considered to need conservative treatment. Previous reports also favor the need of early surgical intervention [18,19]. The policy of early surgical intervention has been applied in our institutions since 1978, and all of our patients were operated within a week after the commencement of antimicrobial regimen. Further support for early surgical intervention comes from Al-Kasab et al. [3], who in 1988 reported the development of a vegetation on the mitral valve of a patient treated medically for 3 weeks and as a result of this experience all remaining patients were operated within 5 days of medical therapy. The ideal valves in cases of endocarditis are thought to be the homograft valves; however, their low availability combined with our limited experience with homografts has led us to the use of the familiar mechanical valves in combination with aggressive antibiotic therapy. Notably, no patient in our series had infectious involvement of extracardiac tissues (i.e. perivalvular abscess) and this may have favored the good results of our strategy.

Ideally, the antimicrobial agents used for Brucella endocarditis should be bactericidal and able to penetrate the infected cells and exert their activity inside the phagosome. This last property may be paramount to avoid relapse [20]. Our patients were treated with a triple-antibiotic regimen consisting of doxycycline, streptomycin and co-trimoxazole and two-antibiotic therapy after valve replacement. A synergistic effect between doxycycline and streptomycin has been well demonstrated [21–23]. Brucella organisms also present a high sensitivity to co-trimoxazole [11,12]. Triple-antibiotic therapy or even four-drug therapy [10,23] is favored by most authors in the active preoperative phase of the infection, while a two antibiotic regimen is recommended after valve replacement. Treatment failure has been reported when only two-antibiotic therapy is prescribed in the preoperative phase [3].

The duration of antimicrobial therapy after valve replacement remains controversial. Periods as short as 2 weeks or as long as 13 months have been reported [3,10,23]. The decision to stop treatment could be individualized after a thorough clinical observation and evidence of progressive drop in anti-agglutinin titer. In our series, treatment was continued for a median of 1 year postoperatively with a combination of tetracyclines and co-trimoxazole with obviously good results. In one of our patients two-antibiotic therapy was continued for 15 months because of a delayed decrease of agglutination titers.

In conclusion, Brucella, although not one of the most prevalent causes of infective endocarditis world-widely, demonstrates a tendency toward a severe destruction of the affected valves, clinically characterized by the presence of large valve vegetations, tissue ulceration and a definite risk of dangerous complications, such as embolization. Medical therapy alone may be insufficient to eradicate the infection from a native valve. The results of our policy support the necessity of medical therapy combined with early surgical intervention for the accomplishment of a successful outcome.

References


